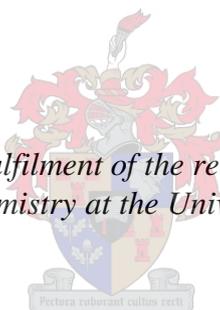


A Study Towards the Synthesis of Dithiadiazolyl Functionalised Calix[4]arenes

by
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*Thesis presented in partial fulfilment of the requirements for the degree
Master of Science in Chemistry at the University of Stellenbosch*



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Declaration

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Abstract

Dithiadiazolyl heterocyclic radicals form part of an ever-growing research field in the quest for organic magnets and conducting materials due to the lone electron located within the heterocyclic ring. These compounds could potentially be used as electrical current conductors and transistors which may be developed into a molecular switch or other types of molecular devices.

This thesis describes the successful synthesis of three nitrile functionalised calix[4]arenes, mono-, distal- and tetra-, as bulky scaffolds to be used as precursors in the synthesis of dithiadiazolyl functionalised calix[4]arenes. The crystal structures of these three nitriles are reported herein for the first time. Dithiadiazolyls tend to dimerise in the solid state, thus by selecting a calix[4]arene as a bulky R-group, it was hoped to inhibit dimerisation. Furthermore, synthesis of the radicals on different positions of the calix[4]arene may also inhibit dimerisation in the solid state. The typical reaction in the synthesis of dithiadiazolyls involves the reaction between a nitrile and lithium bis(trimethylsilyl)amide followed by the formation of the dithiadiazolylum chloride salt by the addition of sulfur dichloride. The salt is subsequently reduced giving the desired dithiadiazolyl. However, the addition of lithium bis(trimethylsilyl)amide to mono-nitrile calix[4]arene in the synthesis of the mono-dithiadiazolyl functionalised calix[4]arene was unsuccessful. To investigate the incompatible nature of the electrophile and nucleophile, computational and physical experiments were conducted on the mono-nitrile calix[4]arene derivative. These avenues were pursued to determine whether the unreactive nature of the nitrile in this case is due to electronic effects.

Changes in the reaction conditions (i.e. temperature, solvent and the equivalents of nucleophile) were all varied, but this proved to be unsuccessful. Computationally, through charge calculations, it was determined that the electronic properties of the nitrile were similar to that of nitrile examples known to work in the literature. Therefore, it was established that steric effects of the calix[4]arene are playing a critical role in the unreactive nature of the nitrile. There are two non-degenerate LUMO orbitals for the nitrile as one is conjugated and the other is planar (LUMO + 1) to the aromatic system. It has been established that nucleophilic attack through the lowest energy LUMO would result in a high energy transition state due to the loss of conjugation and attack through the higher energy LUMO + 1 would result in a lower energy transition state. However, this was not possible due to the steric conditions surrounding its position relative to the nitrile. The results obtained from this study were, therefore, able to confirm that the normally suitable reaction procedure seems to be limited to less sterically encumbered nitriles.

Opsomming

Dithiadiazolyl heterosikliese radikale vorm deel van 'n steeds groeiende navorsingsveld in die soeke na organiese magnete en material met geleidingsvermoë as gevolg van die ongepaarde elektron wat binne in die heterosikliese ring geleë is. Hierdie verbindings kan moontlik gebruik word as elektriese stroom geleiers en transistors wat tot 'n molekulêre skakelaar of ander tipe molekulêre toestelle ontwikkel kan word.

Hierdie tesis beskryf die suksesvolle sintese van drie nitriël gefunksionaliseerde calix[4]arene, mono-, distale- en tetra-, as lywige steiers om as voorgangers in die sintese van dithiadiazolyl gefunksionaliseerde calix[4]arene gebruik te word. Die kristal strukture van hierdie drie nitriële is hier in vir die eerste keer gerapporteer. Dithiadiazolyls is geneig om te dimeriseer in die vaste toestand. Daarom is die redenasie agter die keuse van die calix[4]arene as 'n lywige R-groep, as dimeriseering te inhibeer. Sintese van die radikale op verskillende posisies van die calix[4]arene kan dimeriseering in die vaste toestand inhibeer. Die tipiese reaksie in die sintese van dithiadiazolyls behels die reaksie tussen 'n nitriël en litium bis(trimetiëlsilil)amied gevolg deur die vorming van die dithiadiazolylum chloried sout deur die byvoeging van swaeldichloried. Die sout is dan gereduseer om die gewenste dithiadiazolyl te vorm. Die toevoeging van litium bis(trimetiëlsilil)amied mono-nitriël calix[4]arene in die sintese van die mono-dithiadiazolyl calix[4]arene was egter onsuksesvol. Om die oënskyklik onvereenigbare aard van die elektrofiel en nukleofiel te ondersoek, is rekenaar-berekeninge en fisiese eksperimente uitgevoer op die mono-nitriël calix[4]arene afgeleide. Hierdie twee maniere is gevolg om te bepaal of die onreaktiewe aard van die nitriël in hierdie geval as gevolg van elektroniese effekte is.

Wysigings in die reaksie omstandighede (d.w.s. temperatuur, oplosmiddel en die ekwivalente van nukleofiel) is gemaak, maar dit was onsuksesvol. Deur middle van ladings-berekeninge, is dit bepaal dat die elektroniese eienskappe van die nitriël soortgelyk is aan dié van nitriël voorbeelde wat in die literatuur gerapporteer is. Daarom is dit vasgestel dat die steriese effekte van die calix[4]arene 'n kritieke rol in die onreaktiewe aard van die nitrile speel. Daar is nie-ontaarde LUMO orbitale vir die nitriël soos 'n mens is verwoeg en die ander is planêr (LUMO + 1) na die aromatiese stelsel. Daar is vasgestel dat nukleofieliese aanval deur die laagste energie LUMO sal lei tot 'n hoë energie oorgangstoestand as gevolg van die verlies van konjugasie. Aanval deur die hoër energie LUMO + 1 sou lei tot 'n laer energie oorgangstoestand. Dit was egter nie moontlik nie, as gevolg van die steriese toestande rondom die orbital se posisie met betrekking tot die nitriël. Die resultate van hierdie studie bevestig, dus, dat die gewone reaksie proses beperk is tot minder steries verhinderde nitriële.

Publications

(Not part of this work)

2-({4-[(1H-Imidazol-2-ylsulfanyl)methyl]-2,5-dimethylbenzyl}sulfanyl)-1H-imidazole
Acta Crystallographica, Section E: Structure Reports Online, **2010**, E66(11), o2749.

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Though questions of knowledge are important, the greatest question is
whether you have left everything to follow
Him.

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List of Technical Abbreviations

ATR-IR	Attenuated Total Reflection Infrared Spectroscopy
ESI	Electron Spray Ionization
EPR	Electron Paramagnetic Resonance
IR	Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
tlc	Thin Layer Chromatography
ASAP	Atmospheric Solid Analysis Probe
ASU	Asymmetric Unit
NOE	Nuclear Overhauser Effect

Chapter 1

General Introduction

1.1 Review of Calix[4]arene Chemistry

1.1.1 Introduction

Calix[n]arenes (Figure 1.1) are a class of well studied molecules¹ and are employed in various fields of research which include, to name but a few: solid phase gas storage^{2,3} and separation,⁴ enzyme mimics⁵⁻⁸ and as ligands in asymmetric catalysis.⁹⁻¹²

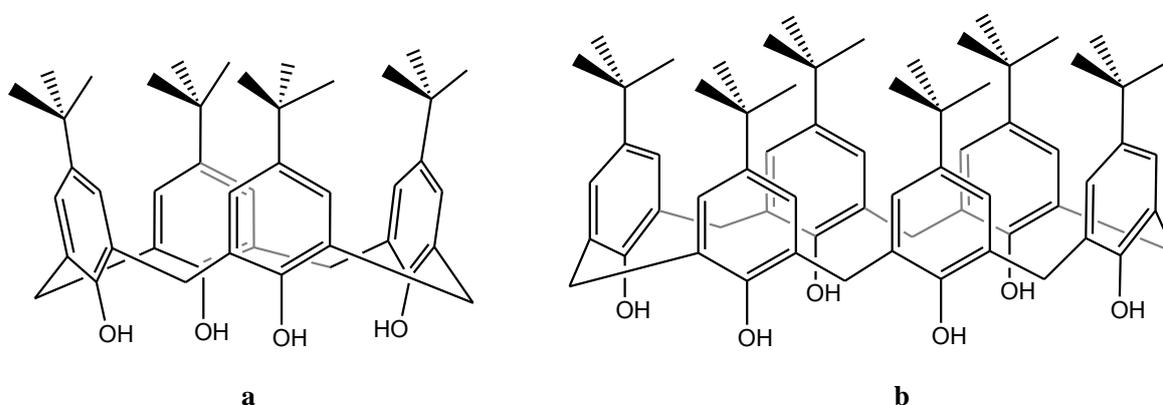
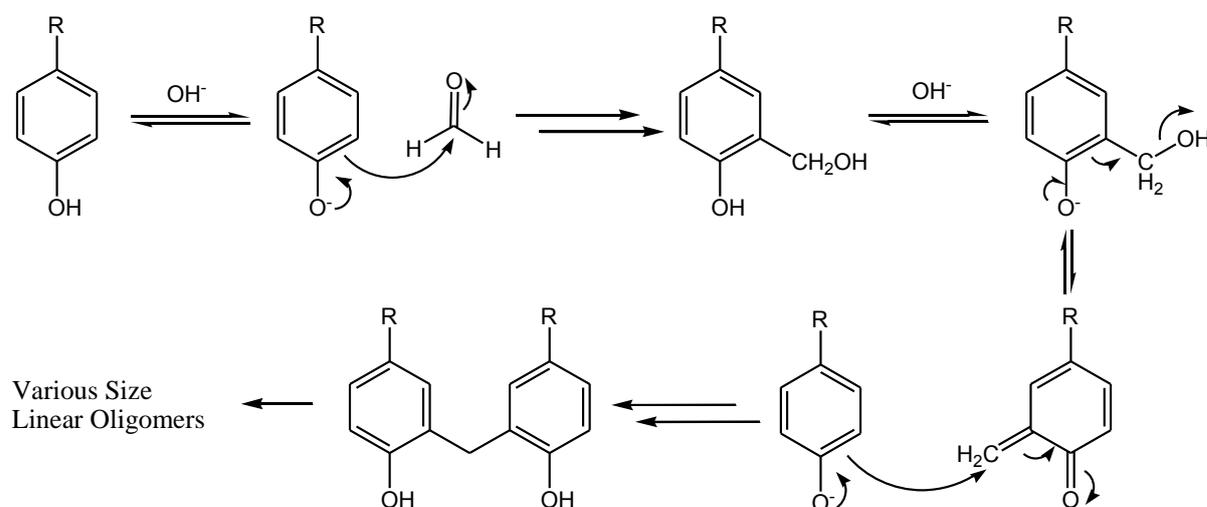


Figure 1.1: Two examples of calix[n]arene compounds: (a) *p-tert*-butyl-calix[4]arene and (b) *p-tert*-butyl-calix[6]arene

The synthesis of calixarenes originated as a totally unknown field of phenol-formaldehyde chemistry and was initiated by Adolph von Baeyer as far back as 1872. Baeyer was better known at the time for his elucidation and synthesis of the dye indigo, as well as work on carbocyclic ring compounds. However, in the late 19th century he started experimenting with phenols and formaldehyde – work which was communicated in three separate papers in *Chemische Berichte*.¹³⁻¹⁵ He described his products as a black resin or tar. A research boom in phenol formaldehyde chemistry came after 1902 when Leo Baekeland established the synthesis of Bakelite[®] which was the first material to be termed a plastic.¹⁶ Research in this field was so prosperous that he was able to file more than 400 patents, describing Bakelite's[®] non-conductive and heat resistant properties. Generally, the plastic products of this era were still ill defined. It was not until the use of *para* substituted phenols that Alois Zinke and his co-worker Erich Ziegler managed to produce a pure non-plastic substance from the reaction of formaldehyde and phenol¹⁷ and shortly after this, Joseph Niederl and his co-worker Heinz Vogel managed to crystallise a pure substance from this reaction for the first time.¹⁸

Generating this pure material was made possible by minimising the amount of dehydration products that could form. This was achieved by using *para* substituted phenols. Unsubstituted phenols are able to react at both the *ortho* and *para* sites resulting in various branched products. The reaction of these materials is difficult to control due to the similar reactivity of the *ortho* and *para* sites. With the introduction of *para* substituted phenols the only plausible products would be a variation in size of linear oligomers. Linear oligomers are, however, able to bond intramolecularly to form cyclic compounds. The cyclic products initially proposed by Niederl and Vogel were eventually accepted by Zinke in 1944.¹⁹ This was later proved by the stepwise synthesis by Hayes and Hunter.²⁰



Scheme 1.1: The mechanism for the formation of linear oligomers in the calix[n]arene synthesis¹

Due to the almost infinite number of linear polymer chains that could potentially form it is not hard to imagine that a broad range of calix[n]arene molecules could be synthesised. This is indeed the case with *n* ranging from 4-12 and beyond.²¹ There are methodologies, which over the years have been specifically tailored to give only the required calix[n]arene. Many conditions need to be considered. These include the nature and concentration of base, as well as the temperature at which the reaction is performed.¹

1.2.1 Calix[4]arenes

Calix[4]arenes are formed by the dehydration reaction of cheap starting materials such as *para* substituted phenols and formaldehyde.²² As already mentioned, there are specific conditions for the formation of the calixarene tetramer. The reaction conditions have been well documented; however, the exact mechanism is still a matter of debate.¹ The first step in the reaction is the formation of a hydroxy-methyl phenyl unit which could go on to form various

size linear oligomers (Scheme 1.1). It is due to this that there are a number of potential approaches that could be followed to synthesise the calix[4]arene, all resulting in the formation of the desired tetramer. The different size oligomers could come together as four discrete monomers through a hydrogen-bonded archetype, two dimeric units or as one four membered oligomer. Calix[4]arenes have also been found to form via the bowl fragmentation of calix[8]arenes.¹ Although the actual pathway is still not clear, the driving force in the reaction is the potential to form octameric hydrogen bonding across the lower rim phenolic positions (Figure 1.2).^{23, 24} The hydrogen bonding is cooperative across the lower rim in either a clockwise or anti clockwise fashion and therefore increases the stability of the calix[4]arene bowl.²⁵ This is evident in the IR spectrum where the OH band is noted at a lower frequency than expected.^{21, 26} It is due to this significant intramolecular interaction that calix[4]arenes are fixed in what can be described as the cone conformation (Figure 1.2).

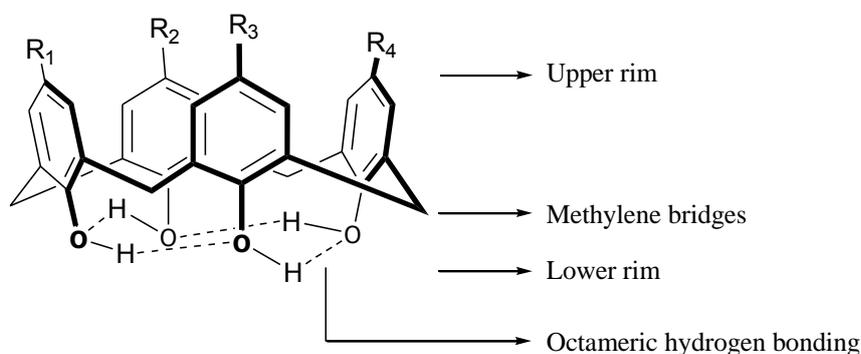


Figure 1.2: The calix[4]arene in the cone conformation with the labels indicating the regions described in the text

1.2.2 Calix[4]arene mobility

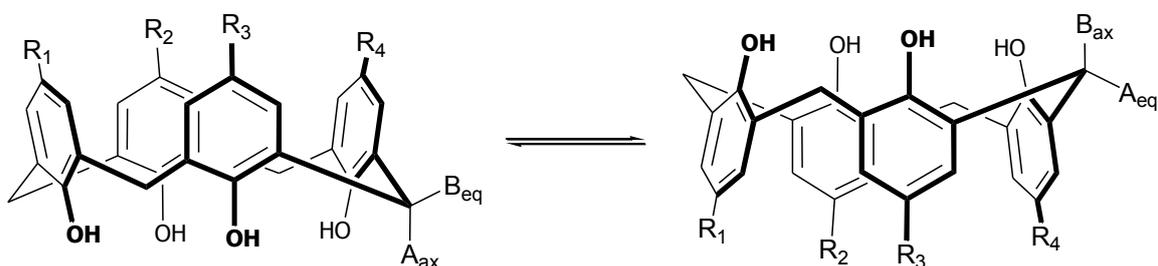


Figure 1.3: Interconversion of calix[4]arenes in solution

The cone conformation is immobilised through the hydrogen bonding across the lower rim of the calix[4]arene. The two hydrogens bonded at the methylene bridge are magnetically inequivalent. One hydrogen could be described as being axial and the other equatorial relative to the horizontal plane of the calix[4]arene. Therefore two doublets should be observed in the

^1H NMR spectrum. However, this is only the case at temperatures below 25 °C. At elevated temperatures the hydrogen bonding across the lower rim is destroyed and a singlet is observed in the ^1H NMR spectrum. The singlet is observed as a result of each aromatic ring having the potential to flip through the annulus, in a manner analogous to the ring flip of cyclohexane.^{27,28} Therefore the axial hydrogen would flip into the equatorial position and *vice versa* for the equatorial hydrogen (Figure 1.3). To observe the inequivalent protons, ^1H NMR spectroscopy should be performed at 0 °C as the interconversion rate at room temperature, of 100 s^{-1} , is too fast for the acquisition rate of the instrument.²⁸

When considering the cone conformation, the calix[4]arene molecule has some distinct regions: the lower rim, upper rim and the methylene bridges (Figure 1.2). The lower rim can be functionalised, destroying the hydrogen bonding allowing for a more flexible bowl. This flexibility, depending on the degree of functionalisation, leads to various conformations which are able to interconvert (Figure 1.4). The different conformations as illustrated in figure 1.4 include the partial cone as well as the 1,2 alternate and 1,3 alternate conformations.²⁹

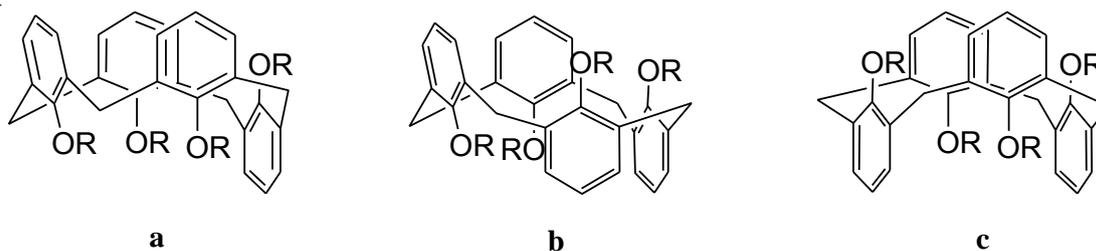


Figure 1.4: Various conformations of calix[4]arenes include (a) partial cone, (b) 1,2 alternate and the (c) 1,3 alternate

The interconversion of these conformers could occur in two possible ways: “oxygen through the annulus” (lower rim) or the “*para* substituent through the annulus” (upper rim). It has been shown that for the calix[4]arenes the interconversion route is the former.¹ However, the interconversion can be prevented, resulting in an immobilised bowl. A large enough R-group bonded at the phenolic positions will not be able to fit through the cavity of the bowl and therefore the calix[4]arene would be conformationally stable. It has been indicated that the shortest linear alkyl chain that efficiently immobilises interconversion is the propyl group.³⁰

1.2.3 Calix[4]arene symmetry

When the lower rim of the calix[4]arene is functionalised, the symmetry of the bowl is distorted slightly from C_4 to C_{2v} . The C_{2v} symmetry is due to what is known as the pinch cone conformation (Figure 1.5) where two opposite aryl rings are parallel and upright compared to

the two alternate opposite rings which are positioned further apart and outward from each other.³¹ Therefore, if the calix[4]arene is synthesised in such a way as to immobilise the bowl in the pinched cone conformation with C_{2v} symmetry, the axial and equatorial hydrogens of the methylene bridges would result in two doublet signals.

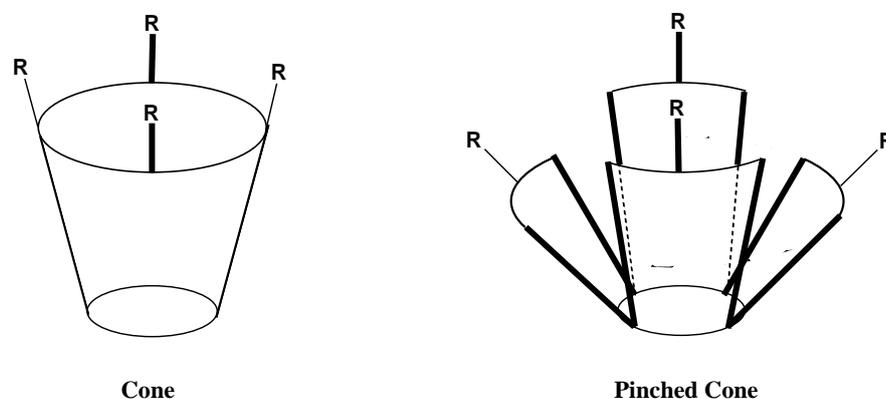


Figure 1.5: The difference between (a) the cone and (b) the pinched cone conformation

If the calix[4]arene is synthesised in such a way as to immobilise the bowl in a different conformation, the occurrence of more signals in the ^1H NMR spectrum would be observed. For example, if the calix[4]arene was synthesised as the partial cone conformer, the axial and equatorial hydrogens of the methylene bridges adjacent to the aromatic ring would be in a different spatial arrangement. Therefore, as a result of breaking the symmetry the bowl, an extra pair of doublets would be observed in the ^1H NMR spectrum.

Upper rim functionalisation may lead to a range of possible products. These products could either be mono-, distal-, proximal-, tri-, or tetra-substituted (Figure 1.6).

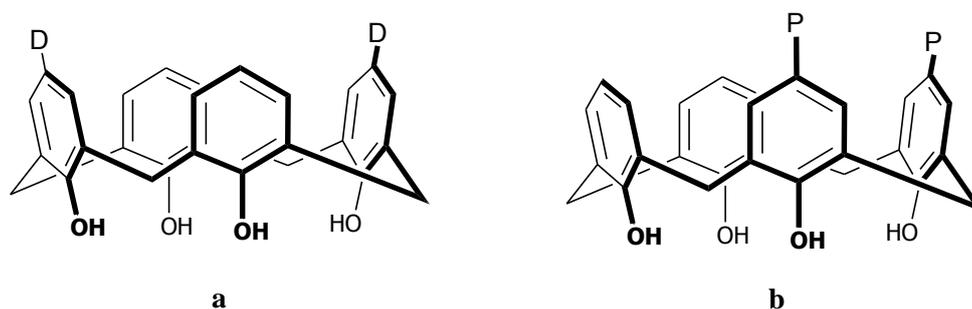


Figure 1.6: Upper rim functionalisation where (a) is the distal and (b) is the proximal product

Calix[4]arenes can be denoted using a convenient means of classification proposed by Shinkai *et al.*^{32, 33} In terms of the cone conformation, if synthesised from identical monomers, a symmetrical product would form. This may be denoted as an AAAA structure with C_4 geometry (Figure 1.7). Furthermore, upper rim, as well as lower rim functionalisation, would

transform the symmetry of the molecule. The symmetry would be reduced to C_v once mono functionalisation had taken place (AAAB). Distal (ABAB) and proximal (ABBA) functionalisation reduces the symmetry to C_{2v} and C_v respectively.

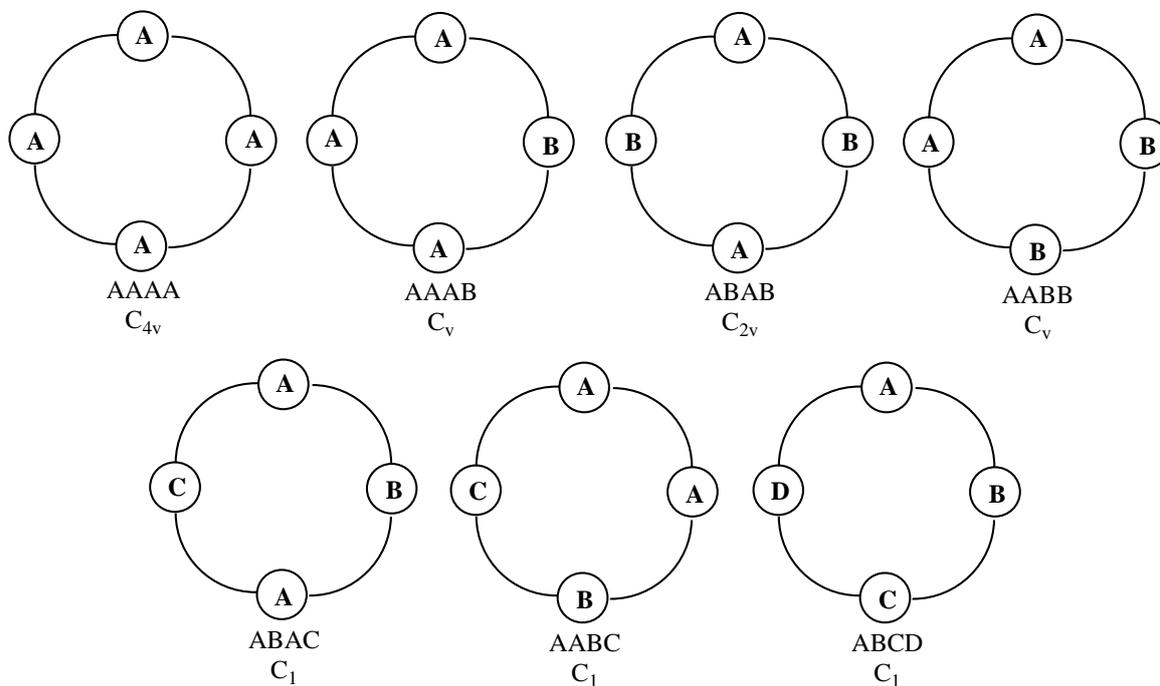


Figure 1.7: Denotation for the systematic classification of calix[4]arenes^{32, 33}

Figure 1.7 represents all the configurations of only the cone conformation of the calix[4]arene tetramer. With the introduction of three (ABAC or AABC) or four (ABCD) different substituents, symmetry is completely reduced to the point group C_1 . The three dimensional nature as well as the asymmetrical nature of the C_1 calix[4]arenes generates the possibility for inherently chiral calix[4]arenes.^{32, 33} This is evident for both the AABC and ABCD configurations as their mirror images are non-superimposable. The inherently chiral calix[4]arenes are interesting in themselves and can be utilised as ligands in asymmetric catalysis.^{10, 12}

1.2 Review of Dithiadiazolyl Chemistry

1.2.1 Introduction

Radicals are of particular interest in the laboratory environment, since some are stable enough to work with and have been shown to exhibit magnetic and conductive properties.^{34, 35}

The first non-metallic organic polymer to exhibit conductive properties was poly(sulfur nitride).³⁶ This is not a radical, but was the beginning of the exploration into $[\text{SN}]_x$ materials. The first molecule consisting of sulfur and nitrogen to exhibit interesting properties was $[\text{S}_3\text{N}_2^+]\text{Cl}^-$, which was synthesised as far back as 1880 (Figure 1.8).³⁷ However, the structure was only elucidated nearly 100 years later, in 1974.³⁸ To further investigate the properties of the sulfur nitrogen heterocycle, substitution of the S^+ with an $\text{R}-\text{C}$ group has led to a few of the most studied sulfur-nitrogen containing radicals. The molecules obtained by this substitution result in isoelectronic systems with the formulae RCN_2S_2 and are known as dithiadiazolyls (Figure 1.9).



Figure 1.8: $[\text{S}_3\text{N}_2^+]\text{Cl}^-$, the first of the $[\text{SN}]_x$ materials

The 1,2,3,5 dithiadiazolyl radical was first synthesised in 1980 and forms part of the group of sulfur nitrogen heterocyclic radicals.³⁹ The solid-state structure of the dithiadiazolyls can be manipulated, by varying the R-group. By doing so, it is possible to change the solid state properties, which may result in novel materials with magnetic⁴⁰ and conductive³⁹ properties.

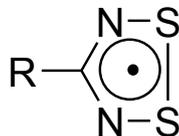


Figure 1.9: The 1,2,3,5-dithiadiazolyl radical

1.2.2 The 1,2,3,5-dithiadiazolyl radical

Dithiadiazolyl heterocycles could potentially occur in four possible isomers (Figure 1.10), however, only **1** and **2** are reported in the literature.⁴¹ The most thermodynamically stable isomer is **1**. Isomerisation of **2** to **1** occurs through a photochemically induced concerted

mechanism *via* a bimolecular approach where each molecule exchanges both a nitrogen and sulfur atom.^{42, 43} From molecular orbital calculations it has been determined that **3** and **4** are also possible but there is a potential for the loss of dinitrogen.⁴¹ In all of these isomeric forms nitrogen donates one electron and sulfur two electrons for π -bonding. This results in a 7π system with an unpaired electron.

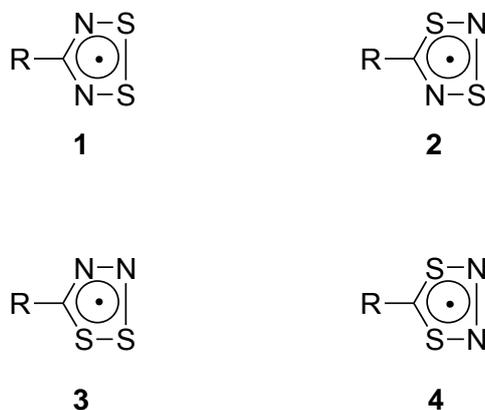


Figure 1.10: Possible dithiadiazolyl isomers

The unpaired electron is situated in a Singly Occupied Molecular Orbital (SOMO) of $2a_2$ symmetry.⁴¹ Theoretical calculations have shown that the SOMO is nodal at the carbon of the dithiadiazolyl.⁴¹ Therefore, the unpaired electron is localised on the NSSN fragment and the contribution of the R-group on the electronic properties of the dithiadiazolyl has no significant effect. Dithiadiazolyls tend to dimerise in the solid state due to the pairing up of the unpaired electrons (Figure 1.11). This is a favourable process estimated to be $35 \text{ kJ}\cdot\text{mol}^{-1}$.⁴⁴

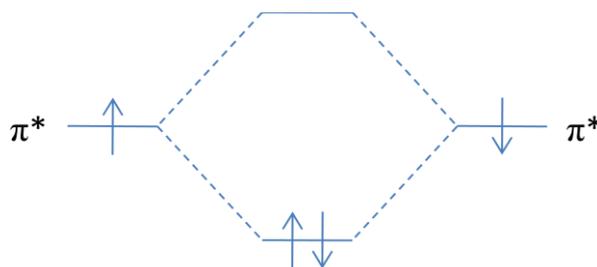


Figure 1.11: The molecular orbital diagram of the SOMO-SOMO interaction in dimers of the dithiadiazolyl radical

The dithiadiazolyls are able to dimerise in five possible configurations (Figure 1.12). All these interactions are favourable, due to the interaction of the SOMOs of two monomers, as illustrated in figure 1.10. The first two dimers (Figure 1.12a and 1.12b) are the most commonly observed configurations in the literature. This is due to the strong S...S contacts and some weaker S...N contacts between the monomers. When the R-group is non-planar the resultant

configuration is twisted (Fig. 1.12a). This both minimises steric repulsion and is stabilised by one strong S...S contact. The distance of this interaction is between 2.99 and 3.11 Å ($2.99 < d_{ss} < 3.11 \text{ \AA}$). This configuration can be found in the adamantyl derivative (AdCNSSN)₂⁴⁵ as well as (Me₂NCNSSN)₂⁴⁵ and (CH₃CNSSN)₂.⁴⁶ In most 1,2,3,5-dithiadiazolyls studied the R-group is a planar aryl substituent and this typically results in the cis-oid configuration (Figure 1.12b). The S...S contacts are longer and therefore more delocalised with distances between 3.10 and 3.13 Å ($3.10 < d_{ss} < 3.13 \text{ \AA}$). However, bonding is not weaker, since there are two S...S contacts. This configuration can be found in examples (PhCNSSN)₂³⁹ and (*m*- and *p*-CNPhCNSSN)₂.⁴⁷ The trans-oid (Figure 1.12c) and trans-cofacial (Figure 1.12d) are dimer configurations that do not occur as frequently. This can probably be attributed to the sum of the interactions being weaker than that for the twisted and cis-oid configurations. As an example, in the trans-oid configuration there are only two S...S contacts compared to the three contacts (two S...N and an S...S) in the twisted configuration. The orthogonal dimer configuration (Figure 1.12e) has only recently been reported for the ortho chloro derivative (2-CIC₆H₄CNSSN)₂.⁴⁸ The two S...S interactions have distances of 3.29 and 3.24 Å, and the two S...N distances are 3.27 and 3.47 Å. The energy difference between the dimers is minimal, with values calculated at approximately 5 kJ/mol.⁴⁹

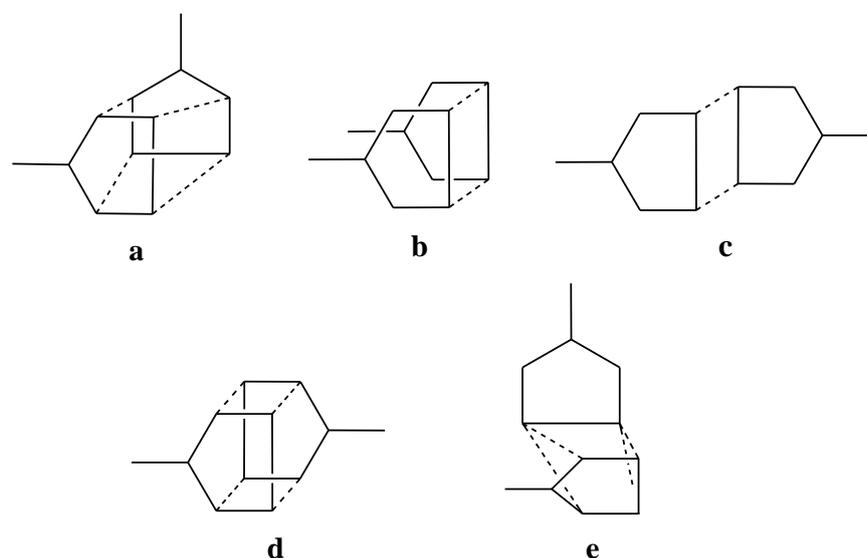
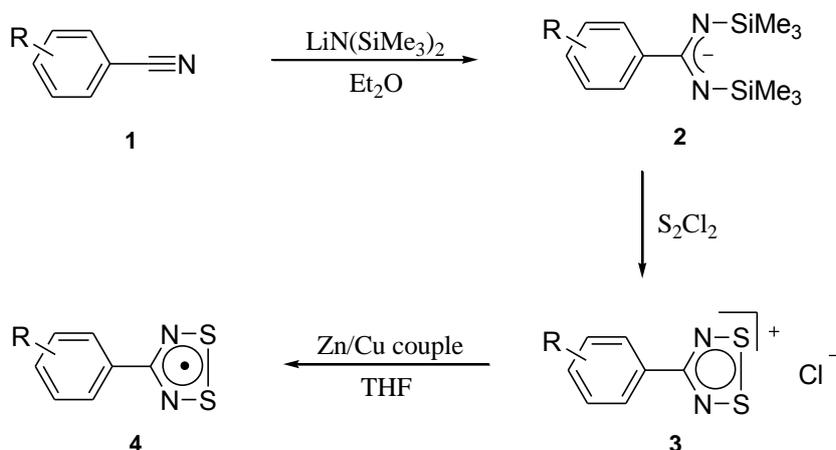


Figure 1.12: Five possible configurations of the 1,2,3,5-dithiadiazolyl radical dimer (a) twisted, (b) cis-oid, (c) trans-oid (trans-cofacial), (d) trans-antarafacial and (e) orthogonal

1.2.3 Synthesis of the 1,2,3,5-dithiadiazolyl

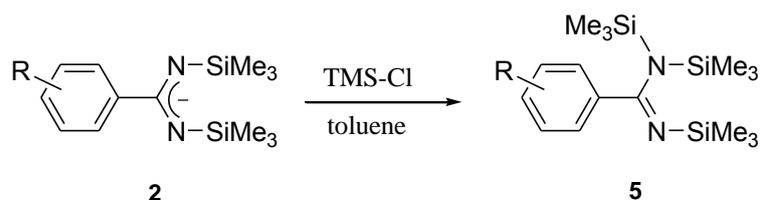
1.2.3.1 Addition of $\text{Li}[\text{N}(\text{SiMe}_3)_2]$

Aryl 1,2,3,5-dithiadiazolyls are conventionally synthesized from aromatic nitriles according to a one-pot literature method (Scheme 1.2).⁴¹ The aromatic nitrile is reacted with lithium bis(trimethylsilyl)amide, ($\text{Li}[\text{N}(\text{SiMe}_3)_2]$), to form what can be described as a persilylated amidinate intermediate, **2**. This intermediate is condensed with either SCl_2 or S_2Cl_2 to form a 6π dithiadiazolylum chloride salt, **3**. The salt, upon reduction, gives the dithiadiazolyl radical, **4**. The reduction is typically performed using Zn/Cu couple, Ag powder or Ph_3Sb . The radicals can be purified by sublimation, under reduced pressure, from the crude mixture.



Scheme 1.2: The general one-pot 1,2,3,5-dithiadiazolyl radical synthesis

The abovementioned procedure is based on the lithium bis(trimethylsilyl)amide acting as a nucleophile. However, lithium bis(trimethylsilyl)amide is generally applied in synthesis to work as a base.⁵⁰ Therefore this method is only applied to the synthesis of 1,2,3,5-dithiadiazolyls that have non-protic substituents. Examples of the many non-protic substituents are CN, F, Cl, Br, I, NO_2 , CF_3 and OMe.⁵¹⁻⁵⁵ In an analogous manner, protons α to the nitrile group react with lithium bis(trimethylsilyl)amide, and therefore substituents with this characteristic are not able to follow the synthetic procedure stated in scheme 1.2.⁵⁶

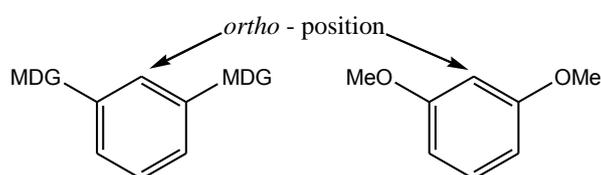


Scheme 1.3: Synthesis of the fully silylated amidine, **5**, by the addition of TMS-Cl in toluene

Furthermore, the silylated intermediate, **2**, can be converted into a fully silylated amidine, **3**, by the addition of trimethyl silyl chloride (TMS-Cl) in toluene (Scheme 1.3). Isolation of **3** was reported in 1987 by Oakley *et al.*⁵⁶ The fully silylated amidine would spontaneously condense with sulfur dichloride to furnish the desired dithiadiazolylum chloride salt and upon reduction would render the dithiadiazolyl radical.

1.2.3.2 Ortholithiation

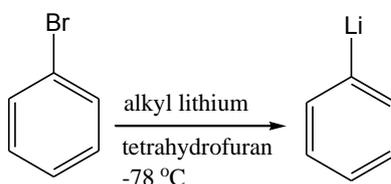
A second synthetic approach, less common in the literature, is ortholithiation.⁵⁷ This method can be applied when there are metal-directing groups (MDGs) in the *ortho* positions relative to the position on the aryl ring where the reaction needs to be performed (Scheme 1.4).



Scheme 1.4: The MDGs and the *ortho* position shown with 1,5 dimethoxy phenyl as an example of a starting material for an ortholithiation reaction

The two MDGs *ortho* to the desired position acidify the proton. This permits an organo-lithium reagent, such as butyl-lithium, to deprotonate regioselectively. The lithium-proton exchange converts the aryl compound into a nucleophile. To acquire the same persilylated amidinate intermediate, **2** (Scheme 1.2), bis(trimethylsilyl)carbodiimide is used as an electrophile.⁵⁸ Further condensation with either SCl_2 or S_2Cl_2 , followed by reduction with Zn/Cu couple, Ag powder or Ph_3Sb gives the desired dithiadiazolyl as the product.

1.2.3.3 Lithium-halogen exchange

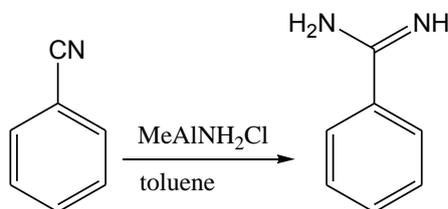


Scheme 1.5: Lithium-halogen exchange

Another approach using organo-lithium reagents is lithium-halogen exchange.⁵⁹ Organo-lithium reagents are able to exchange, as the name suggests, a halogen for lithium (Scheme 1.5). The lithiated intermediate which is formed can once again react with bis(trimethylsilyl)carbodiimide⁵⁸ to furnish the silylated intermediate.

1.2.3.4 Through an amidine precursor

An unsubstituted amidine precursor is a suitable candidate in the synthesis of dithiadiazolyls as it is analogous to the persilylated amidinate intermediate formed in the typical reaction procedure (Scheme 1.2).



Scheme 1.6: Garigipati's procedure for synthesising an amidine using MeAlNH₂Cl in toluene

A procedure developed by Garigipati presents a unique method of preparing unsubstituted amidines (Scheme 1.6).⁶⁰ The synthetic procedure makes use of Weinreb's aluminium amide reagent, MeAlNH₂Cl.^{61, 62} The nucleophilic attack of this reagent results in the formation of an unsubstituted amidine which can easily be converted to the dithiadiazolyl by following the typical reaction procedure.

1.2.4 Characterisation of the dithiadiazolyl radical

In the solid state, dithiadiazolyls are generally associated as dimers. However, in solution the dimers exist in equilibrium between the dimer and monomer. Therefore, in a dilute solution at room temperature the dimers almost completely dissociate.⁴¹ Electron paramagnetic resonance is often used in the characterisation of the discrete 1,2,3,5-dithiadiazolyl radicals.⁴¹ The lone electron in the π -system couples to the two equivalent nitrogen nuclei ($I = 1$), resulting in a pentet distribution of 1 : 2 : 3 : 2 : 1. This pentet arises due to nitrogen being spin active and obeying the $2n(I) + 1$ rule. The radical could also potentially couple to sulfur but due to the low abundance of the ³³S isotope, this is generally not observed.⁴¹

1.3 Solid state properties of the dithiadiazolyl

1.3.1 Conductivity

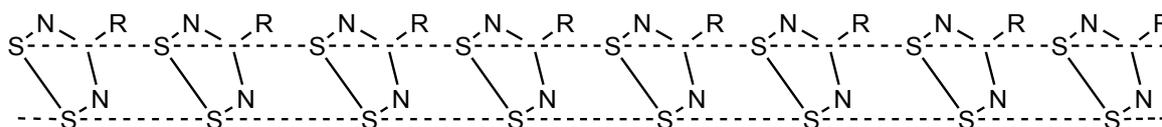


Figure 1.13: An idealized illustration of molecular π -stacking for the conductivity of dithiadiazolyl radicals

Haddon suggested that non-metallic molecular conductors could be prepared from neutral, rather than charged radicals.⁶³ Therefore, due to dithiadiazolyl radicals being neutral, it is no surprise that they have been exploited in this field. In order to maximise the conductivity potential of the dithiadiazolyls, a half filled energy band should be generated and this would arise through the one-dimensional uniform packing of the radical units (Figure 1.13).⁶⁴ However, organic systems have a few drawbacks when compared to inorganic systems. The overlap of the molecules is anisotropic, which causes a one-dimensional stack of molecules. Weak intermolecular interactions between the molecules in the stack are not ideal for propagating charge transfer through the system. Also, the molecules are only separated by distances of the van der Waal's contacts and therefore shortening of these distances is not possible without incurring large electron repulsion effects. Therefore, when dimerisation occurs, the degeneracy of the SOMOs throughout the one dimensional stack is lifted, lowering the energy of the system despite the increase in repulsion energy. The result of this is a band-gap at the Fermi level contributing to the formation of either a semi-conducting or insulating material. The distortion of the one-dimensional band leads to a stack of long and short contacts resulting in an overall lowering of the energy, and this phenomenon is known as Peierls distortion.⁶⁵ Minimising or avoiding this effect can be potentially achieved by modifying the solid-state structure properties through varying the R-group of the dithiadiazolyl.

There have been many attempts at the synthesis of dithiadiazolyl based conductive solids, specifically by Oakley and co-workers, which have shown some promise.^{47, 66-71} These dithiadiazolyl derivatives have been found to pack more compactly in the solid state, and thus exhibit conductive properties. Numerous examples of dithiadiazolyls have been synthesised and conductivity studies performed.⁶⁶⁻⁷⁰ As an example, the disjoint diradical 4,4'-bis(1,2,3,5-dithiadiazolyl) [$S_2N_2C-CN_2S_2$] forms slipped stack parallel units similar to that shown in figure 1.13. However, the conductivity measurements reveal that the molecule is effectively a very weak conductor with similar results to other stacked dithiadiazolyl radicals.⁶⁸ To improve the conductivity of the radicals it has been shown that p-type doping can be employed to raise the energy band away from the half-filled point associated with neutral radicals.⁶⁶ This can be achieved by co-subliming the radical with iodine, resulting in a charge transfer salt.⁶⁸ When the radical is subjected to these conditions the resultant material, [$S_2N_2C-CN_2S_2$][I], has conductive properties at ambient temperature. The single crystal conductivity is $4.6 \times 10^5 \text{ S.m}^{-1}$ (siemens per meter) at room temperature compared to $<10^{-4} \text{ S.m}^{-1}$ for the diradical [$S_2N_2C-CN_2S_2$].⁶⁸ The conductivity is comparable to values for graphite⁷² ($3 \times 10^5 \text{ S.m}^{-1}$) and mercury⁷³ ($1.02 \times 10^6 \text{ S.m}^{-1}$) and is only two orders of magnitude less than copper⁷⁴ ($5.96 \times 10^7 \text{ S.m}^{-1}$).

Therefore, as far as non-metallic conductors are concerned, dithiadiazolyls show promising results.

1.3.2 Magnetism

The magnetic behaviour of dithiadiazolyls have also been of particular interest.³⁴ The syntheses of organic magnets using dithiadiazolyls have proven to be quite challenging, due to the difficulty in overcoming the dimerisation energy of the radicals. Dimers in the solid state are diamagnetic and therefore have no potential for interesting magnetic properties. Overcoming this problem could potentially lead to the development of solid materials which exhibit bulk magnetic ordering. For this to be accomplished, short contacts between areas of unpaired spin density need to be established (i.e. between nitrogen and sulfur atoms of neighbouring rings).

The first monomer of a dithiadiazolyl to be published was the *p*-NCC₆F₄CN₂SSN• and can originate as one of two polymorphs.^{75, 76} In the α -phase of this radical, chains form with short contacts between the nitrile on one compound and S–S on another compound. The chains are held together by S...S and S...N contacts. However, due to the antiparallel stacking of these chains the α -phase is diamagnetic.⁷⁵ However, it was reported that the β -phase exhibits weak ferromagnetism at 36K.^{76, 77} In this instance the chains are also held together by S...S and S...N contacts, except for in the β -phase the chains are co-parallel (Figure 1.14), which implies that all the spins align in the same direction.

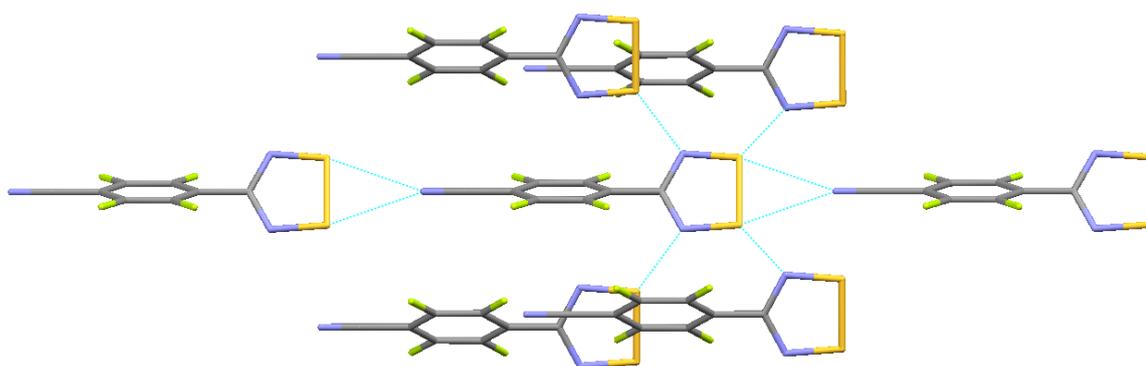


Figure 1.14: The crystal packing of the *p*-NCC₆F₄CN₂SSN• β -phase illustrating the co-parallel chains and S...N contacts which are shorter than the sum of the van der Waal's radii and are indicated in light blue. The 3D network of S...N contacts transmit the electronic interactions through the magnetic pathway

1.3.3 Solid state modification and properties

Interesting properties such as conductivity and magnetism in dithiadiazolyls arise if the molecule packs in such a way as to avoid dimerisation. By modifying the substituents bonded to the dithiadiazolyl it is possible to change the crystal packing characteristics and, therefore, the solid-state properties. Two different routes have been employed in an attempt to overcome the dimerisation energy. Firstly, by introducing substituents such as nitriles and halogens to the backbone of the dithiadiazolyl, short intermolecular contacts may be able to form with the sulfur atoms of the dithiadiazolyl radical. Secondly, a bulky R-group can be used. A bulky substituent is envisaged to separate the dithiadiazolyl radicals from each other.

Most dithiadiazolyls synthesised and described in the literature have planar R-groups. This, more often than not, results in the formation of dimers in the solid state. However, there is only one reported R-group that is non-linear and bulky and this is the adamantyl group.⁷⁸ The adamantyl group also does not inhibit the formation of dimeric dithiadiazolyl units in the solid state and the twisted arrangement of the dimer is observed (Figure 1.15).⁵⁴

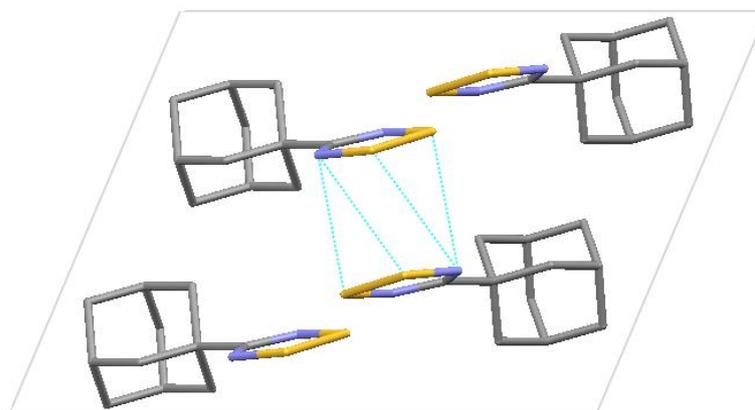


Figure 1.15: Crystal packing of the adamantyl dithiadiazolyl radical in the twisted dimeric state viewed down the *b*-axis. The light blue lines indicate the S...N contacts shorter than the sum of the van der Waal's radii

Therefore, to further investigate the effects a bulky R-group has on the crystal packing, the calix[4]arene scaffold was chosen in a further attempt to inhibit the formation of dimeric units in the solid state. It is envisaged that the tetra-dithiadiazolyl derivative would need to be synthesised due to the fact that the mono- and distal- candidates would most likely dimerise in a one-up-one-down motif (Figure 1.16). In the case of the distal-dithiadiazolyl calix[4]arene a one dimensional chain may be possible.

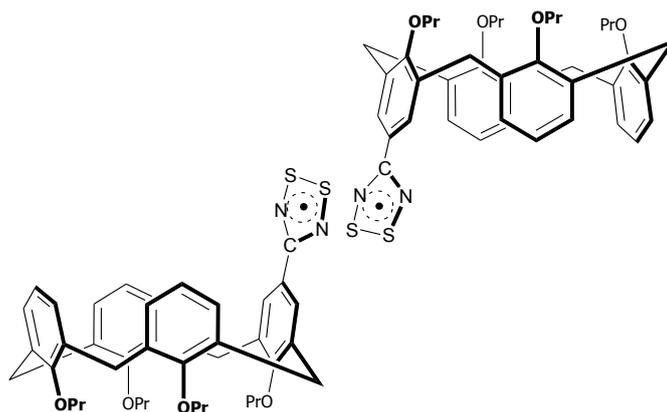


Figure 1.16: The possible up-down packing motif of the mono-dithiadiazolyl calix[4]arene

1.4 The calix[4]arene dithiadiazolyl precursor

1.4.1 Synthesis of nitrile functionalised calix[4]arenes

It has now been established that the synthesis of dithiadiazolyls generally stem from nitrile starting materials. Therefore, three nitrile functionalised calix[4]arenes, mono-, distal- and tetra-, were synthesised as starting materials. The nitrile derivatives can be synthesised from their bromo counterparts using copper cyanide and refluxing in *N*-methyl pyrrolidinone.⁷⁹ The synthetic procedure applied to this work makes use of a microwave procedure⁸⁰⁻⁸² and dimethyl formamide was used as the solvent. This procedure is discussed in further detail in the following chapter. A drastic reduction in reaction time without a decrease in yield is the main advantage gained by employing this procedure in the syntheses of the desired nitrile compounds.

1.4.2 Further functionalisation of nitrile functionalised calix[4]arenes

Literature precedent for further functionalisation of the nitrile calix[4]arene derivatives is rather sparse. There is only one reference for mono-nitrile calix[4]arene being used as the starting material. The nitrile is reduced to a primary amine using borane.⁸³ This reduction is also reported for both the distal- and tetra-nitrile calix[4]arenes.⁸³ The distal functionalised calix[4]arene has but one other reference as the starting material. A triazine ring is synthesised onto the periphery with cyanoguanidine in potassium hydroxide.⁸⁴ The tetra-nitrile calix[4]arene has been used in the synthesis of an unsubstituted amidine⁸⁵ as well as a carboxylic acid⁸⁵ derivative. The unsubstituted amidine was synthesised from an ethyl chloro aluminium amide reagent (AlNH_2ClMe) and hydrolysis was performed in ethanol and water under basic conditions using potassium hydroxide.

Therefore, to aid in increasing the amount of work performed on bulky nitrile substituents in the synthesis of dithiadiazolyls, the three nitrile calix[4]arenes **7** – **9** (page 4 | 2), were used as the starting compounds.

1.5 Project aims

The calix[4]arene scaffold is well studied in supramolecular chemistry and has been used before in both sorption and inclusion studies.⁸⁶ Based on the fact that the calix[4]arene has been employed in solid state studies, the calix[4]arene was initially employed to further determine the effects a bulky R-group would have on the solid state properties of the 1,2,3,5-dithiadiazolyl radical.

Firstly, mono-, distal- and tetra-nitrile calix[4]arenes, as precursors in the synthesis of dithiadiazolyl functionalised calix[4]arenes needed to be synthesised and this work is described in chapter 2. As highlighted in section 1.4.2, not much work has been performed on further functionalising the three nitrile calix[4]arene derivatives. Therefore, synthesising the nitrile functionalised calix[4]arenes would extend the amount of work performed on the nitrile precursors.

However, as the project started taking shape it was found that the typical reaction procedure of reacting lithium bis(trimethylsilyl)amide with a nitrile presented itself to be quite a challenge. As a result, the focus shifted to determine the reason behind this occurrence.

Therefore, the ultimate aim of this project was to investigate both the electronic properties of the nitrile functionalised calix[4]arenes with the aid of computational and experimental work. Furthermore, the steric bulk surrounding the nitrile was determined with the aid of crystal structures. Determining the unreactive nature of the nitrile functionalised forms the crux of the work and will be described in much detail in chapter 3.

1.6 References

- (1) Gutsche, C. D., *Calixarenes: an introduction* 2nd ed., **2008**, RSC Publishing: Cambridge.
- (2) Voronova, M. I.; Surov, O. V.; Plevina, E. V.; Mamardashvili, N. Z.; Zakharov, A. G., *Trends Phys. Chem.* **2010**, *14*, 14-25.
- (3) Atwood, J. L.; Barbour, L. J.; Jerga, A., *Science* **2002**, *296*, 2367-2369.
- (4) Atwood, J. L.; Barbour, L. J.; Jerga, A., *Angew Chem Int Ed Engl.* **2004**, *43*, 2948-2950.
- (5) Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O., *J. Am. Chem. Soc.* **1986**, *108*, 2409-2416.
- (6) Gutsche, C. D.; Iqbal, M.; Nam, K. S.; See, K.; Alam, I., *Pure Appl. Chem.* **1988**, *60*, 483-488.
- (7) Gutsche, C. D.; Alam, I., *Tetrahedron* **1988**, *44*, 4689-4694.
- (8) Schuehle, D. T.; Peters, J. A.; Schatz, J., *Coord. Chem. Rev.* **2011**, *255*, 2727-2745.
- (9) Li, Z.; Chen, J.; Liu, Y.; Xia, W.; Wang, L., *Curr. Org. Chem.* **2011**, *15*, 39-61.
- (10) Shirakawa, S.; Kimura, T.; Murata, S.; Shimizu, S., *J. Org. Chem.* **2009**, *74*, 1288-1296.
- (11) Shirakawa, S.; Shimizu, S., *Eur. J. Org. Chem.* **2009**, *12*, 1916-1924.
- (12) Xu, Z.; Li, G.; Chen, C.; Huang, Z., *Tetrahedron* **2008**, *64*, 8668-8675.
- (13) Baeyer, A., *Chem. Ber.* **1872**, *5*, 25.
- (14) Baeyer, A., *Chem. Ber.* **1872**, *5*, 280.
- (15) Baeyer, A., *Chem. Ber.* **1872**, *5*, 1094.
- (16) Baekeland, L. H., US Patent 942,699, October **1908**.
- (17) Zinke, A.; Ziegler, E., *Ber. Dtsch. Chem. Ges. B* **1941**, *74B*, 1729-1736.
- (18) Niederl, J. B.; Vogel, H. J., *J. Am. Chem. Soc.* **1940**, *62*, 2512-2514.
- (19) Zinke, A.; Ziegler, E.; Martinowitz, E.; Pichelmayer, H.; Tomio, M.; Wittmann-Zinke, H.; Zwanziger, S., *Ber. Dtsch. Chem. Ges. B* **1944**, *77B*, 264-272.
- (20) Hayes, B. T.; Hunter, R. F., *J. Appl. Chem.* **1958**, *8*, 743-748.
- (21) Gutsche, C. D., *Acc. Chem. Res.* **1983**, *16*, 161-170.
- (22) Gutsche, C. D.; Iqbal, M.; Stewart, D., *J. Org. Chem.* **1986**, *51*, 742-745.
- (23) Gutsche, C. D.; Bauer, L. J., *J. Am. Chem. Soc.* **1985**, *107*, 6052-6059.

- (24) Rudkevich, D. M., *Chem.–Eur. J.* **2000**, *6*, 2679-2686.
- (25) Janssen, R. G.; van Duynhoven, J. P. M.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N., *J. Am. Chem. Soc.* **1996**, *118*, 3666-3675.
- (26) Pavia, D.; Lampman, G.; Kriz, G., *Introduction to Spectroscopy* 4th Ed., **2000**, Brooks/Cole, Belmont.
- (27) Bauer, L. J.; Gutsche, C. D., *J. Am. Chem. Soc.* **1985**, *107*, 6063-6069.
- (28) Kaemmerer, H.; Happel, G.; Caesar, F. *Makromol. Chem.*, **1972**, *162*, 179-197.
- (29) Van Loon, J. D.; Groenen, L. C.; Wijmenga, S. S.; Verboom, W.; Reinhoudt, D. N., *J. Am. Chem. Soc.* **1991**, *113*, 2378-2384.
- (30) Iwamoto, K.; Araki, K.; Shinkai, S., *J. Org. Chem.* **1991**, *56*, 4955-4962.
- (31) Dahan, E.; Biali, S. E., *J. Org. Chem.* **1991**, *56*, 7269-7274.
- (32) Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S., *J. Am. Chem. Soc.* **1993**, *115*, 12228-12228.
- (33) Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1993**, *115*, 3997-4006.
- (34) Veciana, J., (Ed.), *π -Electron Magnetism: From Molecules to Magnetic Materials*, **2001**, Springer-Verlag, Berlin.
- (35) Haynes, D. A., *CrystEngComm* **2011**, *13*, 4793-4805.
- (36) Rawson, J. M.; Longridge, J. J., *Chem. Soc. Rev.* **1997**, *26*, 53-61.
- (37) Demarcay, E. *Compt. Rend.* **1880**, 1032-1033.
- (38) Banister, A. J.; Clarke, H. G.; Rayment, I.; Shearer, H. M. M., *Inorganic & Nuclear Chemistry Letters* **1974**, *10*, 647-654.
- (39) Vegas, A.; Perezsalazar, A.; Banister, A. J.; Hey, R. G., *J. Chem. Soc. Dalton Trans.* **1980**, 1812-1815.
- (40) Chiarelli, R.; Novak, M. A.; Rassat, A.; Tholence, J. L., *Nature* **1993**, *363*, 147-149.
- (41) Rawson, J. M.; Banister, A. J.; Lavender, I., *Adv. Het. Chem.* **1995**, *62*, 137-247.
- (42) Passmore, J.; Sun, X. P., *Inorg. Chem.* **1996**, *35*, 1313-1320.
- (43) Aherne, C.; Banister, A. J.; Luke, A. W.; Rawson, J. M.; Whitehead, R. J., *J. Chem. Soc. Dalton Trans.* **1992**, 1277-1282.
- (44) Fairhurst, S. A.; Johnson, K. M.; Sutcliffe, L. H.; Preston, K. F.; Banister, A. J.; Hauptman, Z. V.; Passmore, J., *J. Chem. Soc. Dalton Trans.* **1986**, 1465-1472.

- (45) Cordes, A. W.; Haddon, R. C.; Oakley, R. T.; Schneemeyer, L. F.; Waszczak, J. V.; Young, K. M.; Zimmerman, N. M., *J. Am. Chem. Soc.* **1991**, *113*, 582-588.
- (46) Banister, A. J.; Hansford, M. I.; Hauptman, Z. V.; Wait, S. T.; Clegg, W., *J. Chem. Soc. Dalton Trans.* **1989**, 1705-1713.
- (47) Cordes, A. W.; Haddon, R. C.; Hicks, R. G.; Oakley, R. T.; Palstra, T. T. M., *Inorg. Chem.* **1992**, *31*, 1802-1808.
- (48) Alberola, A.; Carter, E.; Constantinides, C. P.; Eisler, D. J.; Murphy, D. M.; Rawson, J. M., *Chem. Commun.* **2011**, *47*, 2532-2534.
- (49) Hoefs, H. U.; Bats, J. W.; Gleiter, R.; Hartmann, G.; Mews, R.; Eckert-Maksic, M.; Oberhammer, H.; Sheldrick, G. M., *Chem. Ber.* **1985**, *118*, 3781-3804.
- (50) Arnett, E. M.; Moe, K. D., *J. Am. Chem. Soc.* **1991**, *113*, 7288-7293.
- (51) Aherne, C. M.; Banister, A. J.; Hibbert, T. G.; Luke, A. W.; Rawson, J. M., *Polyhedron* **1997**, *16*, 4239-4245.
- (52) Aherne, C. M.; Banister, A. J.; Gorrell, I. B.; Hansford, M. I.; Hauptman, Z. V.; Luke, A. W.; Rawson, J. M., *J. Chem. Soc. Dalton Trans.* **1993**, 967-972.
- (53) Boere, R. T.; Moock, K. H.; Parvez, M., *Z. Anorg. Allg. Chem.* **1994**, *620*, 1589-1598.
- (54) Bricklebank, N.; Hargreaves, S.; Spey, S. E., *Polyhedron* **2000**, *19*, 1163-1166.
- (55) Barclay, T. M.; Cordes, A. W.; George, N. A.; Haddon, R. C.; Itkis, M. E.; Oakley, R. T., *Chem. Commun.* **1999**, 2269-2270.
- (56) Boere, R. T.; Oakley, R. T.; Reed, R. W., *J. Organomet. Chem.* **1987**, *331*, 161-167.
- (57) Haynes, D. A.; McInnes, E. J. L.; Passmore, J.; Rawson, J. M., *Phosphorus Sulfur.* **2004**, *179*, 869-873.
- (58) Edelmann, F. T., *Coord. Chem. Rev.* **1994**, *137*, 403-481.
- (59) Larsen, M.; Jorgensen, M., *J. Org. Chem.* **1996**, *61*, 6651-6655.
- (60) Garigipati, R. S., *Tetrahedron Lett.* **1990**, *31*, 1969-1972.
- (61) Levin, J. I.; Tuross, E.; Weinreb, S. M., *Synth. Commun.* **1982**, *12*, 989-993.
- (62) Basha, A.; Lipton, M.; Weinreb, S. M., *Tetrahedron Lett.* **1977**, , 4171-4174.
- (63) Haddon, R. C., *Nature* **1975**, *256*, 394-396.
- (64) Leitch, A. A.; Yu, X.; Winter, S. M.; Secco, R. A.; Dube, P. A.; Oakley, R. T., *J. Am. Chem. Soc.* **2009**, *131*, 7112-7125.
- (65) Wright, J. D., *Molecular Crystals*, **1995**, Cambridge University Press.

- (66) Cordes, A. W.; Bryan, C. D.; Davis, W. M.; Delaat, R. H.; Glarum, S. H.; Goddard, J. D.; Haddon, R. C.; Hicks, R. G.; Kennepohl, D. K.; Oakley, R. T.; Scott, S. R.; Westwood, N. P. C., *J. Am. Chem. Soc.* **1993**, *115*, 7232-7239.
- (67) Cordes, A. W.; Chamchoumis, C. M.; Hicks, R. G.; Oakley, R. T.; Young, K. M.; Haddon, R. C., *Can. J. Chem.* **1992**, *70*, 919-925.
- (68) Bryan, C. D.; Cordes, A. W.; Goddard, J. D.; Haddon, R. C.; Hicks, R. G.; MacKinnon, C. D.; Mawhinney, R. C.; Oakley, R. T.; Palstra, T. T. M.; Perel, A. S., *J. Am. Chem. Soc.* **1996**, *118*, 330-338.
- (69) Bryan, C. D.; Cordes, A. W.; Haddon, R. C.; Hicks, R. G.; Oakley, R. T.; Palstra, T. T. M.; Perel, A. J., *J. Chem. Soc. Chem. Commun.* **1994**, 1447-1448.
- (70) Cordes, A. W.; Haddon, R. C.; Hicks, R. G.; Kennepohl, D. K.; Oakley, R. T.; Palstra, T. T. M.; Schneemeyer, L. F.; Scott, S. R.; Waszczak, J. V., *Chem. Mater.* **1993**, *5*, 820-825.
- (71) Cordes, A. W.; Haddon, R. C.; Oakley, R. T., *Adv Mater* **1994**, *6*, 798-802.
- (72) Hugh O. P., *Handbook of carbon, graphite, diamond and fullerenes: properties, processing and applications*, **1993**, Noyes Publications: New Jersey.
- (73) Giancoli, D. C., *Physics: Principles with Applications* 4th ed., **1995**, Prentice Hall: London.
- (74) Griffiths, D., 7. *Electrodynamics*, **1999**, In Alison Reeves (ed.). *Introduction to Electrodynamics* 3rd ed., Prentice Hall: New Jersey.
- (75) Banister, A. J.; Bricklebank, N.; Clegg, W.; Elsegood, M. R. J.; Gregory, C. I.; Lavender, I.; Rawson, J. M.; Tanner, B. K., *J. Chem. Soc. Chem. Commun.* **1995**, 679-680.
- (76) Banister, A. J.; Bricklebank, N.; Lavender, I.; Rawson, J. M.; Gregory, C. I.; Tanner, B. K.; Clegg, W.; Elsegood, M. R. J.; Palacio, F., *Angew. Chem. Int. Edit.* **1996**, *35*, 2533-2535.
- (77) Palacio, F.; Antorrena, G.; Castro, M.; Burriel, R.; Rawson, J.; Smith, J. N. B.; Bricklebank, N.; Novoa, J.; Ritter, C., *Phys. Rev. Lett.* **1997**, *79*, 2336-2339.
- (78) Bridson, J. N.; Copp, S. B.; Schriver, M. J.; Zhu, S. G.; Zaworotko, M. J., *Can. J. Chem.* **1994**, *72*, 1143-1153.
- (79) Pinkhassik, E.; Sidorov, V.; Stibor, I., *J. Org. Chem.* **1998**, *63*, 9644-9651.
- (80) Ghaffarzadeh, M.; Bolourtchian, M.; Halvagar, M. R.; Hosseini, M., *J. Chem. Res.* **2003**, 814-815.
- (81) Arvela, R. K.; Leadbeater, N. E.; Torenus, H. M.; Tye, H., *Org. Biomol. Chem.* **2003**, *1*, 1119-1121.
- (82) Cai, L. Z.; Liu, X.; Tao, X. C.; Shen, D., *Synth. Commun.* **2004**, *34*, 1215-1221.

- (83) Casnati, A.; Fochi, M.; Minari, P.; Pochini, A.; Reggiani, M.; Ungaro, R., *Gazz. Chim. Ital.* **1996**, *126*, 99-106.
- (84) Vreekamp, R. H.; Verboom, W.; Reinhoudt, D. N., *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 363-370.
- (85) Sasine J. S; Brewster R. E; Caran K. L; Bentley A. M; Shuker S. B., *Org. Lett.* **2006**, *8*, 2913.
- (86) Dalgarno, S. J.; Thallapally, P. K.; Barbour, L. J.; Atwood, J. L., *Chem. Soc. Rev.* **2007**, *36*, 236-245.

Chapter 2

The Synthesis and Characterisation of Nitrile Functionalised Calix[4]arenes

2.1 Introduction

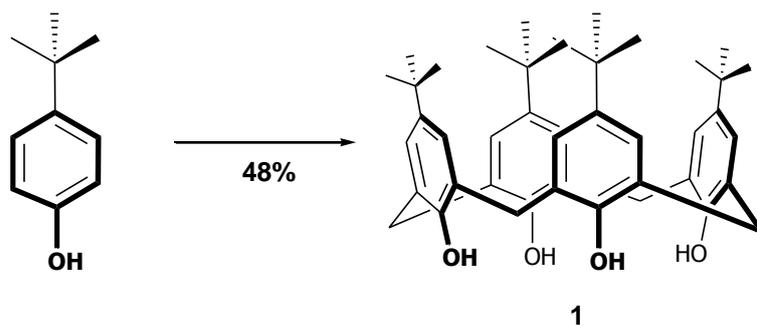
Nitrile functionalised compounds are one of the more common precursors for the synthesis of dithiadiazolyls.^{1, 2} This chapter focuses on the synthesis and characterisation of three nitrile functionalised tetrapropoxycalix[4]arenes: mono-, distal- and tetra-substituted. The three nitrile functionalised calix[4]arenes were synthesised via their bromo derivatives which were in turn synthesised from tetrapropoxy calix[4]arene.

All the molecules to be discussed have previously been reported in the literature. However, the crystal structures of the final nitrile derivatives in the desired conformation have not been reported. These will be discussed and illustrated. The conformation of the molecules in solution and solid state will also be compared.

2.2 Tetrapropoxy-calix[4]arene synthesis

Calix[n]arene synthetic procedures have been optimised fully to yield almost exclusively the desired number of aromatic rings in the bowl.³ With regards to the calix[4]arene, the optimised reaction conditions have been well known from the 1970's when Gutsche and co-workers developed a base catalysed procedure using *para*-substituted phenols and formaldehyde.³ For this project *para-tert*-butyl phenol was utilised resulting in *p-tert*-butylcalix[4]arene, **1**.⁴ The reaction was carried out under an inert atmosphere where formaldehyde and NaOH were added to 4-*tert*-butylphenol. The reaction was heated to 120 °C for 2 hours. At this point a viscous yellow solid formed. Diphenyl ether was added and the resultant heterogeneous mixture was allowed to stir overnight. Toluene was added and the reaction was heated to 180 °C to drive off any remaining H₂O as an azeotrope. Once the H₂O had been driven off, the reaction was set up to reflux at 260 °C for a further 4 hours. Ethyl acetate was added once the reaction had cooled down and the mixture was stirred for an hour. The solid that formed was washed with ethyl acetate and then triturated with acetic acid; the resultant white solid required no further purification.

The synthetic procedure described results in strong intramolecular hydrogen bonding, which as a result, locks calix[4]arene **1** into its bowl-like structure with a specific geometry, C₄.^{5, 6}



Scheme 2.1: Synthesis of calix[4]arene **1**. Reagents and reaction conditions: (i) NaOH, 120 °C; (ii) Ph₂O, 180 °C

This conformation can be confirmed using ¹H NMR and is very much temperature dependent. This dependence is noted in the methylene bridge protons having a wide range of ¹H NMR signals at temperatures as low as 25 °C. This is due to the decrease in hydrogen bond strength which, in turn, results in more free movement of the phenyl rings. When a ¹H NMR spectrum is obtained at 0 °C, the two signals for the methylene bridge protons are observed as a two doublets. These signals arise from what can be described as axial and equatorial protons on the methylene bridge carbons. The axial protons are less shielded and are further downfield (4.3 ppm) than the equatorial protons in a more shielded environment (3.5 ppm) as seen in figure 2.1. This was proven by Ungaro *et al* with the aid of NOE experiments.⁷ The sharp signal at 10.4 ppm is indicative of a strong hydrogen bonded O-H...O moiety.

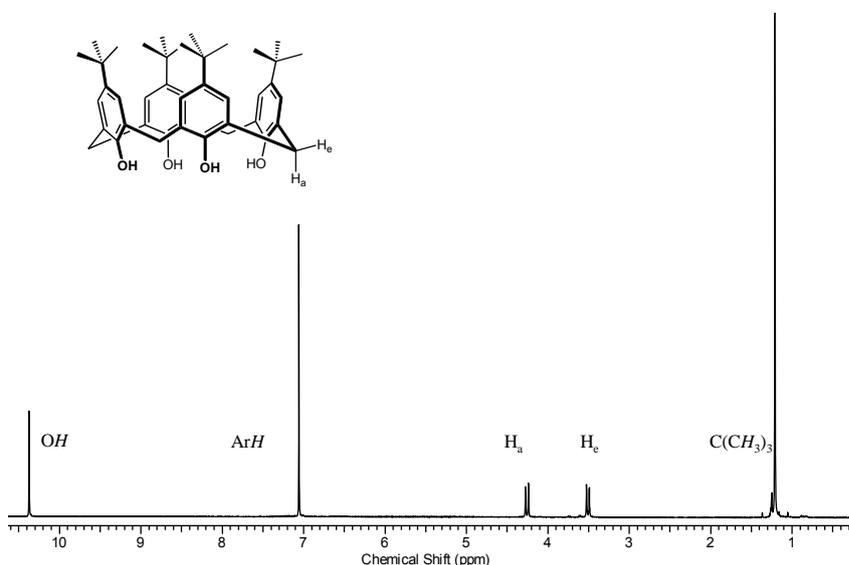
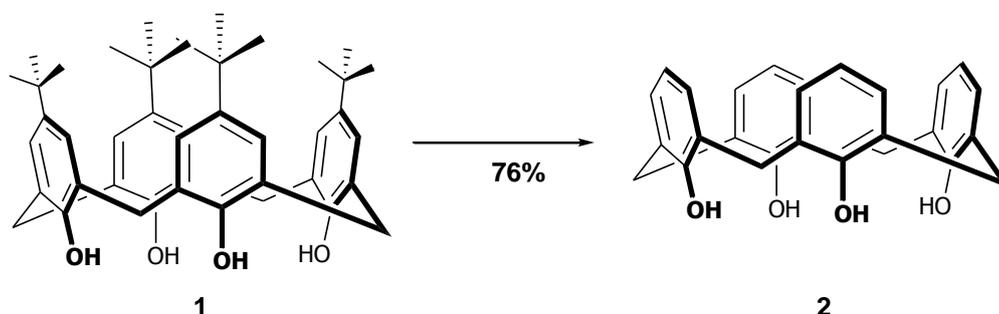


Figure 2.1: ¹H NMR spectrum of calix[4]arene **1** obtained at 0 °C

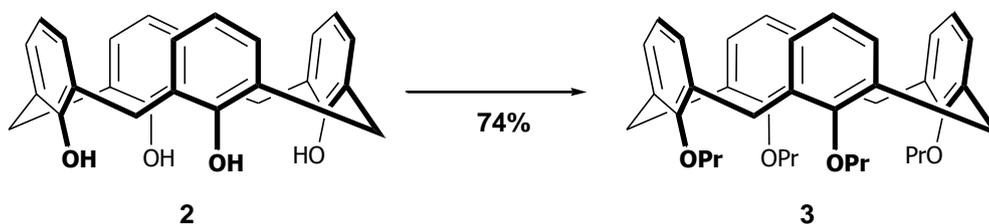
Calix[4]arene **1** was subsequently subjected to a reverse Friedel-Crafts reaction.⁷ Phenol was added to a mixture of **1** in toluene and the mixture was stirred for 10 minutes. Aluminium trichloride was added to the mixture with vigorous stirring and the reaction was allowed to

react for a further 2-3 hours. The reaction mixture was poured into a beaker of ice, taking care as HCl gas rapidly evolved. Once the ice had melted, dichloromethane was used in the extraction process. The crude product was triturated with diethyl ether which gave rise to a white powder, calix[4]arene **2** in a yield of 76%.



Scheme 2.2: Synthesis of calix[4]arene **2**. Reagents and reaction conditions: phenol, AlCl₃, toluene, RT

This now leaves one step in the synthesis of the desired calix[4]arene backbone. As was described in chapter 1, conformationally stable calix[4]arene requires a minimum of a three carbon chain at the phenolic position.³ Therefore propyl iodide was added to a solution of sodium hydride and calix[4]arene **2** in dimethyl formamide, and the reaction was stirred for 12 hours. After purification the product was dried under vacuum furnishing calix[4]arene **3**.⁷



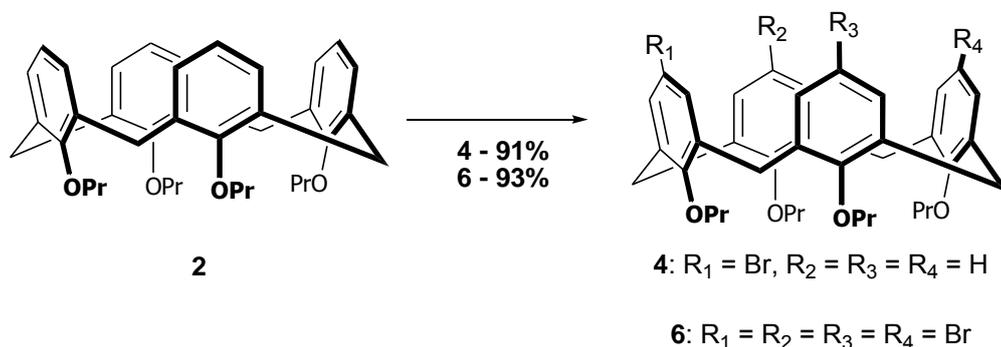
Scheme 2.3: Synthesis of calix[4]arene **3**. Reagents and reaction conditions: NaH, propyl iodide and DMF, RT

¹H NMR spectroscopy and melting point determination confirmed the successful synthesis of calix[4]arenes **1**, **2** and **3**. It is noticeable from the ¹H NMR spectrum that calix[4]arene **3** is also in the desired pinched cone conformation.

2.3 Bromo-functionalised calix[4]arene derivatives

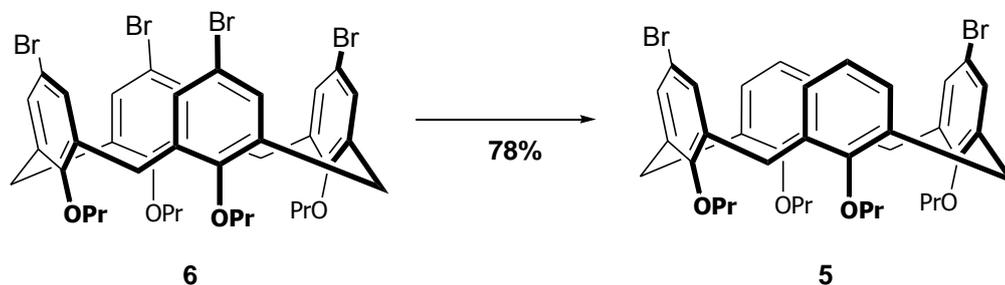
The calix[4]arene brominated derivatives were synthesised from **3** using procedures previously reported by Gutsche *et al*,⁸ for **4** and **6** (Scheme 2.4), and Larsen *et al* for **5** (Scheme 2.5).⁹ For calix[4]arene **4** and **6**, one and four equivalents of *N*-bromosuccinimide (NBS) were added respectively. The mono-bromonation reaction must be performed with as much accuracy as

possible by using precisely one equivalent of the bromine source. If more is used, a mixture of mono- and di-substituted products have to be separated, which is not possible using column chromatography due to the similar polarity. The downside to this is that the reaction does not proceed to completion and therefore, due to the degree of accuracy that needs to be followed, there is always a mixture of starting material and the desired mono-bromonated product. These unfortunately cannot be separated either, using column chromatography for the same reasons and therefore, the yield reported is inclusive of the small amount of starting material still present in the product. The starting material is removed from the sample once further functionalisation has occurred.



Scheme 2.4: Synthesis of calix[4]arene **4** and **6**. Reagents and reaction conditions: NBS, butanone, RT

The same procedure could not be applied for the synthesis calix[4]arene **5** due to the possibility of various isomers that could form apart from the required distal product. The possibilities include a mixture of proximal, tri- and mono-substituted isomers. However, Larsen *et al* have demonstrated that calix[4]arene **6** underwent selective distal lithium-halogen exchange with 2 equivalents of *n*BuLi in tetrahydrofuran. The lithium intermediate is quenched with methanol, affording calix[4]arene **5**.



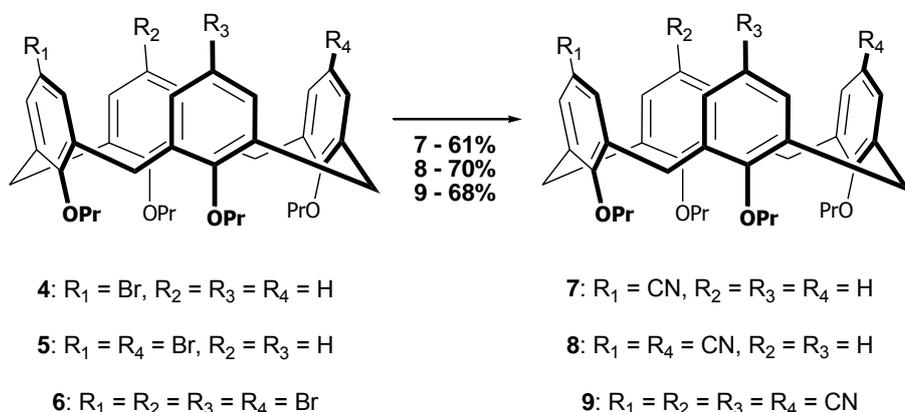
Scheme 2.5: Synthesis of calix[4]arene **5**. Reagents and reaction conditions: *n*BuLi, THF, -78 °C, MeOH

¹H NMR spectroscopy and melting point determination confirmed the successful synthesis of calix[4]arenes **4**, **5** and **6** (Chapter 5.2).

2.4 Nitrile functionalised derivatives

2.4.1 Synthesis

The nitrile functionalised calix[4]arenes to be discussed in the sections below have been synthesised previously. The nitrile functionalities on calix[4]arenes can be introduced using the Rosenmund-von Braun reaction procedure,¹⁰⁻¹³ or by the dehydration of aldoximes,¹⁴ to give but one other example. The Rosenmund-von Braun reaction was chosen due to the ease of the reaction in terms of time when using microwave irradiation, compared to the conventional method of refluxing in *N*-methyl pyrrolidine.¹⁵



Scheme 2.6: Synthesis of calix[4]arenes **7 – 9**. Reagents and reaction conditions: Copper cyanide, DMF, microwave at 210 °C

The Rosenmund-von Braun cyanations on calix[4]arenes have never, according to literature, been attempted using microwave irradiation. There have, however, been reports of microwave technology being used on aromatic compounds.^{16, 17} Calix[4]arenes **7 - 9** were synthesised using microwave irradiation at 210 °C and the yields compared very well to the conventional refluxing in *N*-methyl pyrrolidine. Something to consider when performing these reactions is that the cuprous halide by-product can coordinate to the aromatic nitriles and these complexes are soluble in DMF. A method to inhibit this coordination is to add iron(III) chloride which oxidises copper(I) to copper(II).¹³ The iron(III) chloride is the oxidising agent and therefore it is reduced, forming iron(II). Both the copper(II) and the iron(II) are soluble in water making separation by liquid-liquid extraction simple. To facilitate an easier work-up concentrated HCl was added carefully as there is a great potential for hydrogen cyanide gas to develop. To ensure that all the hydrogen cyanide gas had evolved, the solution was allowed to stir for one hour. The most advantageous aspect about this method is that reactions times are shortened from over four hours to just 30 minutes.

^1H NMR spectroscopy and melting point determination confirmed the successful synthesis of the three calix[4]arenes. In the case of mono nitrile calix[4]arene **7**, the yield was lower (61%) than that of **8** and **9** (70 and 68% respectively). This can be attributed to the unreacted starting material from the preceding bromination reaction.

2.4.2 Crystal structures

In the previous section it was discussed that calix[4]arenes **7** – **9** have been synthesised previously. However, their crystal structures are yet to be reported. The crystal structures of all three derivatives were determined in the course of this study and were grown from slow evaporation of the combination of ethyl acetate and petroleum ether.

2.4.2.1 Calix[4]arene **7**

Calix[4]arene **7** with an AAAB arrangement crystallises in the space group $P2_1/n$ with a complete molecule in the asymmetric unit (ASU) making up one quarter of the unit cell.

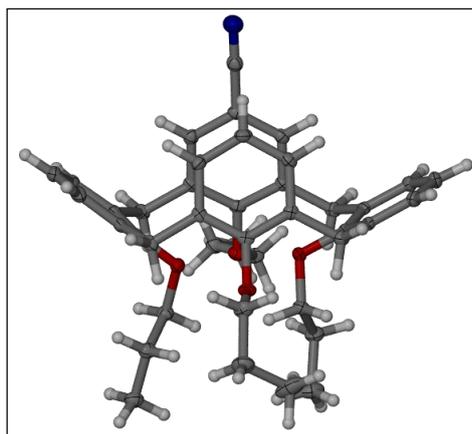


Figure 2.2: 50% probability thermal ellipsoid plot of the ASU of calix[4]arene **7**

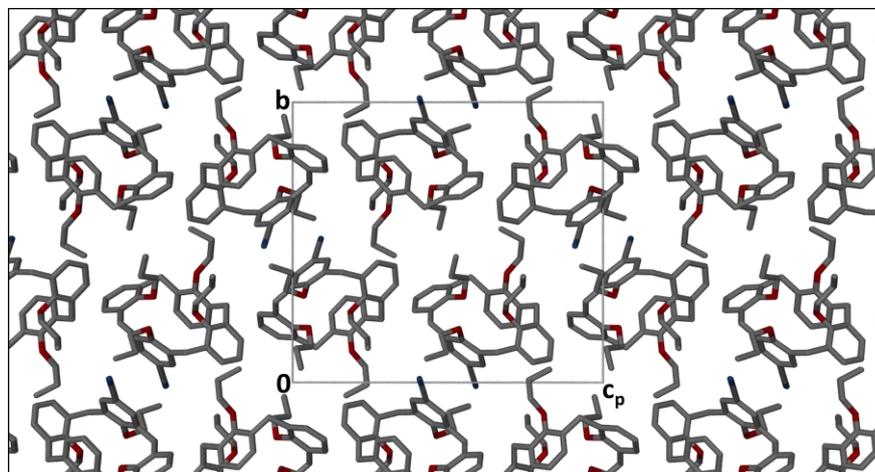


Figure 2.3: Crystal packing of calix[4]arene **7** viewed down the *a*-axis

The packing of this particular calix[4]arene is based purely on space filling. There are no significant intermolecular interactions to speak of and this is clear from Figure 2.3. However, what is observed is there are two distinct layers, where one has the nitrile group pointing up and the other down.

2.4.2.2 Calix[4]arene 8

Calix[4]arene **8**, with an ABAB arrangement in the cone conformation, has the nitrile functionalities on opposite phenyl rings which are facing outward and crystallises in the space group $P-1$ with a complete molecule in the ASU. The unit cell is made up of the ASU and one other molecule and based on the space group it can be concluded that the inversion centre lies between these two molecules. One of the propoxy groups on the lower rim is disordered over the two terminal carbons which have an occupancy factor of 0.5/0.5.

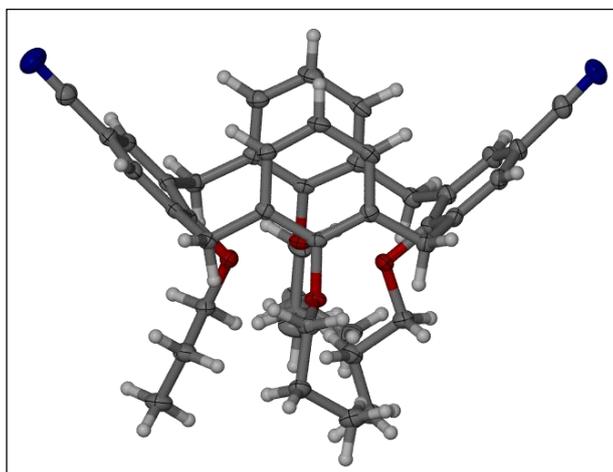
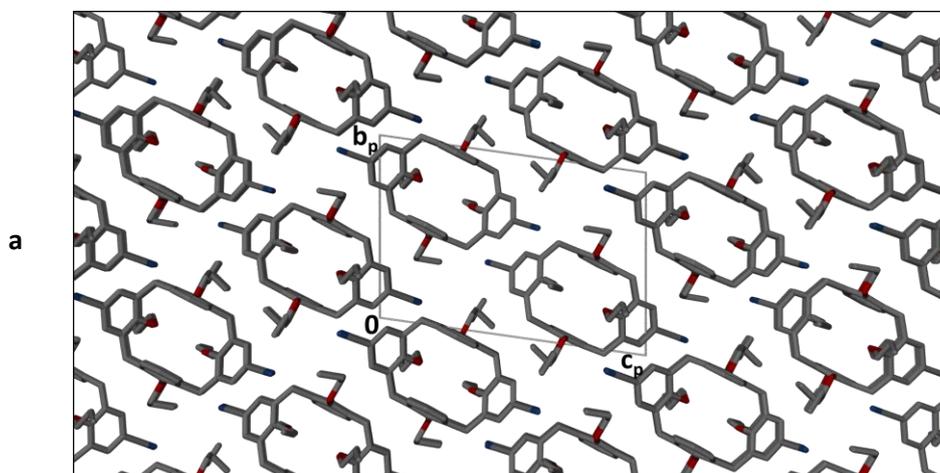


Figure 2.4: 50% probability thermal ellipsoid plot of the ASU of calix[4]arene **8**

When the crystal packing is viewed down the a -axis (Figure 2.5) it is observed that the two molecules of the unit cell form the basis of two head-to-tail anti-parallel columns. Therefore each column is surrounded by four anti-parallel columns (Figure 2.5b).



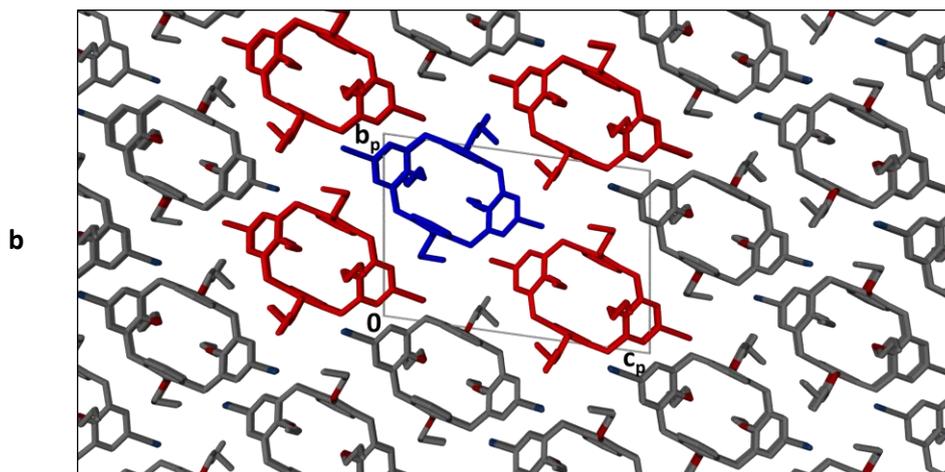


Figure 2.5: Crystal packing of calix[4]arene **8**, (a) viewed down the *a*-axis. (b) Also viewed down the *a*-axis where the red colour shows a column with the upper rim coming out the page and the blue colour shows an anti-parallel column going into the page

The manner of packing in the crystal structure is most likely a result of space filling. However, the packing is also stabilised by weak non-classical C-H \cdots N hydrogen bonding motifs. This has previously been reported by Holakovský *et al.* for an analogous calix[4]arene.¹⁸ The hydrogen bonding occurs on both sides of the calix[4]arene with either of the nitrile groups forming one dimensional chains through the crystal structure (Figure 2.6). The characteristics of the unconventional hydrogen bonding between **a** and **b** as well as **b** and **c** are also illustrated. There are no other specific intermolecular interactions of significant importance.

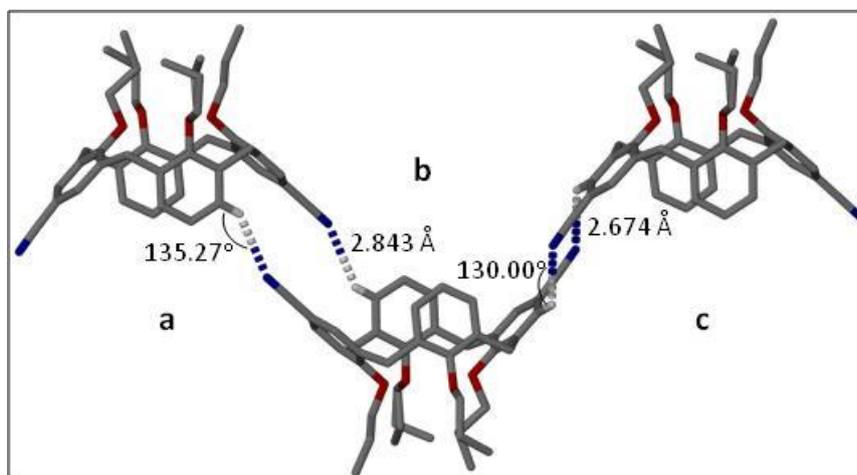


Figure 2.6: Non-classical C-H \cdots N hydrogen bonding motif between **a** and **b** and **b** and **c**. The values on the figure represent the N \cdots H distance and C-H \cdots N angle. Only the hydrogen atoms involved in hydrogen bonding are shown and the rest are omitted for clarity.

2.4.2.3 Calix[4]arene **9**

Calix[4]arene **9**, with a AAAA arrangement in a cone conformation crystallises in the space group $P2_1/n$. The asymmetric unit contains just one molecule making up a quarter of the unit cell. All the nitrile groups should have an angle consistent with sp hybridised bonds of 180° . This is indeed the case for the nitriles on the outward facing phenyl rings. However, the angles for the nitriles on the upright phenyl rings are 187.6 and 184.9 degrees.

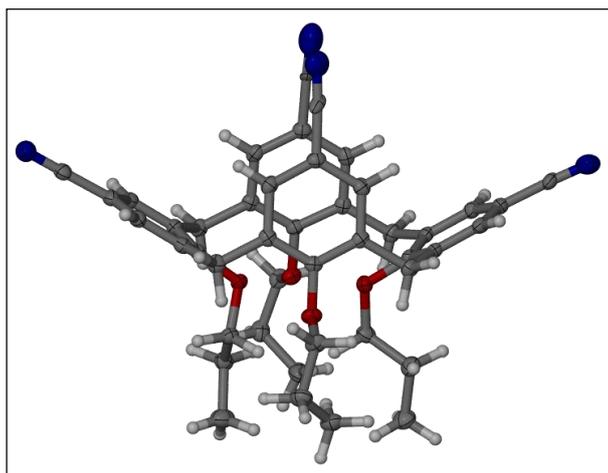


Figure 2.7: 50% probability thermal ellipsoid plot of the ASU of calix[4]arene

The packing of this particular calix[4]arene is largely based on space filling. There is also, as for calix[4]arene **7**, weak $C-H \cdots N$ hydrogen bonding. The hydrogen bonding motifs result in a 3D network across the whole crystal structure. There are no other significant intermolecular interactions and this is clear in the illustrations presented in the figure below.

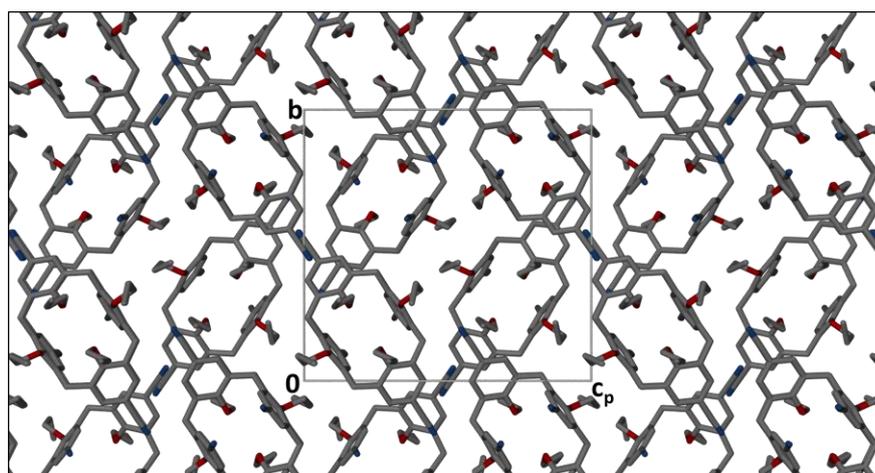


Figure 2.8: Crystal packing of calix[4]arene **9** viewed down the a -axis

2.4.2.4 Crystal packing comparisons

The crystal packing of all three crystals structures are viewed down the same axis. However, calix[4]arene **7** is the only molecule that is at an angle relative to the *a*-axis. Therefore, this view distorts the perceived length of the propoxy chain.

The 50 percent probability ellipsoids for the terminal carbons of the propoxy chains shown in the ASU of the three calix[4]arene derivatives have a larger volume and this is most likely due to the fact that they are in terminal positions.

Another comparison of the crystal structure packing is that only calix[4]arene **8** packs in a head to tail-column like fashion. This can be attributed to the bowl being “open” as there are no nitrile groups bonded on the upright phenyl rings. Therefore, the propoxy tails from another molecule can pack into this “open” space. Both calix[4]arenes **7** and **9** have nitriles on the upright phenyl rings, blocking off the bowl.

2.5 Conformational studies

The elucidation of the conformation of the nitrile functionalised calix[4]arenes in solution compared to the solid state is important to understand, as will become apparent in the following chapter. The conformation of calix[4]arene **9** does not need much description. The point has already been made that when the lower rim is functionalised with propoxy groups the calix[4]arene is fixed in the cone or pinched cone conformation.³ This means that two opposite phenyl rings are in an upright position and the other two phenyl rings are in an outward position. This is the case with calix[4]arene **7** and **8** too. However, the question remains: is the nitrile functionality on the same upright or outward facing phenyl rings in solution as what is shown in their respective crystal structures?

2.5.1 Calix[4]arene **7**

From the ASU in the crystal structure for calix[4]arene **7**, it is observed that the nitrile group is on one of the upright phenyl rings. In terms of the ¹H NMR spectrum, six signals would be expected for the aromatic protons. This is not apparent from the spectrum (figure 2.9) due to the observation that the *para* protons on the phenyl rings have a very similar shift compared to that of the *meta* protons.

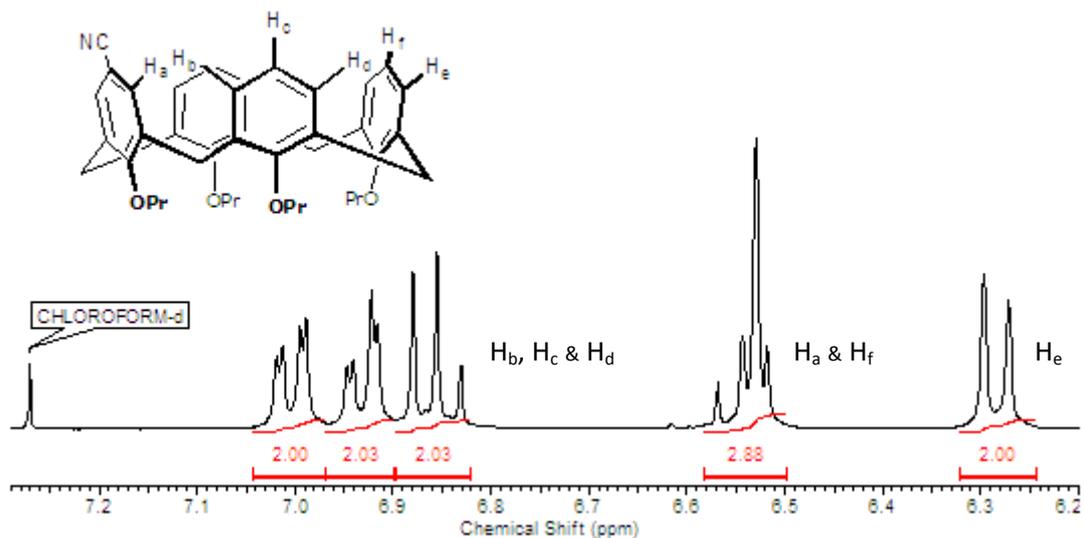


Figure 2.9: ^1H NMR spectrum of calix[4]arene **7** over the area of 7.30-6.20 ppm indicating the aromatic region

The aromatic section in the ^1H NMR spectrum (Figure 2.9) has two distinct regions that can be observed relative to what can be expected for aromatic signals. The region further downfield is more de-shielded due to the protons experiencing more of an anisotropic effect. These two regions can be differentiated by means of their splitting patterns and integration. We would expect three signals for the protons on the two opposite unsubstituted phenyl rings which should in total integrate for six. One signal for the *para* proton (H_c) and two signals for the *meta* protons (H_b and H_d) as these are in different magnetic environments with respect to the nitrile. According to the integration, these signals are further downfield and coalesce to a certain extent (7.2 – 6.8 ppm). Therefore, three signals would also be expected for the protons on the other two phenyl rings, one for the *meta* protons (H_a) adjacent to the nitrile, one for the *meta* protons (H_e) on the opposite ring and lastly, one for the *para* proton (H_f). However, as mentioned previously, the three signals are not apparent on the spectrum. The singlet expected from the protons (H_a) adjacent to the nitrile and the triplet from the *para* proton (H_f) on the opposite phenyl ring both appear at the same point on the spectrum. The result of this is a distorted triplet that integrates for three protons.

2.5.2 Calix[4]arene **8**

From the ASU in the crystal structure for calix[4]arene **7** it is observed that the nitrile group is on both phenyl rings in an outward position. This is most likely because of repulsion. Due to the ABAB arrangement, the molecule is symmetrical: this is apparent when analysing the ^1H NMR spectrum. There are only three signals in the aromatic region. These signals, as was the case in the previous example, can be separated into two regions: one signal which is a singlet

derived from the four equivalent *meta* protons (H_a) adjacent to the nitriles on the phenyl rings and two signals on the other phenyl rings, a doublet for the *meta* (H_b) which integrate for four and a triplet for the *para* protons (H_c) which integrate for two.

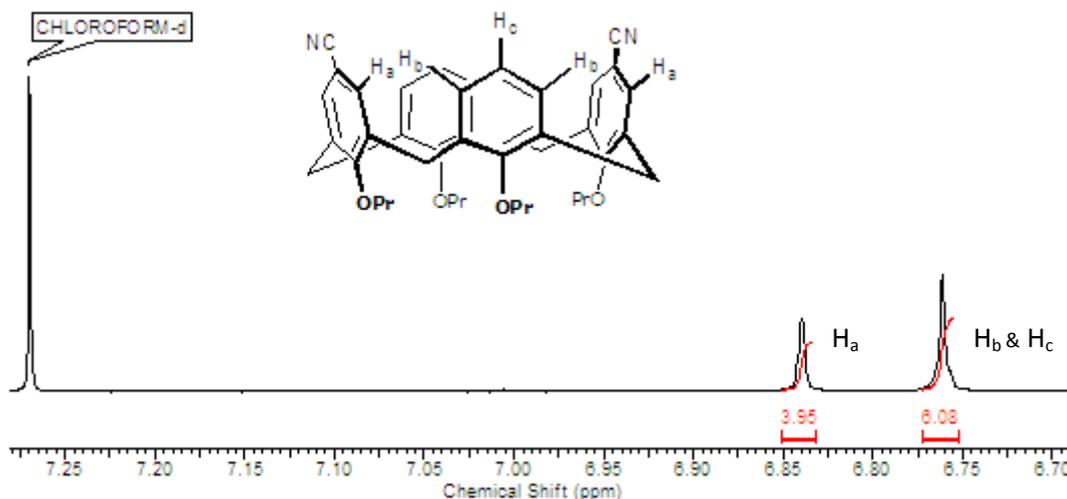


Figure 2.10: ^1H NMR spectrum of calix[4]arene **8** over the area of 7.30-6.70 ppm indicating the aromatic region

The doublet and triplet for the two opposite phenyl rings that do not have a nitrile functional group are not apparent on the spectrum. There is, however, a signal that integrates for six protons. Therefore these two signals coalesce, which is evident from the shoulder to the right of the signal as well as the larger base to the peak. This signal is further upfield and is more shielded due to anisotropic effects.

It is now clear that calix[4]arenes **7** and **8** have their phenyl rings with the nitrile functional groups in a different orientation. This is also the case with the crystal structures. However, to determine whether or not the conformation of calix[4]arene **7** and **8** are the same in solution and in the solid state hinges on which set of phenyl rings, upright or outward, experience the greater amount of shielding due to the anisotropic effect.

It is known that protons perpendicular or close to perpendicular to an aromatic ring experience an anisotropic effect and are therefore shielded, which results in their signal being found further upfield.¹⁹ The aromatic hydrogens on the upright phenyl rings of a calix[4]arene are slightly off the perpendicular relative to the phenyl ring in the outward position. The signal which integrates for six protons is further upfield and therefore experiences the shielding electronic properties of the outward facing phenyl rings. This means that the nitrile functionalised phenyl rings are outward facing due to the signal which integrates for four being

further downfield. Therefore, the ^1H NMR data shown suggests that the conformation of the calix[4]arene nitrile derivatives are uniform in both solution and the solid state.

2.6 Conclusion

The successful synthesis of three nitrile functionalised calix[4]arenes **7** – **9** has been reported and discussed. Although the synthesis of calix[4]arenes **7** – **9** have previously been reported, this is the first reference to their respective crystal structures. The crystal structures do not possess much detail and scope for further crystallographic work and this can probably be attributed to the lack of structure directing factors within the synthesised calix[4]arene framework. It is for this reason that the calix[4]arenes close pack in such a manner as to fill as much space as possible.

The conformation of the calix[4]arenes in the solid state and solution were determined. The crystal structures revealed that for calix[4]arene **7**, the nitrile substituent is on one of the upright phenyl rings and for calix[4]arene **8**, the nitrile substituents are on the opposite phenyl rings in the outward position. From the respective ^1H NMR spectra, it was determined that the conformation of the calix[4]arenes **7** and **8** is identical in solution. The importance of this information will become relevant in the following chapter.

2.7 References

- (1) Boere, R. T.; Oakley, R. T.; Reed, R. W., *J. Organomet. Chem.* **1987**, *331*, 161-167.
- (2) Cordes, A. W.; Haddon, R. C.; MacKinnon, C. D.; Oakley, R. T.; Patenaude, G. W.; Reed, R. W.; Rietveld, T.; Vajda, K. E., *Inorg. Chem.* **1996**, *35*, 7626-7632.
- (3) Gutsche, D. C., *Calixarenes: an introduction* 2ed.; RSC Publishing: Cambridge, **2008**.
- (4) Gutsche, C. D.; Iqbal, M.; Stewart, D., *J. Org. Chem.* **1986**, *51*, 742-745.
- (5) Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S., *J. Am. Chem. Soc.* **1993**, *115*, 12228.
- (6) Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S., *J. Am. Chem. Soc.* **1993**, *115*, 3997-4006.
- (7) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R., *J. Chem. Soc.-Chem. Commun.* **1984**, 981-982.
- (8) Gutsche, C. D.; Pagoria, P. F., *J. Org. Chem.* **1985**, *50*, 5795-5802.
- (9) Larsen, M.; Jorgensen, M., *J. Org. Chem.* **1996**, *61*, 6651-6655.
- (10) Rosenmund, K. W.; Struck, E., *Ber. Dtsch. Chem. Ges. B* **1919**, *52B*, 1749-1756.

- (11) v. Braun, J.; Manz, G., *Ann.* **1931**, 488, 111-126.
- (12) Koelsch, C. F.; Whitney, A. G., *J. Org. Chem.* **1941**, 6, 795-803.
- (13) Ellis, G. P.; Romneyalexander, T. M., *Chem. Rev.* **1987**, 87, 779-794.
- (14) Rogic, M. M.; Vanpeppe.Jf; Klein, K. P.; Demmin, T. R., *J. Org. Chem.* **1974**, 39, 3424-3426.
- (15) Pinkhassik, E.; Sidorov, V.; Stibor, I., *J. Org. Chem.* **1998**, 63, 9644-9651.
- (16) Cai, L. Z.; Liu, X.; Tao, X. C.; Shen, D., *Synth. Commun.* **2004**, 34, 1215-1221.
- (17) Ghaffarzadeh, M.; Bolourtchian, M.; Halvagar, M. R.; Hosseini, M., *J. Chem. Res.-S* **2003**, 814-815.
- (18) Budka, J.; Eigner, V.; Holakovsky, R.; Kovaricek, P.; Louzilova, T., *Acta Crystallogr. Sec. E.* **2010**, 66, O419-U3019.
- (19) Pavia, D.; Lampman, G.; Kriz, G., *Introduction to Spectroscopy* 4th Ed., **2000**, Brooks/Cole, Belmont.

Chapter 3

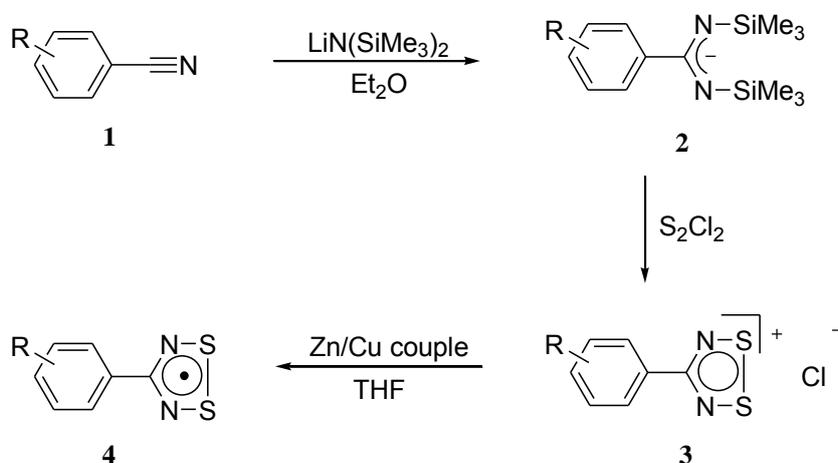
Attempted Synthesis of Dithiadiazolyl Functionalised Calix[4]arenes

3.1 Introduction

In chapter 2 the synthesis of the three nitrile functionalised calix[4]arene derivatives was described. This chapter now describes their use as precursors for the synthesis of the dithiadiazolyl radical.

At the outset it should be mentioned that the attempted synthesis of the dithiadiazolyl functionalised calix[4]arenes ultimately proved unsuccessful. This chapter seeks to explore the unreactive nature of the calix[4]arene nitrile using changes to the reaction conditions as well as with theoretical calculations. Ultimately it will be demonstrated why the nitrile functionalised calix[4]arenes are an unsuitable starting material in the synthesis of the dithiadiazolyl radicals.

3.2 Typical synthetic procedure of the dithiadiazolyl radical



Scheme 3.1: The general one-pot 1,2,3,5-dithiadiazolyl radical synthesis

The standard literature procedures (Scheme 3.1)¹⁻³ for the synthesis of dithiadiazolyl radicals typically involve reacting one equivalent of lithium hexamethyldisilazide, ($\text{Li}[\text{N}(\text{SiMe}_3)_2]$), with an aryl nitrile, **1**, in diethyl ether to produce the partially silylated amidinate, **2**. SCl_2 or S_2Cl_2 is then added at 0 °C and allowed to warm up to ambient temperature. This generates the dithiadiazolium chloride salt, **3**, which is washed with diethyl ether. Reduction of the salt can be performed either in tetrahydrofuran with half an equivalent of Zn/Cu couple as the reducing agent¹, or with silver powder in acetonitrile.¹ For both these reduction methods the solution is

warmed to approximately 50 °C. Reduction can also be performed in the solid state with triphenyl antimony (Ph₃Sb).¹ Purification is achieved by subliming the solid under reduced pressure and analysis can be performed with both mass spectroscopy and electron paramagnetic resonance (EPR).

There are numerous stages in the reaction procedure which can be monitored visually to determine whether or not the reaction is proceeding. Initially the solution of the nitrile is clear and colourless. On addition of the lithium hexamethyldisilazide, the solution changes to yellow which is indicative of the formation of **2**. Secondly, with the addition of SCl₂ a precipitate forms which is generally in the colour range from yellow to reddish-brown. Lastly, once the dithiadiazolyl radical forms, the colour is dark purple.⁴ For spectroscopic confirmation mass spectroscopy can be performed on **3** and **4**.

To test the reaction conditions in our laboratory, benzonitrile, as the simplest aryl nitrile, was used.² The typical reaction procedure was followed which resulted in the desired purple needles of the PhCN₂S₂ radical, the existence of which was confirmed by EPR.

3.3 Attempted dithiadiazolyl synthesis from the nitrile calix[4]arene precursors

All attempts to carry out the reaction in scheme 3.1 with nitrile calix[4]arene starting materials **7** – **9** were unsuccessful. There was no observed colour change at the first step of the reaction and tlc revealed only starting material. This suggested that the first step of the reaction, to form the silylated intermediate **2**, was not successful. It was decided to allow a reaction time longer than the usual four hours, but after the reaction was allowed to react overnight, the result proved to be the same. It was therefore decided that all aspects of this reaction should be examined, chiefly the temperature, solvent and time. The study was conducted on mono-nitrile calix[4]arene **7** and the results are listed in Table 3.1.

Firstly, the solvent was changed from diethyl ether to tetrahydrofuran, toluene and also to 1,4-dioxane. However, this had no effect (entries 1-3) and therefore, the reaction time was extended from four hours to overnight in each case. This change also made no difference to the result. The change in solvent was to determine whether or not the different properties of the various solvents would have a positive effect on the outcome of the reaction. The different properties include solvents with a higher boiling point (dioxane and toluene) as well as tetrahydrofuran and diethyl ether which are solvents with a lower boiling point.

Next, the reactions with diethyl ether and tetrahydrofuran were warmed slightly and for toluene and dioxane the temperature was increased to reflux. However, this was not sufficient to alter the result of the reaction which was confirmed by the observation of only starting material on tlc. Also, increasing the lithium hexamethyldisilazide to two equivalents had no effect on the outcome.

Lithium reagents are known to aggregate in various modes in different solvents.⁵ Therefore, it was thought necessary to add a ligand that could coordinate to the lithium ion and potentially free up the nucleophile, making it more effective.⁵ Both nitrogen and oxygen coordinative modes were introduced using tetramethylethylenediamine (TMEDA) as the nitrogen based ligand, and hexamethylphosphoramide (HMPA) or bis(2-methoxyethyl) ether (diglyme) as the oxygen based ligands. TMEDA was used in combination with tetrahydrofuran, toluene and dioxane (entries 7, 8 and 11). Diglyme was used as both the solvent and ligand (entry 9) and HMPA was used once with dioxane (entry 10). For all the reactions listed the starting material was recovered as confirmed by ¹H NMR spectroscopy.

Table 3.1: Summary of reactions performed using calix[4]arene **7**

Reaction no.	Li[N(SiMe ₃) ₂] (equiv)	Solvent	Additive	Time ^a	Temperature ^b
1	1	Et ₂ O		4 – 12 hours	RT – 30 °C
2	1	THF		4 – 12 hours	RT – 50 °C
3	1	Toluene		4 – 12 hours	RT – 110 °C
4	2	Et ₂ O		4 – 12 hours	RT – 30 °C
5	2	THF		4 – 12 hours	RT – 50 °C
6	2	Toluene		4 – 12 hours	RT – 110 °C
7	2	THF	TMEDA	4 – 12 hours	RT – 66 °C
8	2.5	Toluene	TMEDA	4 – 12 hours	RT – 110 °C
9 ^c	2	Diglyme		4 – 12 hours	RT – 162 °C
10	2	Dioxane	HMPA	4 – 12 hours	RT – 101 °C
11	4	Dioxane	TMEDA	4 – 12 hours	RT – 101 °C

^a In each case the reaction time was increased to 12 hours from the initial four

^b The temperature was increased to the indicated temperature after the 12 hours had elapsed

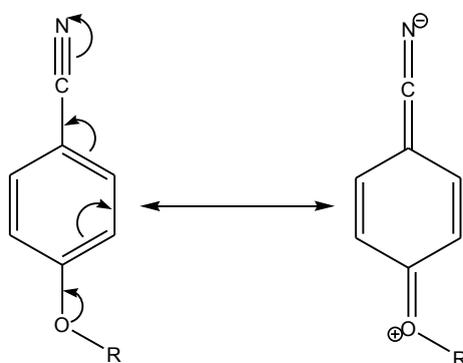
^c For this reaction diglyme was used as the additive as well as the solvent

All these changes to the reaction procedure proved to be fruitless. In order to address this impasse, two important questions needed to be dealt with. Firstly, is there an electronic effect that the calix[4]arene inherently possesses? Secondly, does the steric bulk of the calix[4]arenes have an effect? These questions are pertinent to the matter and will be addressed in the sections to follow.

3.4 Electronic effects

The electronic effects of the *para* substituent are significant as it may increase or decrease the electron density on the nitrile. This is important as the carbon of the nitrile is the electrophilic centre in the reaction and is a key feature in determining the potential reactivity at this centre.

Alkoxy groups have a positive resonance effect into an aromatic system, while the nitrile functional group has the opposite effect, drawing electron density out of an aromatic ring. When these two functional groups are on opposite sides of a benzene ring, or *para* to each other, the net dipole effect is in the direction of the nitrile. This can be illustrated by the resonance of electrons from the lone pair on the oxygen of the alkoxy group through the aromatic ring onto the nitrogen of the nitrile functional group (Scheme 3.2).



Scheme 3.2: Resonance of electrons illustrating the electron donating effect of the *para* alkoxy group. Of course, this resonance picture does not immediately suggest that the nitrile carbon is any less electronegative since the negative charge is placed on the nitrogen atom and not the carbon

In fact, Rawson *et al.*,⁴ Oakley *et al.*² and Boéré *et al.*⁶ have reported the synthesis of the 4-methoxybenzodithiadiazolyl radical which seems to confirm that the resonance effect does not play a significant role in the reactivity of the nitrile calix[4]arenes. However, the calix[4]arene derivatives have a propoxy and not a methoxy group. To determine what effect the change in alkoxy length would have, theoretical calculations were performed. These calculations were also used to gauge whether the calix[4]arene as a whole has an inherent electronic effect on the nitrile.

The electron count on the significant atoms that would take part in the reaction was probed using a density functional theory (DFT) study where the molecule was allowed to reach its minimum energy state. The 6-311G(d,p) basis set was used with the B3LYP functional within the Gaussian 03 software suite.⁷ The electron density may be partitioned to yield charges

according to a variety of schemes. Mulliken charges were compared to those obtained using natural bonding orbital (NBO) analysis

The difference between these two schemes is that for NBO the bonding orbitals between atoms are taken into account, whereas for the Mulliken method the electrons that take part in bonding are separated evenly into two atomic orbitals.⁸ Therefore, the Mulliken population analysis is a simplistic representation of the electron density population calculated in a semiempirical method from just the atomic orbitals of each atom in a molecule.^{8,9} NBO calculations can be considered to be more chemically sensible. The calculation initially localises core orbitals and lone pairs for each atom in what can be described as natural atomic orbitals (NAOs).⁸ The atomic orbitals of each atom involved in forming bonding (or antibonding) orbitals are localised in NBOs.^{8,10} Therefore, as quoted by Cramer, “the NBO analysis provides an orbital picture that is as close as possible to a classic Lewis structure for a molecule.”⁸ Both the Mulliken and NBO results are summarised in Table 3.2.

Table 3.2: Atomic charges of the carbon and nitrogen of the nitrile calculated with DFT at the b3lyp/6-311+G(d,p) level.

Entry	Molecule	atom			
		^a N (Mulliken)	^b N (NBO)	^a C (Mulliken)	^b C (NBO)
1	benzonitrile	-0.200	<i>-0.327</i>	-1.157	<i>0.298</i>
2	4-methoxy benzonitrile	-0.198	<i>-0.328</i>	-1.147	<i>0.298</i>
3	4-propoxy benzonitrile	-0.197	<i>-0.327</i>	-1.509	<i>0.297</i>
4	3,5-dimethyl-4-propoxy benzonitrile	-0.204	<i>-0.335</i>	-1.034	<i>0.300</i>
5	^t butyl-4-cyanophenyl carbonate	-0.181	<i>-0.320</i>	-1.401	<i>0.295</i>
6	Mono-nitrile tetrapropoxy calix[4]arene	-0.204	<i>-0.345</i>	-0.929	<i>0.306</i>
7	Mono-nitrile tetramethoxy calix[4]arene	-0.205	<i>-0.344</i>	-0.999	<i>0.305</i>
8	Mono-nitrile tetrahydroxy calix[4]arene	-0.215	<i>-0.332</i>	-1.265	<i>0.298</i>

^a. Bold text indicates the **Mulliken** charges.

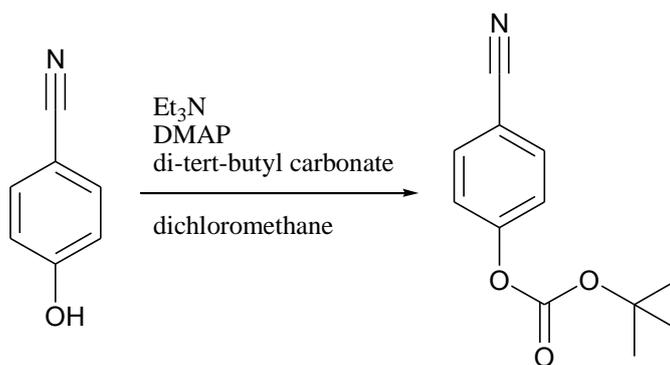
^b. Italics indicate the *NBO* charges.

The calculated charge values of the mono-nitrile calix[4]arene **7** were compared to the test compound, benzonitrile, as well as the model compound, 4-methoxybenzonitrile. The results are tabulated in Table 3.2. The difference between the charge on the nitrile carbon of benzonitrile and the charge on the same carbon of the mono-nitrile calix[4]arene (Entries 1 and 6) is negligible as they are 0.008 and 0.228 for the NBO and Mulliken calculations respectively.

The Mulliken charge results for the carbon of the three calix[4]arene derivatives are unusual. The inductive effect of a longer alkoxy chain should increase the resonance towards the nitrile (this is indeed the case for the model compounds). However, according to the results, the opposite is observed for the calix[4]arene derivatives. The Mulliken charge values are -0.929 for the propoxy derivative, -0.999 for the methoxy derivative and -1.265 for the hydroxy derivative. This could possibly be attributed to the lone pairs on the oxygen not being able to overlap with the *pi* orbitals of the phenyl ring, meaning the oxygen atom's electronegativity is more important than its resonance effect. This in turn could be attributed to the fact that the longer the alkoxy chain, the more sterically encumbered the lower rim of the calix[4]arene becomes. The same logic cannot be applied to the NBO values as these give a reasoning that makes chemical sense. The more negative the charge on the nitrogen results in more of a positive charge on the carbon. These two charge systems, Mulliken and NBO, thus give differing results. However, the distribution of charge for the NBO calculations makes more chemical sense. As shown in Scheme 3.2 the resonance of the electrons is in the direction of the electronegative nitrogen. Therefore, we would expect more electron density to be situated on the nitrogen compared to that of the carbon of the nitrile. This is indeed the case for the NBO charges. The Mulliken charges show the complete reverse and have a larger negative value for the carbon of the nitrile. According to the values in table 3.2 the NBO charges seem to be more sensible than Mulliken and therefore will be used to help explain the reactivity of the nitrile in the rest of this section.

To determine whether or not the methylene bridges of the calix[4]arene contribute towards the charge of the nitrile, the minimum energy of an analogous structure, 3,5-dimethyl-4-propoxybenzonitrile, was determined and the charges calculated (entry 4 in Table 3.2). In this case the Mulliken and NBO charges correspond better with that of the mono-nitrile calix[4]arene compared to that of 4-propoxybenzonitrile. This is probably due to the inductive effect of the methyl groups into the aromatic system. Although the charge values are more closely matched to those of the mono-nitrile calix[4]arene (entry 6) the effect does not seem to indicate that it would have a significant effect on the reactivity of the nitrile.

Both theoretical and experimental work was performed on two untested model compounds, 4-propoxybenzotrile and *tert*-butyl-4-cyanophenyl carbonate (entries 3 and 5 in Table 3.2), to further demonstrate that the resonance effect of a *para* substituent does not have a strong effect on the reactivity. These two compounds were chosen because the *para*-substituents have opposite electronic effects, where the propoxy group has an inductive effect towards the nitrile and conversely the carbonate group's inductive effect is directed towards the carbonyl.



Scheme 3.3: Synthesis of *tert*-butyl-4-cyanophenyl carbonate from 4-hydroxy benzonitrile

tert-Butyl-4-cyanophenyl carbonate was synthesised from a solution of 4-hydroxybenzotrile and dichloromethane.¹¹ Triethylamine and an acyl transfer catalyst, 4-dimethylaminopyridine (DMAP), were added to the reaction and allowed stir for 15 minutes. Di-*tert*-butyl carbonate was added and then the reaction was stirred for another six hours. After work-up and purification a quantitative yield was acquired for the product.

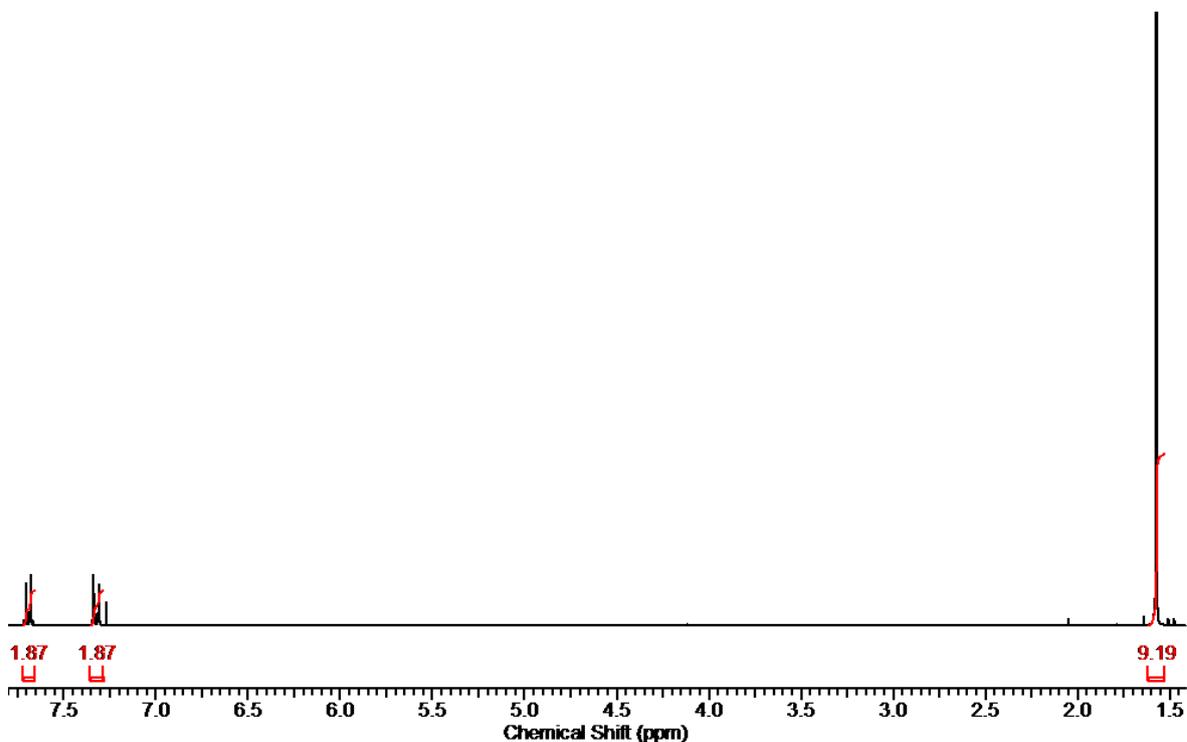


Figure 3.1: ¹H NMR spectrum for *tert*-butyl-4-cyanophenyl carbonate in the region of 7.8 – 1.5 ppm

^1H NMR spectroscopy was used to confirm the synthesis of the product. From the ^1H NMR spectrum a singlet signal far upfield integrating for nine protons indicates the presence of the *tert*-butyl group. Also, the aromatic protons shift further downfield due to less of an anisotropic effect of the aromatic system which stems from the electron withdrawing effects of the carbonate substituent.

From the theoretical results, NBO charge values show that the negative charge on the nitrogen has a smaller value than the nitrogen of benzonitrile. This value, once again, makes chemical sense as electron density has been withdrawn from the nitrile. These values do not differ significantly from those of benzonitrile and therefore suggests that the reaction with lithium hexamethyldisilazide in diethyl ether should result in the partially silylated amidinate. This is indeed the case as a definite colour change is observed from a clear to yellow solution. The yellow colour of the amidinate changes to reddish-brown when SCl_2 is added and allowed to react for four hours. The formation of the dithiadiazolylium chloride salt was confirmed by high resolution mass spectroscopy. The peak observed at 297.0368 corresponds exactly with the actual mass of the positive fragment (Figure 3.2). The peak visible at 297.0802 is due to some unidentified compound. The salt was reduced with Zn/Cu couple in tetrahydrofuran. The expected colour change was observed, however, confirmation of the presence of the radical by EPR was not conclusive. This can most likely be attributed to the insolubility of the radical in dichloromethane which is the typical solvent for EPR studies.

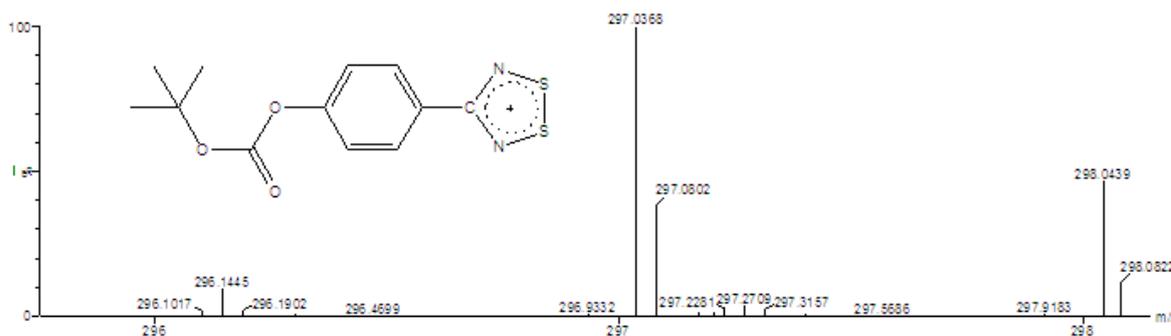
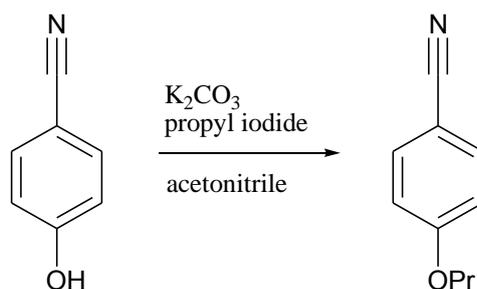


Figure 3.2: High resolution mass spectrum of the *tert*-butyl-4-dithiadiazolyliumphenyl carbonate chloride salt. $M[+] = 297.0368$

4-propoxybenzonitrile was also synthesised from 4-hydroxybenzonitrile.¹² The reaction was performed in acetonitrile with potassium carbonate as the base. The reaction was allowed to stir for approximately 15 minutes after which propyl iodide was added with stirring taking place for a further 24 hours. After work-up and purification, the product was isolated as a white solid in a good yield of 74%.



Scheme 3.4: Synthesis of 4-propoxy benzonitrile

For the confirmation of the successful synthesis of 4-propoxy benzonitrile from 4-hydroxy benzonitrile a number of changes in the 1H NMR spectrum should arise. Three signals for the propyl chain should be observed in the upfield region and the disappearance of a broad O-H signal should confirm the synthetic modification at the phenolic position. The 1H NMR spectrum (Figure 3.3) does indeed indicate these changes.

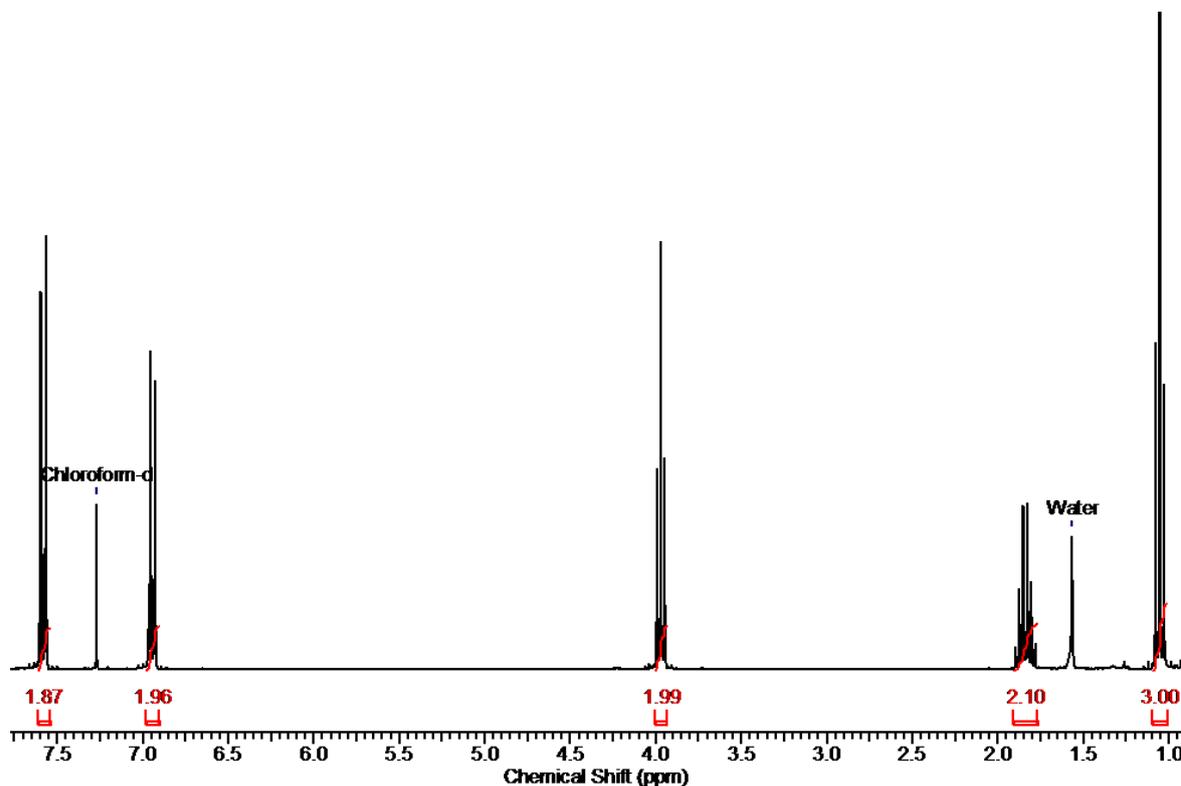


Figure 3.3: 1H NMR spectrum for 4-propoxy benzonitrile in the region of 7.8 – 1.0 ppm

According to the theoretical results the NBO charge value for the carbon of the nitrile for 4-propoxy benzonitrile is the same as that for 4-methoxy benzonitrile. This would therefore indicate that the typical reaction conditions could be followed for the synthesis of the dithiadiazolyl radical. This is indeed the case as synthesis of the dithiadiazolium chloride salt

proved successful and was confirmed by high resolution mass spectroscopy. A peak is observed at 239.0305 which corresponds to the actual mass of the positive fragment.

Furthermore, this salt was subjected to reduction using zinc-copper couple in tetrahydrofuran at approximately 40 °C. A colour change was observed resulting in a dark purple solid. Electron paramagnetic resonance (EPR) was performed on a solution of the solid dissolved in dichloromethane. The EPR signal is split due to the lone electron coupling to both nitrogen atoms in the ring. The resultant signal is a pentet (Figure 3.4) which is due to the $2n(I) + 1$ rule where $I = 1$, which is the spin state of the nitrogen nucleus.¹³

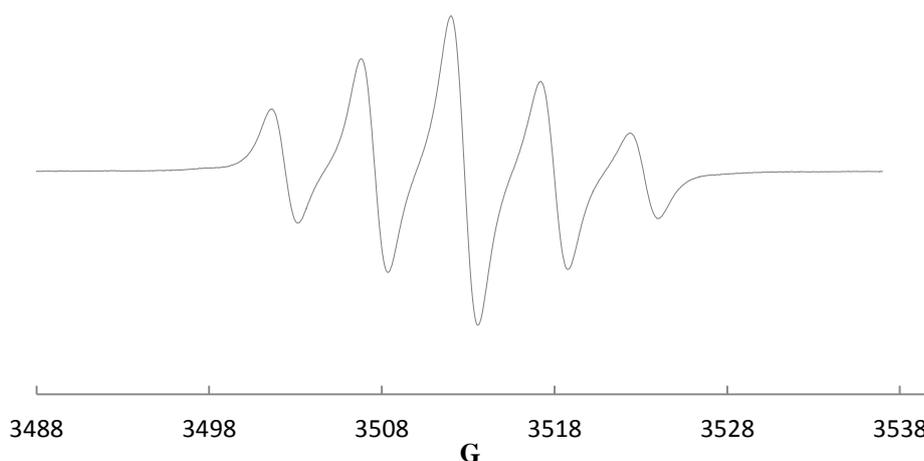


Figure 3.4: EPR spectrum of the 4-propoxy dithiadiazolylbenzene radical performed in dichloromethane. The y-axis has been omitted as it is just an arbitrary measure of intensity

Therefore, the positive results obtained with these two model compounds, is strong evidence that the reactivity of the nitrile is not dependent on the electronic effects of the para substituent. This does beg the question as to why the nucleophilic attack of lithium hexamethyldisilazide failed to occur on the calix[4]arene. It was then decided to consider whether steric effects may have a role to play in the failure of the reaction.

3.5 Steric effects

The tetrapropoxy calix[4]arene is a large molecule and its upper rim functionalised derivatives are fixed in the cone conformation with a specific conformation in solution. Mono-nitrile calix[4]arene **7** has the nitrile on one of the upright phenyl rings as confirmed by the NMR shifts of the aromatic protons (Chapter 2.5). The nitrile could be subjected to nucleophilic

attack from either the endo face (the space on the inside of the bowl) or the exo face (outside the bowl) of the nitrile functionality.

When considering the available space on the endo face for the bulky nucleophile it is clear that attack cannot occur from this side of the nitrile. This is illustrated by a space-fill diagram of the crystal structure, generated using the standard van der Waal's radii (Figure 3.5). As discussed in Chapter 2, the conformation of these molecules is the same in the solid state as it is in solution. The gap between the carbon of the nitrile and the *para* hydrogen on the opposite upright phenyl ring is approximately 0.65 Å. The van der Waal's radius of a nitrogen atom is significantly larger than this value. Therefore, the gap is too small for the nitrogen atom of the nucleophile, lithium hexamethyldisilazide, to fit through. It is safe to say that this specific nucleophile is too sterically encumbered to attack the endo face of the nitrile.

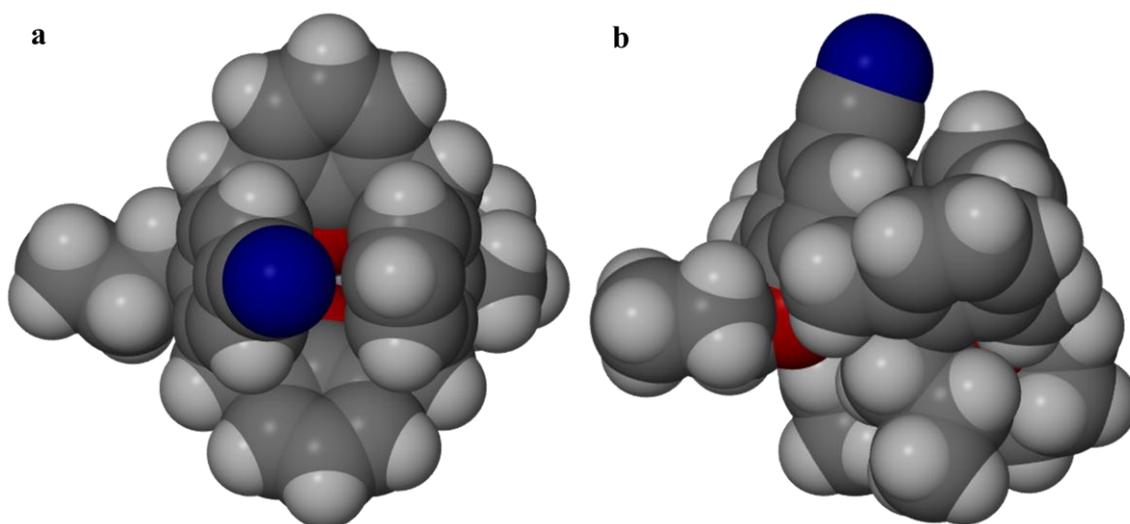


Figure 3.5: Top (a) and side view (b) of calix[4]arene **7** illustrating the limited space of the endo face of the nitrile

Now that it is established that there are definitely steric effects that should be taken into account it would be safe to assume that the reaction rate would significantly decrease. However, there is still an exo face to the nitrile where the reaction could occur. Where exactly attack would occur on the exo face of the nitrile is determined by the spatial orientation of the lowest unoccupied molecular orbital (LUMO). Due to the orbital overlap of the planar aromatic system with the nitrile there are two non-degenerate LUMOs.¹⁴ One is conjugated to the aromatic system and the other is perpendicular to the aromatic system (Figure 3.6). In 2003 Wagner considered these orbitals in his studies on the cycloaddition of nitrones to nitriles. Here he found that the higher energy, non-conjugated LUMO + 1 was the preferred orbital in those reactions.^{14, 15}

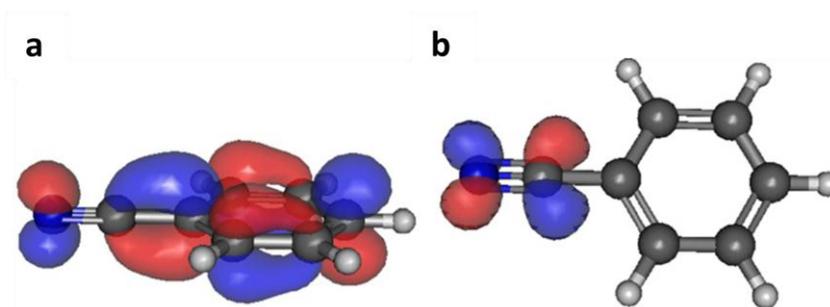


Figure 3.6: The two non-degenerate LUMO's of an aryl nitrile: (a) conjugated LUMO and (b) perpendicular LUMO + 1 (adapted from Bokach *et al.*)¹⁵

The perpendicular LUMO + 1 orbital may have a higher energy and occupy a space that is less accessible to the nucleophile, however, once the nucleophile has attacked, the sp^2 transition state would remain conjugated into the aromatic system (Figure 3.7a). If the attack happened from the most accessible side, i.e. *via* the conjugated LUMO, the sp^2 transition state would have the nitrogen pointing towards the opposite phenyl ring of the calix[4]arene (Figure 3.7b). This transition state would not be conjugated into the aromatic ring. Nucleophilic attack of the nitrile could, therefore, occur at the lower energy LUMO giving rise to a higher energy transition state or attack could occur at the higher energy LUMO + 1 which would give rise to a lower energy conjugated transition state.

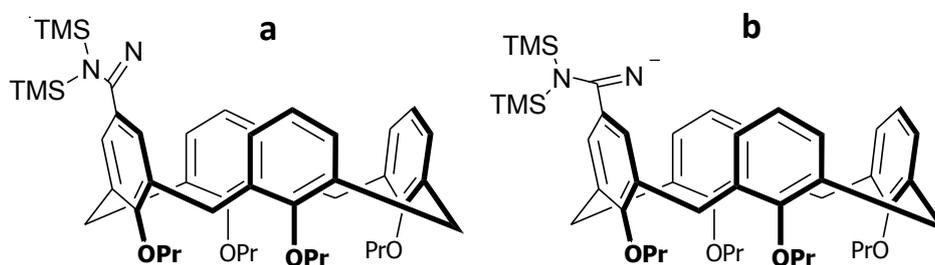


Figure 3.7: Possible sp^2 transition states; (a) conjugated lower energy and (b) unconjugated higher energy

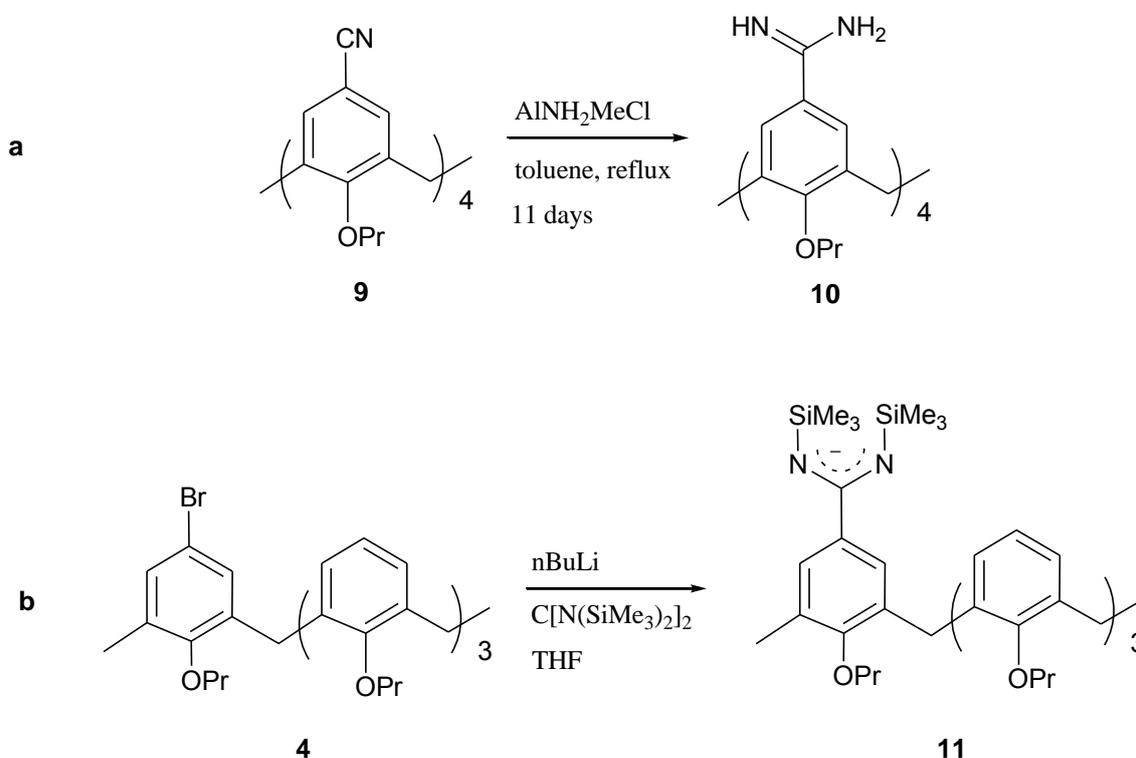
Therefore the unreactive nature of the nitrile can possibly be attributed to the fact that the only accessible LUMO, due to steric hindrance, gives rise to an unstable transition state. This may result in an equilibrium between the starting nitrile and the transition state lying predominantly in the direction of the starting nitrile.

In chapter 1 a list of reactions was discussed based on the nitrile calix[4]arenes as starting materials. This list was not very extensive and may be due to the high energy transition state through the only accessible LUMO. Borane, which reduces the nitrile to the primary amine, proves to be successful possibly due to the fact that sterically it is not a large nucleophile. In

actual fact all the reagents used to further functionalise the periphery of the nitrile calix[4]arenes, are not sterically encumbered.

3.6 Further attempts at the synthesis of dithiadiazolyl functionalised calix[4]arenes

There are other routes to synthesise dithiadiazolyls as described in chapter 1.¹ Two of these were selected and briefly examined using the calix[4]arene scaffold as the R-group. In one case it was decided to isolate the amidine intermediate as shown in scheme 3.5a, prior to the synthesis of the dithiadiazolyl target molecule by condensation with sulfur dichloride and secondly, a procedure using a nucleophilic attack on a carbodiimide would be used (Scheme 3.5b).



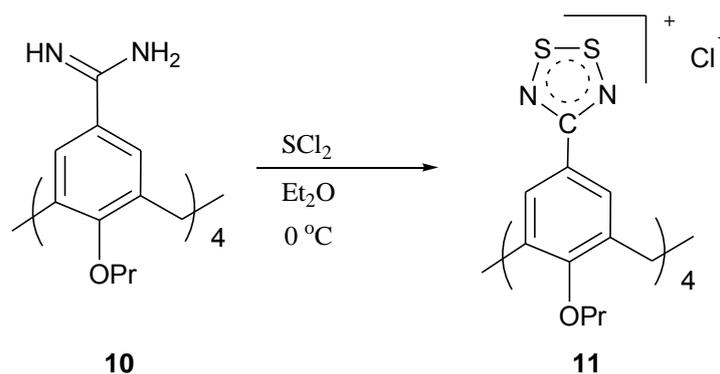
Scheme 3.5: Two further attempts at the synthesis as the synthesis of dithiadiazolyl functionalised calix[4]arenes: (a) Synthesis of the tetra-amidine calix[4]arene and (b) Lithium-halogen exchange followed quenching with the appropriate electrophile

3.6.1 Synthesis of the amidine functionalised calix[4]arene

Synthesis of a tetra-amidine functionalised calix[4]arene, **10**, has previously been reported by Shuker *et al.* with a good yield of 73%.¹⁶ The reaction is a one step procedure where the alkyl chloride aluminium amide, AlNH_2MeCl , is synthesised *in situ* from trimethyl aluminium

(AlMe₃) and ammonium chloride (NH₄Cl) in 1,2-dichloroethane.^{16, 17} The nucleophile reacts with the tetra-nitrile calix[4]arene, **9**, over a period of nine days in toluene at reflux conditions.

The amidine would be a suitable intermediate in the synthesis of dithiadiazolyl functionalised calix[4]arenes as it is comparable to the partially silylated intermediate. In the synthesis of the dithiadiazolyl the following reaction step (Scheme 3.6) would generate the dithiadiazolylium chloride salt after the condensation of the amidine with sulfur dichloride (SCl₂). In this case the by-product would be HCl gas rather than trimethylsilyl chloride (TMSCl).

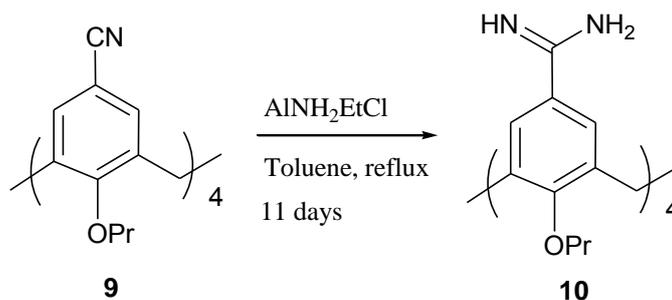


Scheme 3.6: Synthesis of the dithiadiazolylium chloride salt from the tetra-amidine calix[4]arene

The methodology reported for converting the tetra-nitrile to tetra-amidine involves an alkylchloroaluminium amide derivative as the nucleophile. Reinhoudt *et al* report that use of AlMe₃ in the synthesis of the corresponding alkylchloroaluminium amide is crucial for the synthesis of the unsubstituted amidine.¹⁸ For the synthesis of various substituted amidines, diethylaluminiumchloride (Et₂AlCl) was used with the appropriate alkylamine.

This being said, the synthesis of the tetra-amidine was attempted using triethyl aluminium (Et₃Al)*, instead of trimethyl aluminium, and ammonium chloride to synthesise ethyl chloro aluminium amide (NH₂AlClEt) *in situ*. Effervescing of the reaction mixture was observed during the formation of the nucleophile and once this ceased, the electrophile substrate, tetra-nitrile calix[4]arene, was added and allowed to react under inert conditions, refluxing for eleven days (Scheme 3.7). After this time had elapsed, only a mixture of intractable products was observed by tlc.

* Trimethyl aluminium can only be delivered via shipping and in terms of the time left in the project it was deemed too late to purchase it due to shipping taking at least 3 months.



Scheme 3.7: Attempted synthesis of the unsubstituted tetra-amidine calix[4]arene

Due to the fact that Reinhoudt *et al.* specifically used trimethyl aluminium to synthesise the tetra-amidine calix[4]arene it was thought that pursuing this route with the incorrect alkyl aluminium would not result in the desired material for further synthesis and was therefore set aside as future work.

3.6.2 Nucleophilic attack on a carbodiimide

The methodology of lithium halogen exchange is well documented¹⁹ and has also been applied in the synthesis of dithiadiazolyls.²⁰ However, as the name suggests, halogen derivatives of the calix[4]arene would be needed as the starting material. This procedure therefore eliminates one synthetic step from the procedure. This procedure may be more atom economical but it was not deployed from the outset because the required electrophile is very expensive. Due to the battle of trying to synthesise the dithiadiazolyl this route was looked into, albeit very briefly.

Although there were three bromo-derivatised calix[4]arenes it was decided that only mono-bromo calix[4]arene **4** would be used. Calix[4]arene **4** was added to tetrahydrofuran in a Schlenk flask and cooled to $-78\text{ }^{\circ}\text{C}$. One equivalent of *n*-butyl lithium (*n*BuLi) was added and the solution was stirred for 15 minutes. One equivalent of bis(trimethylsilyl)carbodiimide ($\text{C}[\text{N}(\text{SiMe}_3)_2]_2$) was added to the reaction mixture and was stirred overnight. This should potentially result in the same partially silylated amidinate, shown in scheme 3.5b, as that of the typical reaction procedure (Scheme 3.1).

However, according to tlc only one spot was observed under ultraviolet light. This spot corresponded to the fully protonated calix[4]arene **3**. This indicated that the intended reaction failed to take place. The unusual unreactive nature of these two highly reactive species is possibly due to both the calix[4]arene nucleophile and the carbodiimide electrophile being sterically encumbered. Since this project focused on the reactivity of the nitrile functionalised calix[4]arenes, this avenue was not explored any further.

3.7 Conclusion

The attempted synthesis of the dithiadiazolyl functionalised calix[4]arene proved unsuccessful. Modification of experimental parameters such as the time, temperature and solvent unfortunately also had no impact on the outcome of the reaction.

Both steric and electronic reasons for this lack of reactivity were explored in much detail to attempt to elucidate which factors were responsible for the unreactive nature of the nitrile functionalised calix[4]arenes.

The electronic route was explored with the aid of both theoretical calculations and experimental work. The calculations determined how much electron density was situated on both the carbon and nitrogen of the nitrile (Table 3.2). The change in electron densities measured by Mulliken and NBO charges were minimal across the spectrum of test, model and calix[4]arene compounds. Therefore, the calculations as well as the experimental results revealed that the unreactive nature of the nitrile was not due to any electronic factors.

The second argument entailed looking into the steric effects surrounding both the calix[4]arene and the lithium hexamethyldisilazide nucleophile. By using the mono-nitrile calix[4]arene's crystal structure, it was found that there was no way for the nucleophile to attack the nitrile from the endo face of the calix[4]arene bowl. This led us to believe that the most accessible LUMO was the one on the exo face which is conjugated to the aromatic system. This LUMO, according to Wagner, has a lower energy than the perpendicular LUMOs. Therefore, the planar LUMO seemed to be the best candidate for nucleophilic attack. However, the sp^2 transition state that arises would break the conjugation of the π system of the nitrile with the aromatic ring, resulting in a high energy transition state. In comparison the transition state which arises from attack through the perpendicular LUMO + 1 conserves the conjugation providing a lower energy transition state. However, the reaction does not occur and this is possibly due to the inaccessibility of the LUMO + 1 orbital to the lithium hexamethyldisilazide nucleophile.

Even after all the experimental changes, the mono-nitrile calix[4]arene did not react. With the use of theoretical calculations, electronic effects were ruled out as the cause. Therefore, it seems that the unreactive nature of the nitrile functionalised calix[4]arenes is due to the inaccessibility of the higher energy LUMO + 1. This is due to the steric bulk of the calix[4]arene scaffold as well as the lithium hexamethyldisilazide nucleophile.

3.8 References

- (1) Rawson, J. M.; Banister, A. J.; Lavender, I., *Adv. Het. Chem.*, **1995**, *62*, 137-247.
- (2) Boere, R. T.; Oakley, R. T.; Reed, R. W., *J. Organomet. Chem.* **1987**, *331*, 161-167.
- (3) Cordes, A. W.; Goddard, J. D.; Oakley, R. T.; Westwood, N. P. C., *J. Am. Chem. Soc.* **1989**, *111*, 6147-6154.
- (4) Aherne, C. M.; Banister, A. J.; Gorrell, I. B.; Hansford, M. I.; Hauptman, Z. V.; Luke, A. W.; Rawson, J. M., *J. Chem. Soc. Dalton Trans.* **1993**, 967-972.
- (5) Snieckus, V., *Chem. Rev.* **1990**, *90*, 879-933.
- (6) Boere, R. T.; Moock, K. H.; Parvez, M., *Z. Anorg. Allg. Chem.* **1994**, *620*, 1589-1598.
- (7) Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, **2004**.
- (8) Cramer, C. J., *Essentials of Computational Chemistry: Theories and Models* 2nd Ed. **2004**, Wiley: England.
- (9) Mulliken, R. S., *J. Chem. Phys.* **1955**, *23*, 1833-1840.
- (10) Weinhold, F.; Landis, C. R., *Chem. Educ.: Res. Pract. Eur.* **2001**, *2*, 91-104.
- (11) Saito, Y.; Yoshimura, Y.; Takahata, H., *Tetrahedron Lett.* **2010**, *51*, 6915-6917.
- (12) Harper, R. W.; Herron, D. K.; Bollinger, N. G.; Sawyer, J. S.; Baldwin, R. F.; Roman, C. R.; Rinkema, L. E.; Fleisch, J. H., *J. Med. Chem.* **1992**, *35*, 1191-1200.
- (13) Pavia, D.; Lampman, G.; Kriz, G., *Introduction to Spectroscopy* 4th Ed., **2000**, Brooks/Cole, Belmont.
- (14) Wagner, G., *Chem. Eur. J.* **2003**, *9*, 1503-1510.
- (15) Bokach, N. A.; Kuznetsov, M. L.; Kukushkin, V. Y., *Coord. Chem. Rev.* **2011**, *255*, 2946-2967.

- (16) Sasine J. S.; Brewster R. E.; Caran K. L.; Bentley A. M.; Shuker S. B., *Org. Lett.* **2006**, *8*, 2913.
- (17) Garigipati, R. S., *Tetrahedron Lett.* **1990**, *31*, 1969-1972.
- (18) Corbellini, F.; Fiammengo, R.; Timmerman, P.; Crego-Calama, M.; Versluis, K.; Heck, A.; Luyten, I.; Reinhoudt, D., *J. Am. Chem. Soc.* **2002**, *124*, 6569-6575.
- (19) Clayden, J., *Organolithiums: Selectivity for Synthesis.* **2002**, Pergamon: London, Vol. 23.
- (20) Edelmann, F. T., *Coord. Chem. Rev.* **1994**, *137*, 403-481.

Chapter 4

Conclusions and Future Work

4.1 Conclusions

The initial aim was to synthesise dithiadiazolyl functionalised calix[4]arenes to investigate what effect the bulky calix[4]arene scaffold would have on the potential solid state properties (i.e. magnetic or conductive). However, the main aim shifted and focused on the reactivity of the nitriles synthesised onto the periphery of the calix[4]arene. The findings of this project are concluded in the sections below.

The successful synthesis of three nitrile functionalised calix[4]arenes **7 – 9** has been reported and discussed and this is the first time their respective crystal structures have been reported. As nitrile precursors are generally used as starting materials in the typical synthesis of dithiadiazolyls, the three calix[4]arene precursors were used as the starting materials. However, in this case the reaction failed to proceed. It was at this point that the project changed course and the reason behind the failure of the reaction was explored. This was investigated experimentally in the laboratory, computationally and with the aid of ^1H NMR spectroscopy and the crystal structures.

With the combination of variations to the synthetic procedure, as well as computational work it was determined that it is unlikely that the electronic properties (i.e. the electrophilicity of the nitrile carbon) influenced the outcome of the reaction.

Using ^1H NMR spectroscopy and the crystal structures it was established that the conformations of the calix[4]arenes are the same in both the solid-state and in solution. Furthermore, by assessing the calix[4]arene crystal structures, it is clear that there is no way for the nucleophile to attack the nitrile from the endo face of the calix[4]arene bowl. This led us to believe that the most accessible LUMO was on the exo face, conjugated to the aromatic system. This LUMO, according to Wagner, has a lower energy but peculiarly is not the LUMO involved in bonding.¹ The reason for this is due to the lower energy sp^2 transition state that would arise through bonding with the higher energy LUMO + 1. This transition state has a lower energy as it remains conjugated to the aromatic system. Therefore, the unreactive nature of the reaction between the calix[4]arene nitrile and lithium bis(trimethylsilyl)amide may be attributed to the sterically encumbered nature of both the nucleophile as well as the nitrile functionalised calix[4]arene.

4.2 Future work

4.2.1 Computational chemistry

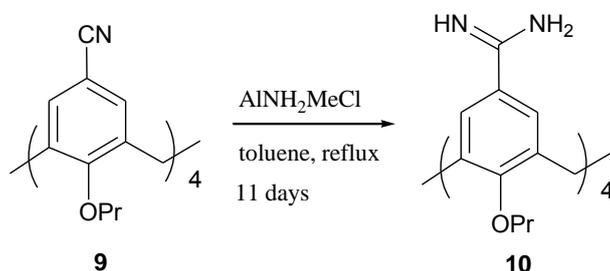
In this work, exploration into the field of computational chemistry proved to be a helpful tool in determining the reason behind the non-reactivity of the nitrile functionalised calix[4]arenes. This work can be extended further by determining the difference in energy of the two extreme sp^2 transition states (i.e. the conjugated transition state and the orthogonal transition state) computationally.

4.2.2 Experimental procedures for the synthesis of the dithiadiazolyl radical

Initially, the bulk of this work was aimed at the synthesis of dithiadiazolyl functionalised calix[4]arenes using the typical reaction procedure. This route has been exhausted and the conclusions of this work indicate that this route proves unsuccessful in the case of these obstinate nitriles. However, there are a number of other synthetic pathways which could be investigated to acquire the desired material. The sections which follow will demonstrate this.

4.2.2.1 Via the unsubstituted amidine

As mentioned in chapters 1 and 3, an unsubstituted amidine is a highly plausible starting material in the synthesis of dithiadiazolyls as it would easily condense with sulfur dichloride to form the dithiadiazolylum chloride salt. A brief communication by Garigipati in 1990 described a novel route to the synthesis of unsubstituted amidines.² His work was extended to nitrile functionalised calix[4]arenes by Shuker *et al.*³ As described in the conclusions of chapter 3, trimethyl aluminium is required for the synthesis of the correct alkyl aluminium amide. With this in hand synthesis of the amidine substituted calix[4]arenes (Scheme 4.1) can be achieved in high yields.

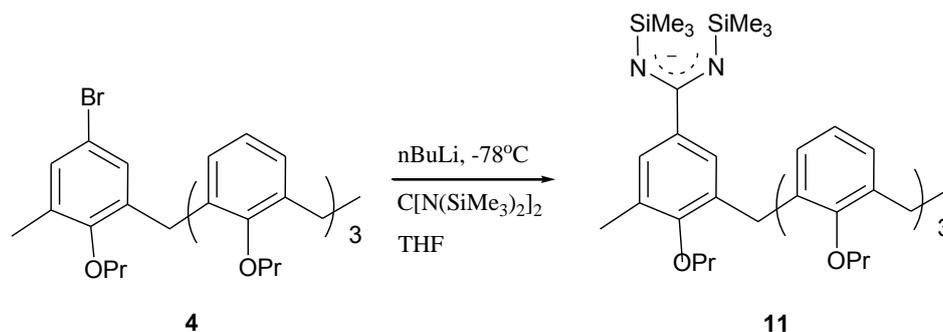


Scheme 4.1: Garigipati's procedure for the synthesis of unsubstituted amidines

Other than the long synthesis time, the relative ease and good yields of the amidine synthesis suggest that this procedure will probably be the most beneficial route to synthesise dithiadiazolyl functionalised calix[4]arenes.

4.2.2.2 Addition of a suitable carbodiimide

Chapter 3 describes the unsuccessful attempt at the synthesis of the partially silylated calix[4]arene via lithium halogen exchange, followed by a quench with a suitable carbodiimide. This section of work was only briefly looked into at what can be described as normal conditions for the exchange and quench reaction (Scheme 4.2).



Scheme 4.2: Attempted synthesis of the partially silylated amidine *via* lithium halogen exchange

This route utilises two normally reactive species, a negatively charged phenyl and a carbodiimide. Therefore, with further studies, changes in the reaction conditions (i.e. temperature and solvent), before the electrophile is added may result in the reaction proving successful. Lithium-halogen exchange reactions occur rapidly at -78 °C and within 15 minutes the starting material is completely lithiated. Therefore, with the lithiated intermediate in hand, the reaction conditions can be changed to optimise the yield of product. The temperature can be increased systematically to approximately 60 °C with tetrahydrofuran for the carbodiimide electrophile quench. If required the solvent can be substituted with toluene to further increase the temperature.

4.2.2.3 NH₄Cl and S₂Cl₂ in nitro benzene

Another synthetic procedure, which was not attempted in this study, requires the addition of ammonium chloride and sulfur dichloride to a nitrile derivative in refluxing nitro benzene.⁴ The reaction is not high yielding but may prove to be a useful method of synthesising the dithiadiazolyl functionalised calix[4]arene radicals.

4.2.3 Synthesis of distal and tetra substituted products

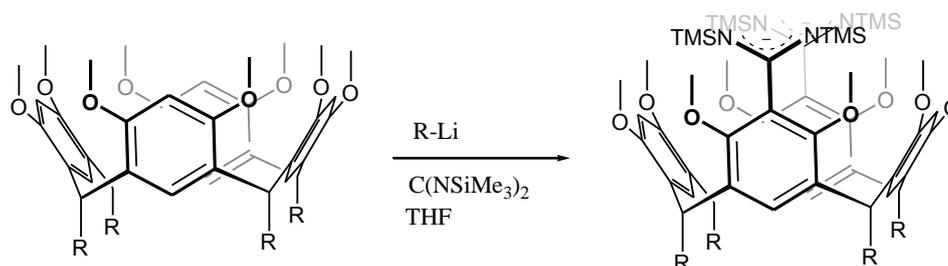
Of course the initial aim of this work was to synthesise the three different dithiadiazolyl functionalised calix[4]arenes (i.e mono, distal and tetra). Therefore, the reaction utilising the lithium hexamethyldisilazide should be extended from the mono substituted starting material to the distal and tetra compounds to determine whether the nitrile functional group on the phenyl rings in an outward position would bring about a different outcome of the reaction.

Also, the reaction concerning the carbodiimide should be extended to attempt to synthesise both the distal and tetra counterparts by the stoichiometric addition of lithium reagent followed by the electrophilic carbodiimide.

This would give a more complete representation of the conclusions made based on the reactions performed with just the mono-functionalised starting material

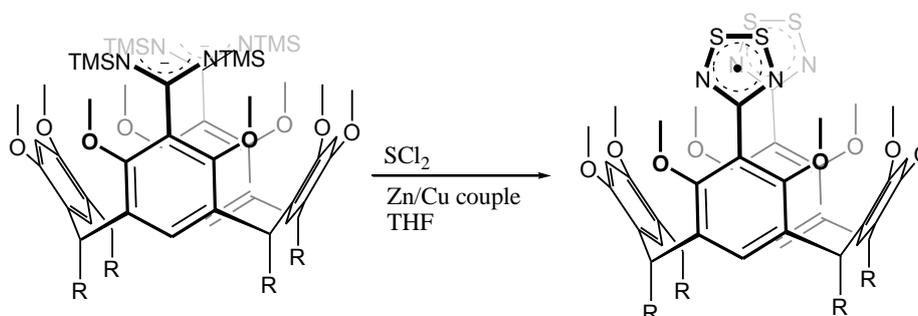
4.2.4 Resorcinarenes as an analogous scaffold

In our lab there has been an impressive amount of work completed on ortholithiation methodology behind selectively functionalising the resorcinarene framework.⁵ At present selective distal functionalisation has been given the most attention, and rightly so, as percentage yields in the high eighties are being obtained. Therefore, with this methodology in hand, distally functionalising the resorcinarene bowl would require an alkyl lithium to deprotonate ortho to the two methoxy groups on opposite phenyl rings, followed by quenching with an electrophile, bis(trimethylsilyl)carbodiimide (Scheme 4.3). The result of the quench would result in the partially silylated amidine.



Scheme 4.3: Selective distal ortholithiation followed by an electrophile quench

The partially silylated amidine could undergo a condensation reaction with sulfur dichloride to yield the distally functionalised dithiadiazolylum chloride salt. Reduction of the salt would then furnish the dithiadiazolyl radical (Scheme 4.4).



Scheme 4.4: Further reactions involved in the synthesis of the distally functionalised dithiadiazolyl radical

4.3 References

- (1) Wagner, G., *Chem. Eur. J.* **2003**, 9, 1503-1510.
- (2) Garigipati, R. S., *Tetrahedron Lett.* **1990**, 31, 1969-1972.
- (3) Sasine J. S; Brewster R. E; Caran K. L; Bentley A. M; Shuker S. B., *Org. Lett.* **2006**, 8, 2913.
- (4) Alange, G. G.; Banister, A. J.; Bell, B.; Millen, P. W., *J. Chem. Soc. Perkin Trans. 1.* **1979**, 1192-1194.
- (5) Ngodwana, L.; Arnott, G. E., "Selective distal functionalisation of resorcinarenes." Unpublished manuscript, **2011**.

Chapter 5

Supplementary Data

5.1 General Procedures

5.1.1 Solvents:

All chemicals used were bought from Merck or Aldrich. Tetrahydrofuran, diethylether and toluene were dried over sodium wire/sand and distilled under an atmosphere of nitrogen with benzophenone as an indicator. Dichloromethane was distilled over calcium hydride, also under an inert atmosphere of nitrogen. Butanone, DMF, diglyme as well as other solvents and reagents were purified according to standard literature procedures.^{1, 2} The molarity of *n*BuLi was determined using a method as described in the literature.³

5.1.2 Temperature control:

All reactions were performed under anhydrous conditions under either nitrogen or argon atmosphere, unless stated otherwise. Low temperature reactions were performed in a Dewar using dry ice in acetone ($-78\text{ }^{\circ}\text{C}$), ice in water ($0\text{ }^{\circ}\text{C}$) or a slurry of ethanol. Microwave reactions were performed in a Biotage Initiator microwave reactor.

5.1.3 Spectroscopic techniques:

All ^1H and ^{13}C nuclear magnetic resonance spectra were obtained using a 300 MHz Varian VNMRS (75 MHz for ^{13}C) or a 400 MHz Varian Unity Inova (100 MHz for ^{13}C). Chloroform-*d* was used as standard solvent, unless otherwise stated. Chemical shifts (δ) were recorded using the residual chloroform peaks (δ 7.26 in ^1H NMR and δ 77.0 in ^{13}C NMR) or the residual DMSO peaks (δ 2.50 in ^1H NMR and δ 39.5 in ^{13}C NMR) in DMSO-*d*₆, as reference. All chemical shifts are reported in ppm and all spectra were obtained at $25\text{ }^{\circ}\text{C}$, unless otherwise stated.

Melting points were obtained using a Gallenkamp Melting Point Apparatus and are uncorrected. Infrared spectra were obtained using a Nexus Thermo-Nicolet FT-IR instrument using the ATR function. High resolution mass spectrometry was performed by the CAF (Central Analytical Facility) Institute at Stellenbosch University using either a Waters API Q-TOF Ultima spectrometer or introduced via the ASAP probe using the Waters Synapt G2 spectrometer. Routine mass spectroscopy was performed using a Waters API Quattro Micro spectrometer. In all cases ESI+ was used as an ionisation method.

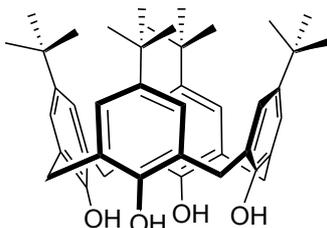
EPR spectra were recorded at 298 K with a Bruker EMX_{plus} X-band EPR spectrometer (8-inch ER 072 magnet, 2.7 kW power supply, EMX-m40X microwave bridge operating from 9.3 to 9.9 GHz), and a high sensitivity continuous-wave resonator. Samples were polycrystalline solids and dilute solutions of arbitrary concentration in dry dichloromethane in an otherwise ambient atmosphere.

5.1.4 Chromatography:

All chromatography was performed using either (or a combination of) petrol ether, ethyl acetate, methanol and dichloromethane. Thin layer chromatography (tlc) was carried out on aluminium backed Merck silica gel 60 F254 plates. Visualization was achieved with UV lamp, iodine vapour or by spraying with a Cerium Ammonium Molybdate solution (CAM) and then heating. All column chromatography was carried out with Merck silica gel 60 (particle size 0.040-0.063 mm).

5.2 Compounds

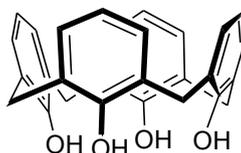
5,11,17,23-tetra(*tert*-butyl)-calix[4]arene, **1**⁴



A reaction mixture of 4-*tert*-butylphenol (20.8 g, 0.139 mol), formaldehyde (12.9 ml of a 37% aqueous solution, 4.77 ml, 0.164 mmol) and NaOH (0.1g, 3.33 mmol) in ca 0.5ml H₂O were heated to 120 °C for 2 hours until the reaction formed a yellow viscous mass that solidified with further stirring. The solidified mass was allowed to cool to room temperature after which diphenyl ether (170 ml) was added and the heterogeneous mixture allowed to stir overnight. Toluene (10 ml) was added and the reaction heated to 180 °C to drive off any remaining water as an azeotrope. The reaction was heated to reflux, after fitting a condenser, for a further 4 hours. After the elapsed 4 hours the reaction was allowed to cool to room temperature and ethyl acetate (120 ml) was added and the mixture allowed to stir for a further hour. The solid that formed was filtered and washed with small portions of ethyl acetate. The crystals were triturated with acetic acid and filtered once more. The crystals were washed with further small portions of ethyl acetate and once dried left calix[4]arene **1** as white crystals in 56% yield (12.7 g, 19.60 mmol).

Mp 342-345 °C (Ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz, 25°C): δ = 1.21 (s, 36H, tCCH_3), 3.48 – 3.54 (d, J = 14.04 Hz, 4H), 4.23 – 4.29 (d, J = 14.04 Hz, 4H), 7.06 (s, 8H, CHar), 10.37 (s, 4H, OH);

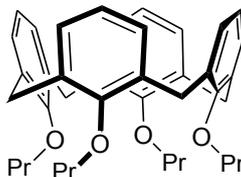
Calix[4]arene, **2**⁵



To a solution of calix[4]arene **1** (10.0 g, 15.4 mmol) and dry toluene (80 ml), phenol crystals (1.75 g, 18.6 mmol) were added and the reaction mixture allowed to stir for 10 min. Excess AlCl_3 (10.0 g, 75.8 mmol) was added quickly and the solution allowed to stir vigorously for a further 2 – 3 hours. The reaction mixture was transferred to a beaker and quenched with ice taking care as HCl gas rapidly evolved. This was then transferred to a separating funnel and the product extracted into CH_2Cl_2 . All the organic portions were then dried over MgSO_4 which was subsequently filtered off. The solvent was then removed under reduced pressure followed by triturating with diethyl ether. Calix[4]arene **2** was then filtered and once dried gave a white powder in 76% yield (4.95 g, 11.7 mmol).

Mp 314-316 °C (Diethyl ether); ^1H NMR (CDCl_3 , 400 MHz, 25°C): δ = 3.59 (s, 4H), 4.29 (s, 4H), 6.76 (t, J = 7.56 Hz, 4H, CHar), 7.08 (d, J = 7.56 Hz, 8H, CHar), 10.23 (s, 4H, OH);

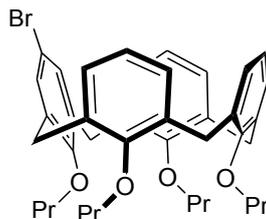
25,26,27,28-tetrapropoxycalix[4]arene, **3**⁵



To a solution of sodium hydride (3.9 g, 162.5 mmol), washed with petroleum ether, and DMF (80 ml), calix[4]arene **2** (4.0 g, 9.43 mmol) and 1-iodopropane (9.2 ml, 9.45 mmol) were added. The reaction was stirred at room temperature for 12 hours or until complete. HCl (2 M, 150 ml) was used to quench the mixture after which a solid formed. This solid was filtered and washed with distilled H_2O . The solid was then heated in methanol to 60 °C and then cooled for 2-3 hours. The product was collected by filtration and once dried gave calix[4]arene **3** as a white solid in 74% yield (4.11 g, 6.94 mmol).

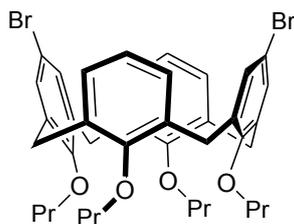
Mp 185°C (Methanol); ^1H NMR (300 MHz; CDCl_3 ; 25°C) δ 1.02 (12H, t, $J=7.41$, $-\text{CH}_2\text{CH}_2\text{CH}_3$), 1.88 – 2.02 (8H, m, $-\text{CH}_2\text{CH}_2\text{CH}_3$), 3.18 (4H, d, $J=13.35$), 3.84–3.92 (8H, m, $-\text{CH}_2\text{CH}_2\text{CH}_3$), 4.48 (4H, d, $J=13.35$) and 6.55–6.66 (12H, m, CH_{ar}); ^{13}C NMR (75.5 MHz; CDCl_3 ; 25°C): δ 10.32 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 23.24 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 30.97 ($\text{C}_{\text{ar}}\text{CC}_{\text{ar}}$), 76.66 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 121.84 (C_{ar}), 128.08 (C_{ar}), 135.12 (C_{ar}) and 156.57 ($\text{C}_{\text{ar}}\text{OPr}$);

5-Bromo-25,26,27,28-tetrapropoxycalix[4]arene, **4**⁶



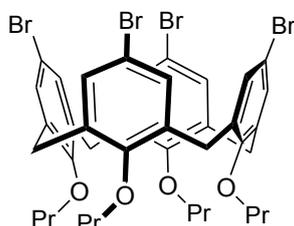
To a solution of calix[4]arene **3** (1.4g, 2.36mmol) in dry 2-butanone (25ml) NBS (420mg, 2.36mmol) was added and the reaction mixture allowed to stir at room temperature for 20 hours. The solvent was removed under reduced pressure and then a solution of 10% chloroform in petroleum ether was added to the residue. The excess NBS which precipitated out was filtered off. The organic solvent was removed under reduced pressure resulting in calix[4]arene **4** as a white solid in 91% yield (1.45 g, 2.16 mmol). This was then recrystallized from DCM/EtOH for further use.

Mp 158°C (DCM/EtOH); $R_f = 0.40$ (CHCl_3 :PetEther, 5:95); ^1H NMR (CDCl_3 , 400 MHz, 25 °C): $\delta = 0.93$ (t, $J = 7.51$ Hz, 6H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.05 – 1.12 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.84 – 1.97 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.12 – 3.22 (m, 4H), 3.71 – 3.87 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.87 – 4.04 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.45 (dd, $J = 13.65$, 3.12 Hz, 4H), 6.28 (d, $J = 7.6$ Hz, 2H, CH_{ar}), 6.51 – 6.57 (m, 3H, CH_{ar}), 6.83 – 6.96 (m, 4H, CH_{ar}), 7.00 (dd, $J = 7.31$, 1.27 Hz, 2H, CH_{ar}); ^{13}C NMR (CDCl_3 , 100 MHz, 25 °C): $\delta = 9.92$, 10.53, 10.65, 23.02, 23.35, 23.41, 30.73, 30.95, 76.68, 76.75, 105.44, 119.73, 122.16, 122.24, 127.61, 128.42, 129.40, 131.65, 133.73, 135.15, 135.89, 136.76, 155.56, 157.32, 159.52;

5,17-Dibromo-25,26,27,28-tetrapropoxycalix[4]arene, 5⁷

Calix[4]arene **6** (2.2g, 2.42mmol) was suspended in dry THF (90ml). To the above solution *n*-BuLi/Hexane (5.1ml, 0.99M, 5.00mmol) was added through a septum while the reaction temperature was kept at -78 °C. The yellow solution was stirred for 15 minutes, and then 980 μ l of MeOH was added and stirred for an additional 10 minutes. To the reaction mixture was added 1M HCl (45ml). This was transferred to a separating funnel and extracted with ethyl acetate (50ml). The organic layer was washed with 1M HCl, distilled H₂O and brine (3 x 40ml). The resultant organic layer was dried with MgSO₄. The drying agent was then filtered off and the solvent removed under reduced pressure. This left calix[4]arene **5** as a white solid in 78% yield (1.72 g, 1.90 mmol). This was then recrystallized from DCM/EtOH for further use.

Mp 238 - 240 °C (Ethyl Acetate/Petroleum Ether); R_f = 0.81 (EtOAc:PetEther, 2:98); ¹H NMR (CDCl₃, 300 MHz, 25 °C): δ = 0.93 – 1.05 (m, 12H, CH₂CH₂CH₃), 1.84 – 1.99 (m, 8H, CH₂CH₂CH₃), 3.12 (d, J = 13.35 Hz, 4H), 3.78 – 3.89 (m, 8H, CH₂CH₂CH₃), 4.41 (d, J = 13.35 Hz, 4H), 6.61 – 6.69 (m, 6H, CHar), 6.78 (s, 4H, CHar); ¹³C NMR (CDCl₃, 75.5 MHz, 25 °C): δ = 10.25, 10.29, 23.17, 30.83, 76.78, 76.89, 114.67, 122.46, 128.39, 130.73, 134.35, 137.19, 155.67, 156.34;

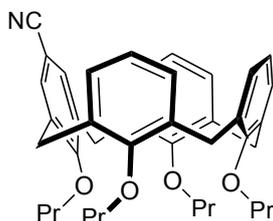
5,11,17,23-Tetrabromo-25,26,27,28-tetrapropoxycalix[4]arene, 6⁷

NBS (8.90 g, 50.3 mmol) was added to a solution of calix[4]arene **3** (3.40 g, 5.74 mmol) in dry butanone (170 ml). The reaction was allowed to stir for 20 hours at 30 °C. The reaction mixture was quenched with 5% sodium thiosulphate (100 ml). Ethyl acetate was added and the phases separated. The organic layer was washed with water/brine and then dried over MgSO₄. The

drying agent was filtered off and the solvent removed under reduced pressure leaving calix[4]arene **6** as a white solid in 93% yield (4.86 g, 5.33 mmol). This was then recrystallized from DCM/MeOH for further use.

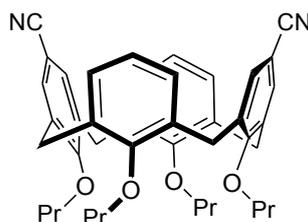
Mp 277°C (DCM/MeOH); $R_f = 0.67$ (EtOAc:PetEther, 2:98); $^1\text{H NMR}$ (CDCl_3 , 300 MHz, 25 °C): $\delta = 0.98$ (t, $J = 7.48$ Hz, 12H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.82 – 1.95 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.09 (d, $J = 13.50$ Hz, 4H), 3.78 – 3.95 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.36 (d, $J = 13.35$ Hz, 4H), 6.81 (s, 8H, CHar); $^{13}\text{C NMR}$ (CDCl_3 , 75.5 MHz, 25 °C): $\delta = 10.20, 23.06, 30.72, 77.00, 115.13, 130.97, 136.42, 155.53$

5-Cyano -25,26,27,28-tetrapropoxycalix[4]arene, **7**^{8,9}



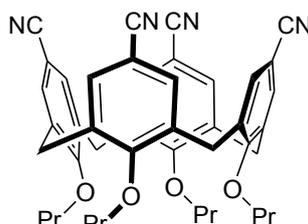
Calix[4]arene **4** (1.5g, 2.24mmol) and copper cyanide (403mg, 4.50mmol) were added to dry DMF (16ml) in a microwave reaction vessel. The reaction mixture was set for 30 minutes at 210 °C. The dark green/black solution was added to a beaker containing FeCl_3 (1.46g, 9.00mmol) dissolved in HCl conc. (50ml). This was performed very cautiously taking care as HCN gas evolves. This was allowed to stir for 1 hour making sure that all the HCN gas has evolved. This was then transferred to a separating funnel and separated using ethyl acetate and concentrated HCl if there was still an emulsion of the layers. The organic layer was dried over magnesium sulfate and the volume was reduced leaving calix[4]arene **7** as a white powder in 60% yield (0.83 g, 1.35 mmol). The product was recrystallized from boiling ethanol for further use.

Mp 179°C (Ethanol); $R_f = 0.38$ (EtOAc:PetEther, 3:97); IR (ATR): 2964 – 2874 (s, Alkane Stretch), 2220 cm^{-1} (m, nitrile); $^1\text{H NMR}$ (CDCl_3 , 300 MHz, 25 °C): $\delta = 0.93$ (t, $J = 7.48$ Hz, 6H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.04 – 1.15 (m, 6H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.83 – 2.00 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.11 – 3.24 (m, 4H), 3.70 – 4.06 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.46 (dd, $J = 13.57, 2.27$ Hz, 4H), 6.28 (d, $J = 7.63$ Hz, 2H, CHar), 6.51 – 6.58 (m, 3H, $-\text{CHar}$), 6.82 – 7.03 (m, 6H, $-\text{CHar}$); $^{13}\text{C NMR}$ (CDCl_3 , 75.5 MHz, 25 °C): $\delta = 9.92, 10.52, 10.64, 23.02, 23.35, 23.40, 30.73, 30.94, 76.57, 76.74, 77.42, 105.43, 119.72, 122.15, 122.24, 127.61, 128.41, 129.40, 131.65, 133.72, 135.15, 135.88, 136.76, 1155.55, 157.31, 159.51$;

5,17-Dicyano -25,26,27,28-tetrapropoxycalix[4]arene, 8^{8,10}

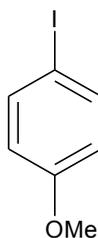
Calix[4]arene **8** was prepared in a procedure analogous to that for calix[4]arene **7** where calix[4]arene **5** (458 mg, 0.611 mmol) and copper cyanide (219 mg, 2.44 mmol) were added to dry DMF (10 ml). After the subsequent steps were followed calix[4]arene **8** was isolated as a white solid in 69% yield (271 mg, 0.422 mmol).

Mp 296°C (EtAOc); $R_f = 0.40$ (EtOAc:PetEther, 50:50); $^1\text{H NMR}$ (CDCl_3 , 400 MHz, 25°C): $\delta = 0.96$ (t, $J = 7.41$ Hz, 6H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.04 (t, $J = 7.41$ Hz, 6H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.86 – 1.96 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.18 (d, $J = 13.65$ Hz, 4H), 3.83 – 3.91 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 4.44 (d, $J = 13.45$ Hz, 4H), 6.76 (s, 6H, CHar), 6.84 (s, 4H, CHar); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz, 25°C): $\delta = 10.09$, 10.34, 23.09, 23.31, 30.71, 76.82, 77.22, 105.65, 118.95, 122.92, 128.81, 131.95, 134.49, 136.22, 156.44, 159.97;

5,11,17,23-Tetracyano -25,26,27,28-tetrapropoxycalix[4]arene, 9^{8,10}

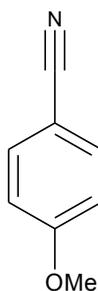
Calix[4]arene **9** was prepared in a procedure analogous to that for calix[4]arenes **7** and **8** where calix[4]arene **6** (454 mg, 0.50 mmol) and copper cyanide (358 mg, 4.0 mmol) were added to dry DMF (8 ml). After the subsequent steps were followed calix[4]arene **9** was isolated as a white solid in 68% yield (236 mg, 0.34 mmol).

Mp °C (>320 °C decomposition); $R_f = 0.40$ (EtOAc:PetEther, 50:50); $^1\text{H NMR}$ (400 MHz, CHLOROFORM-*d*) δ ppm 1.01 (t, $J=7.41$ Hz, 12H, $\text{CH}_2\text{CH}_2\text{CH}_3$) 1.90 (sxt, $J=7.45$ Hz, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$) 3.26 (d, $J=13.84$ Hz, 4H) 3.91 (t, $J=7.51$ Hz, 8H, $\text{CH}_2\text{CH}_2\text{CH}_3$) 4.45 (d, $J=13.84$ Hz, 4H) 7.00 (s, 8H, CHar); $^{13}\text{C NMR}$ (100 MHz, CHLOROFORM-*d*) δ ppm 10.08, 23.17,

1-iodo-4-methoxybenzene (4-iodoanisole)¹¹

To a solution of 4-iodophenol (6.1 g, 27.7 mmol) in acetonitrile (90 ml), sodium carbonate (7.6 g, 71.8 mmol) and dimethyl sulphate (7.3 ml, 80.2 mmol) were added and allowed to stir while heated at reflux. After 24 hours, the reaction had come to completion. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 , filtered and the solvent removed under reduced pressure. The residue was purified by silica gel chromatography (EtOAc:PetEther, 20:80), giving the desired product as a white solid with an aniseed aroma in a 89% yield (5.739 g, 24.5 mmol).

Mp 49-51 °C (EtOAc/PetEther); $R_f = 0.65$ (EtOAc:PetEther, 30:70); ^1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 3.79 (s, 3H, OCH_3), 6.68 (d, $J=9.0$ Hz, 2H, ArH), 7.55 (d, $J=9.0$ Hz, 2H, ArH); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 54.88 (OCH_3), 82.24 (C_{AR}), 115.91 ($2\times C_{\text{AR}}$), 137.75 ($2\times C_{\text{AR}}$), 159.01 (C_{AR}).

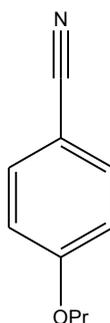
4-methoxybenzonitrile^{8,12}

To a solution of 4-iodoanisole (744 mg, 3.18 mmol) in dry DMF (16 ml), CuCN (570 mg, 6.36 mmol) was added and the reaction mixture was subjected to μw radiation at 210 °C for 30 min. The resultant solution was then added to a beaker containing FeCl_3 (2.0g, 12.7 mmol) dissolved in HCl and EtOAc. The solution was allowed to stir for 1 hour to evolve possible HCN vapours that may have formed. The product was extracted from EtOAc and water/brine and then the organic phase was dried over MgSO_4 . The drying agent was then filtered off and the solvent

removed under reduced pressure which left the desired compound as an off white solid in 65% yield (272 mg, 2.04 mmol) after sublimation.

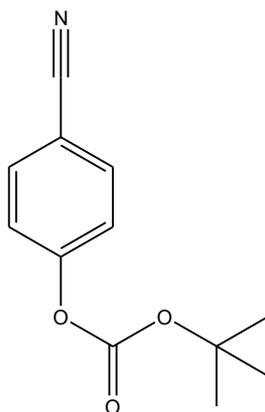
Mp °C (58-59 °C); $R_f = 0.31$ (EtOAc:PetEther, 15:85); $^1\text{H NMR}$ (CDCl_3 , 400 MHz, 25°C): $\delta = 3.87$ (s, 3H, CH_3), 6.96 (m, 2H, CHar), 7.60 (m, 2H, CHar); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz, 25°C): $\delta = 55.54$ (CH_3), 104.01 (CCN), 114.73 (CarCarOCH_3), 133.99 (CarCarCN), 162.83 (CarCOCH_3);

4-propoxybenzonitrile¹³



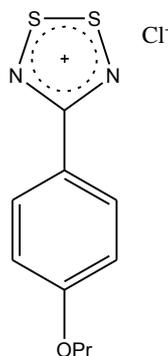
To a solution of 4-hydroxy benzonitrile (5.00 g, 41.9 mmol) in 100 ml of dry acetonitrile, propyl iodide (4.1 ml, 41.9 mmol) and K_2CO_3 (14.5 g, 105 mmol) was added and the solution allowed to stir for 24 hours. The product was extracted from EtOAc and water/brine and then dried over MgSO_4 . Further purification was done by silica gel chromatography (EtOAc:PetEther, 20:80). The solvent was removed which gave the product in a 74% yield (4.99 g, 30.9 mmol) as a white solid.

Mp °C (44-46 °C); $R_f = 0.72$ (EtOAc:PetEther, 20:80); $^1\text{H NMR}$ (CDCl_3 , 300 MHz, 25°C) δ ppm 1.05 (t, $J = 7.41$ Hz, 3H, $\text{OCH}_2\text{CH}_2\text{CH}_3$) 1.77 - 1.91 (m, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_3$) 3.97 (t, $J = 6.53$ Hz, 2H, $\text{OCH}_2\text{CH}_2\text{CH}_3$) 6.91 - 6.97 (m, 2H, CHar) 7.54 - 7.61 (m, 2H, CHar)

tert-butyl 4-cyanophenyl carbonate

To a solution of Et₃N (0.263 ml, 1.87 mmol) and DMAP (5.2 mg, 0.043 mmol) in dry DCM (5 ml), 4-hydroxy benzonitrile (101.5 mg, 0.852 mmol) was added and the clear solution allowed to stir for 15 min. Boc₂O (279 mg, 1.28 mmol) was added and the solution allowed to stir for a further 2 hours and developed a light clear yellow colour. The product was extracted from EtOAc and water/brine and dried over MgSO₄. Further purification was done by silica gel chromatography (EtOAc:PetEther, 15:85). The solvent was removed and gave the product in a quantitative yield (186.7 mg, 0.852 mmol) as an off white solid.

Mp °C (79-82 °C); R_f = 0.66 (EtOAc:PetEther, 20:80); ¹H NMR (CDCl₃, 400 MHz, 25°C): δ = 1.57 (s, 9H, CCH₃), 7.32 (d, J = 8.98 Hz, 2H, CHar), 7.69 (d, J = 8.79 Hz, 2H, CHar); ¹³C NMR (CDCl₃, 100 MHz, 25°C): δ = 27.61 (CCH₃), 84.67 (CCH₃), 109.54 (CarCN), 118.21 (CarCN), 122.23 (Car), 133.63 (Car), 150.66 (CO), 154.23 (CarO);

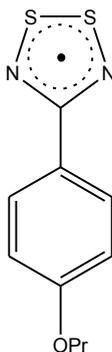
4-propoxy dithiadiazolylum chloride benzene

4-propoxy benzonitrile (500 mg, 3.11 mmol) was added to a solution of lithium bis(trimethylsilyl)amide (0.72 ml, 3.42 mmol) in diethyl ether (20 ml) in a Schlenk flask under an inert atmosphere. The reaction was stirred until a clear yellow solution was observed,

approximately 4 hours. At this point disulfur dichloride (S_2Cl_2) (0.28 ml, 3.43 mmol) was added at 0 °C and the reaction mixture was allowed to react for 1 hour. The reddish/brown precipitate was washed with numerous portions of diethyl ether and then dried under reduced pressure resulting in the required product.

HRMS-TOF (ESI+) (ASAP): m/z $[M+H]^+$ calcd for $C_{10}H_{11}ON_2S_2$: 240.0312; found: 239.0305

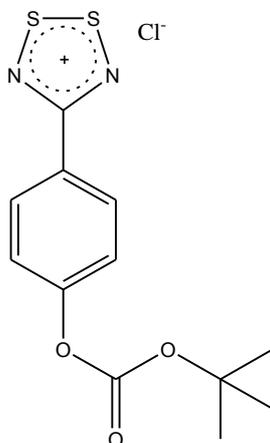
4-propoxy dithiadiazolyl benzene



Reduction of Phenyl-1,2,3,5-dithiadiazolylium chloride salt (180 mg, 0.655 mmol) was achieved under an inert atmosphere in tetrahydrofuran (8.0 ml) by the addition of zinc-copper couple (11.7 mg, 0.182 mmol) to a Schlenk flask. The solution was warmed to 50 °C and allowed to react overnight. The reaction mixture developed a dark purple colour which is indicative of the presence of the desired product. The solvent was removed under reduced pressure leaving behind the product.

EPR (298 K): quintet ($g = 2.00950$) $a_N = 5.203$ G; HRMS-TOF (ESI+) (ASAP): m/z $[M+H]^+$ calcd for $C_{10}H_{11}ON_2S_2$: 240.0391; found: 240.0381

tert-butyl-4-1,2,3,5-dithiadiazolylium chloride-phenylcarbonate



tert-butyl 4-cyanophenyl carbonate (500 mg, 2.28 mmol) was added to a solution of lithium bis(trimethylsilyl)amide (0.53 ml, 2.51 mmol) in diethyl ether (20 ml) in a Schlenk flask under an inert atmosphere. The reaction was stirred until a clear yellow solution was observed, approximately 4 hours. At this point sulfur dichloride (SCl₂) (0.32 ml, 5.02 mmol) was added at 0 °C and the reaction mixture was allowed to react for 1 hour. The reddish/brown precipitate was washed with numerous portions of diethyl ether and then dried under reduced pressure resulting in the required product.

HRMS-TOF (ESI+) (ASAP): *m/z* [M+H]⁺ calcd for C₁₀H₁₁ON₂S₂: 297.0367; found: 297.0386

5.3 Crystal structures

A single crystal was covered in a small amount of paratone oil and mounted on a glass fibre. X-ray intensity data were collected at 100 K on a Bruker SMART APEX CCD with 1.75 kW graphite monochromated Mo radiation. The detector to crystal distance was 60 mm. Data were collected by omega scans. The data were scaled and reduced using the *APEXII* software suite. Unit cell dimensions were refined on all data and the space group was assigned on the basis of systematic absences and intensity statistics. The structure was solved and refined using *SHELX97*.¹⁴ Hydrogen atoms are placed in calculated positions and included in the model during later stages of the refinement. The program *XSEED*,¹⁵ an interface to *SHELX*, was used during the process of refinements and eventual structure solution.

5-cyano -25,26,27,28-tetrapropoxycalix[4]arene, 7

Empirical formula	C ₄₁ H ₄₇ NO ₄	
Formula Weight	617.80	
Temperature (K)	296(2)	
Wavelength (Å)	0.71073	
Crystal system	Monoclinic	
Space group	P2 ₁ /n	
Unit cell dimensions (Å, °)	a = 9.4116(8)	
	b = 18.1780(16)	β = 98.9140(10)
	c = 20.1976(18)	
Volume (Å ³)	3413.8(5)	
Z	4	
Calculated density (g cm ⁻³)	1.202	
Absorption coefficient (mm ⁻¹)	0.080	
F ₀₀₀	1328	
Crystal size (mm ³)	0.44 x 0.15 x 0.15	
θ range for data collection (°)	2.04 to 26.95	
Miller index ranges	-11 < h < 11, -23 < k < 22, -18 < l < 25	
Reflections collected	20005	
Independent reflections	7233 [R _{int} = 0.0270]	
Completeness to θ _{max} (%)	99.8	
Max. and min. transmission	0.9887 and 0.9672	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7233 / 0 / 420	
Goodness-of-fit on F ²	1.034	
Final R indices [I > 2σ(I)]	RI = 0.0422, wR2 = 0.0978	
R indices (all data)	RI = 0.0580, wR2 = 0.1073	
Largest diff. peak and hole (e Å ³)	0.420 and -0.220	

5,11-Dicyano -25,26,27,28-tetrapropoxycalix[4]arene, 8

Empirical formula	C ₄₂ H ₄₆ N ₂ O ₄	
Formula Weight	642.81	
Temperature (K)	100(2)	
Wavelength (Å)	0.71073	
Crystal system	Triclinic	
Space group	<i>P</i> -1	
Unit cell dimensions (Å, °)	a = 9.544(2)	α = 92.432(4)
	b = 12.020(3)	β = 105.926(3)
	c = 17.291(5)	γ = 108.330(3)
Volume (Å ³)	1792.6(8)	
Z	2	
Calculated density (g cm ⁻³)	1.191	
Absorption coefficient (mm ⁻¹)	0.080	
F ₀₀₀	688	
Crystal size (mm ³)	0.36 x 0.34 x 0.13	
θ range for data collection (°)	1.80 to 27.96	
Miller index ranges	-12 < h < 12, -15 < k < 15, -21 < l < 22	
Reflections collected	20195	
Independent reflections	7782 [R _{int} = 0.0257]	
Completeness to θ _{max} (%)	99.4	
Max. and min. transmission	0.9902 and 0.9732	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7782 / 1 / 458	
Goodness-of-fit on F ²	0.992	
Final R indices [I > 2σ(I)]	R1 = 0.0412, wR2 = 0.0974	
R indices (all data)	R1 = 0.0574, wR2 = 0.1079	
Largest diff. peak and hole (e Å ⁻³)	0.281 and -0.258	

5,11,17,23-Tetracyano -25,26,27,28-tetrapropoxycalix[4]arene, 9

Empirical formula	C ₄₄ H ₄₄ N ₄ O ₄	
Formula Weight	692.83	
Temperature (K)	100(2)	
Wavelength (Å)	0.71073	
Crystal system	Monoclinic	
Space group	P2 ₁ /n	
Unit cell dimensions (Å, °)	a = 12.8225(19)	
	b = 16.649(2)	β = 96.867(2)
	c = 17.559(3)	
Volume (Å ³)	3721.6(9)	
Z	4	
Calculated density (g cm ⁻³)	1.237	
Absorption coefficient (mm ⁻¹)	0.080	
F ₀₀₀	1472	
Crystal size (mm ³)	0.22 × 0.16 × 0.10	
θ range for data collection (°)	1.69 to 27.92	
Miller index ranges	-16 < h < 16, -19 < k < 21, -22 < l < 18	
Reflections collected	21975	
Independent reflections	8120 [R _{int} = 0.0578]	
Completeness to θ _{max} (%)	99.8	
Max. and min. transmission	0.9827 and 0.9921	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4902 / 0 / 475	
Goodness-of-fit on F ²	1.024	
Final R indices [I > 2σ(I)]	RI = 0.0565, wR2 = 0.1098	
R indices (all data)	RI = 0.1080, wR2 = 0.1320	
Largest diff. peak and hole (e Å ³)	0.400 and -0.406	

tert-butyl-4-cyanophenyl carbonate,¹⁶

Empirical formula	C ₁₂ H ₁₃ N O ₃
Formula Weight	219.23
Temperature (K)	296(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>
Unit cell dimensions (Å, °)	a = 5.7347(7) b = 14.3237(16) β = 101.1100(10) c = 13.7727(16)
Volume (Å ³)	1110.1(2)
Z	4
Calculated density (g cm ⁻³)	1.312
Absorption coefficient (mm ⁻¹)	0.080
F ₀₀₀	464
Crystal size (mm ³)	0.45 x 0.25 x 0.12
θ range for data collection (°)	2.07 to 27.90
Miller index ranges	-7 < h < 7, -18 < k < 14, -17 < l < 15
Reflections collected	2427
Independent reflections	6536 [R _{int} = 0.0165]
Completeness to θ _{max} (%)	99.9
Max. and min. transmission	0.9887 and 0.9586
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2427 / 0 / 148
Goodness-of-fit on F ²	1.048
Final R indices [I > 2σ(I)]	R1 = 0.0342, wR2 = 0.0868
R indices (all data)	R1 = 0.0397, wR2 = 0.0905
Largest diff. peak and hole (e Å ³)	0.306 and -0.230

5.4 References

- (1) Perrin, D. D.; Armarego, W. L. F., *Purification of Laboratory Chemicals. 3rd Ed.* 1988; p 391.
- (2) Vogel, A. I.; Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R., *Vogel's Textbook of Practical Organic Chemistry. 5 ed.*; Longman Scientific & Technical: London, 1989.
- (3) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, (3), 87-88.
- (4) Gutsche, C. D.; Iqbal, M., *Org. Synth.* **1990**, *68*, 234-237.
- (5) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R., *J. Chem. Soc. Chem. Commun.* **1984**, 981-982.
- (6) Ikeda, A.; Yoshimura, M.; Lhotak, P.; Shinkai, S., *J. Chem. Soc. Perkin Trans. 1.* **1996**, 1945-1950.
- (7) Larsen, M.; Jorgensen, M., *J. Org. Chem.* **1996**, *61*, 6651-6655.
- (8) Callen, J. E.; Dornfeld, C. A.; Coleman, G. H., *Org. Synth.* **1948**, *28*, 34-35.
- (9) Casnati, A.; Fochi, M.; Minari, P.; Pochini, A.; Reggiani, M.; Ungaro, R., *Gazz. Chim. Ital.* **1996**, *126*, 99-106.
- (10) Pinkhassik, E.; Sidorov, V.; Stibor, I., *J. Org. Chem.* **1998**, *63*, 9644-9651.
- (11) Chen, Y.; Kong, H.; Chen, L.; Qin, Z.; Zhou, W.; Li, F.; He, X., *Synth. Met.* **2009**, *159*, 2049-2055.
- (12) Arvela, R. K.; Leadbeater, N. E.; Torenus, H. M.; Tye, H., *Org. Biomol. Chem.* **2003**, *1*, 1119-1121.
- (13) Andrieux, C. P.; Farriol, M.; Gallardo, I.; Marquet, J. *J. Chem. Soc. Perkin Trans. 2.* **2002**, 985-990.
- (14) Sheldrick, G. M., *Acta Crystallogr. Sect. A.* **2008**, *A64*, 112-122.
- (15) Barbour, L. J., *J. Supramol. Chem.* **2003**, *1*, 189-191.
- (16) Applewhite, M. J., *Acta Crystallogr. Sect. E.* **2010**, *E66*, o2681.