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                             Dalgarno, Scott; Heriot-Watt University, Institute of Chemical Sciences  
                             Paterson, Martin; Heriot-Watt University, Institute of Chemical Sciences |
Elucidating the Ring Inversion Mechanism(s) for Biscalixarenes

Paul Murphy, Scott J. Dalgarno, Martin J. Paterson*

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ABSTRACT: Biscalix[4]arene can be constructed from a calix[4]arene by substitution of a methylene bridge hydrogen by another equivalent moiety. The use of biscalix[4]arenes (biscal) as precursors for the creation of new polymetallic clusters such as Single-Molecule Magnets has potential in the fields of data storage and other applications. Polymetallic clusters involving biscal are expected to preferentially involve octadentate binding to two metal centres (one metal centre per tetraphenolic pocket), requiring full inversion of one of the annular rings. In this work we use Density Functional Theory to establish the mechanism behind this process, considering the various energy pathways and providing insight into the preferred route to full and partial inversion. Fourteen possible pathways to full inversion are presented, including all transition states (up to seven per pathway). Subsequently, the lowest energy pathway to full inversion was found to have a barrier height of 19.31 kcal mol$^{-1}$. Solvent optimisations using PCM (with and without SMD) and CPCM solvent models suggest long-range solvent effects may be relatively unimportant in the inversion process. This study represents the first use of Density Functional Theory to elucidate the entire potential energy surface, including barrier heights, of the ring inversion process of biscalix[4]arenes.
Keywords: Reaction Mechansims, Density Functional Theory, Polymetallic Clusters, Macrocycles, Calixarenes.

Introduction

Calix[n]arenes\(^1,2\) are macrocyclic oligomers consisting of “n” methylene-bridged phenolic rings, an example of which is shown in Figure 1. The existence of calix[n]arenes was postulated and confirmed between 1941 and 1952 by Zinke\(^3\). Subsequently, a variety of 4-membered ring structures were synthesised, calix[4]arenes, most notably by Bakelite researchers Hayes and Hunter\(^4\) who introduced the idea of using protection groups to direct and control calixarene synthesis. Cornforth\(^5\) confirmed that the Zinke reactions were indeed producing tetramers, thus validating the entire field of calixarene research at the time, while Gutsche\(^6\) discovered the one-step one-pot, base-induced synthesis of \(p\)-tert-butylcalix[4]arene (TBC4), shown in Figure 1. This development eased the synthesis of these species considerably in comparison to the synthetic routes reported by Zinke and Cornforth. Gutsche’s work into the synthesis of calix[4]arenes resulted in an explosion of variations within this basic framework, notably with a wide variety of substitutions at the \textit{para} and phenolic oxygen positions, but also with modification at the methylene bridge\(^7,8,9\).

As can be seen in Figure 1, four stable conformations of TBC4 are possible: cone, partial-cone, 1,2-alternate and 1,3-alternate. Interconversion between these conformers is achieved \textit{via} annular rotation of the phenyl rings where the OH group passes through the TBC[4] sub-unit annulus. The cone conformation is usually the most stable although this can depend on solvent and the nature of the substituents on the phenyl rings\(^7\). Clusters of TBC4 and transition metals and
lanthanides have been shown to form Single-Molecule Magnets displaying a range of magnetic properties with potential for data storage and other applications\textsuperscript{10,11,12}.

![Figure 1. TBC4 and stable conformations](image)

The biscalix[4]arene\textsuperscript{13} (biscal) shown in Figure 2 represents an important addition to the calixarene family, with substitution occurring at one TBC4 methylene bridge to introduce an equivalent moiety. In this work we present a DFT analysis of the mechanism by which biscal undergoes annular inversion of one calixarene ring and is thus transformed from an \textit{anti-} (Figure 2) to \textit{syn-} arrangement (Figure 3).

![Figure 3. DFT analysis of annular inversion](image)
Figure 2. Biscal showing *anti*- arrangement of annular ring

![Biscal showing anti- arrangement of annular ring](image)

Figure 3. Biscalix showing *syn*- conformation of annular rings

![Biscalix showing syn-conformation of annular rings](image)

In order to form polymetallic clusters involving octadentate ligation, via both TBC4 sub-unit lower rims, biscal must undergo a ring inversion of one calix[4]arene moiety. Whilst calculations of the ring inversion energies of TBC4 have been performed using MM techniques\textsuperscript{14,15,16,17}, and although DFT calculations have elucidated the relative stabilities of the various conformers\textsuperscript{18,19}, no in-depth DFT analysis has been performed on the full set of inversion pathways for TBC4. Furthermore, there is no such analysis in the literature that relates to biscal (Figure 2). Here we present a full analysis of the mechanism by which biscal undergoes the transformation from an *anti* - to *syn*- conformation. In presenting this mechanism we elucidate the key intermediate species, transition states, relative stabilities of the stable conformations and the lowest energy pathway to full inversion.
Computational Details

All calculations were performed using Gaussian 09 D.01\textsuperscript{20}. Geometry optimisations for all computed structures were initially performed using the DFT functional B3LYP\textsuperscript{21,22} and using the basis set 6-31G(d,p). The B3LYP functional was chosen as it has achieved widespread success in modelling organic molecules and indeed has been used as a functional in previous computational work involving calixarenes\textsuperscript{18,19}.

Upon geometry optimisation, the 6-31G(d,p) basis set was used to perform single point energy calculations on each structure with thermal correction values being taken from the 6-31G(d,p) results. Further single point calculations were then performed on each structure using the 6-311G(d,p) basis set with GD3BJ empirical dispersion\textsuperscript{23} included, again with thermal correction values being taken from the 6-31G(d,p) results. All energies are quoted as thermally corrected Gibbs energies at 298.15 K. The process of thermal correction uses standard statistical thermodynamics approximations\textsuperscript{30} for the internal thermal energy and entropy corrections for translation (particle in a box), rotation (rigid rotor), vibration (simple harmonic oscillator) and electronic (single isolated ground state) contributions. Zero point corrections are included.

AM1\textsuperscript{24} calculations were attempted in order to determine whether this semi empirical method would give a qualitative reproduction of the potential energy surface for the ring inversion. Success in this respect would indicate potential suitability for either dynamics simulations on this system or for potential future use on larger systems based on biscal. SVWN\textsuperscript{25,26,27} and BP86\textsuperscript{28,29} calculations were also performed on selected parts of the potential energy surface for the purpose of comparing semi-empirical, LSDA, GGA and hybrid GGA methods. All energies are quoted as thermally corrected Gibbs energies at 298K for AM1, SVWN and BP86 calculations as detailed above.
Analysis of analytical Hessian computations confirmed the nature of critical points as either transition states or minima based on the number of negative eigenvalues of the Hessian (1 or 0 respectively).

Intrinsic Reaction Coordinate (IRC) calculations were attempted and found to work well in regions where the potential energy surface was not too flat. In very flat regions however, an alternative strategy was adopted to connect transition states and corresponding minima. In these cases, transition states were linked to optimised minima in both directions, and thus an entire reaction path elucidated, by inducing a small manual displacement from each transition state in both forward and reverse directions and optimising from both of these resultant structures. The subsequently optimised geometries and energies were checked for consistency with the expected minima.

Finally, long range bulk solvent effects were examined via geometry optimisations on selected transition state and intermediate structures using B3LYP/6-31G(d,p) with both PCM\textsuperscript{31} (with and without SMD\textsuperscript{33}) and CPCM\textsuperscript{32} solvent models with both DMF and methanol (solvents routinely used in the synthesis of biscal clusters). PCM solvent models have been validated in numerous studies\textsuperscript{34} and readily allow the calculation of long range bulk solvent effects without having to perform explicit solvation calculations.

The \textit{anti-} biscal structure from Figure 2 was used as the starting point for geometry optimisation with \textit{p}-t-butyl substituents replaced by hydrogens. In all cases, the inversion of the phenyl ring was considered to be a stepwise procedure rather than a fully concerted mechanism involving more than one ring inverting at the same time: previous studies having investigated and discarded concerted inversion mechanisms\textsuperscript{17} as being energetically unfavourable compared to stepwise mechanisms.
Results and Discussion

Geometry optimisations were performed on the anti- biscal structure with AM1, SVWN/6-31G(d,p), BP86/6-31G(d,p) and B3LYP/6-31G(d,p). In the absence of biscal crystal data, TBC4 crystal data\(^35\) was used to compare the methods. AM1 calculations show considerable distortion of both lower rims of biscal – neither of which results in the expected square planar arrangement of the TBC4 crystal structure. All of the DFT functionals show square planar arrangements and all important geometric measurements from the SVWN, BP86 and B3LYP calculations are provided in Table 1 to allow comparison between the various DFT functionals and available TBC4 crystal data.

Table 1. Lower rim calculated results for biscal geometry optimisation using SVWN, BP86 and B3LYP DFT functionals (all use 6-31G(d,p) basis set and all bond lengths are averaged).

<table>
<thead>
<tr>
<th></th>
<th>TBC4 crystal data(^35)</th>
<th>SVWN</th>
<th>BP86</th>
<th>B3LYP</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-O distance (Å)</td>
<td>1.38541</td>
<td>1.3666</td>
<td>1.3905</td>
<td>1.3819</td>
</tr>
<tr>
<td>O-O cis-distance (Å)</td>
<td>2.67043</td>
<td>2.4850</td>
<td>2.6192</td>
<td>2.6732</td>
</tr>
<tr>
<td>O-O trans-distance (Å)</td>
<td>3.77656</td>
<td>3.5144</td>
<td>3.7041</td>
<td>3.7798</td>
</tr>
<tr>
<td>Phenolic C-C cis-distance (Å)</td>
<td>3.72028</td>
<td>3.6359</td>
<td>3.7307</td>
<td>3.7389</td>
</tr>
<tr>
<td>Phenolic C-C trans- distance (Å)</td>
<td>5.26127</td>
<td>5.1412</td>
<td>5.2764</td>
<td>5.2876</td>
</tr>
<tr>
<td>O atom geometric arrangement</td>
<td>sq. planar</td>
<td>sq. planar</td>
<td>sq. planar</td>
<td>sq. planar</td>
</tr>
</tbody>
</table>
As can be seen, SVWN calculations poorly match the crystal data. In particular, SVWN has difficulty with the O-O bond distances showing 6.9% deviation in both cis and trans distance measurements. Measurements of the phenolic C-C distances however are generally better at around 2.2%. The C-O bond length deviation is also under 1.5%. This strongly suggests that the biggest problem for SVWN is in accurately predicting the hydrogen bonding between the phenolic OH groups as expected for an LSDA DFT functional. BP86 calculations at the GGA level of DFT would therefore be expected to lead to improved results in comparison to SVWN and this is clearly seen with 1.9% deviation in the O-O bond distances and around 0.3% for all other bond lengths. B3LYP shows further improvement with O-O bond distance deviation of around 0.1% and excellent agreement of less than 0.5% deviation on all other bond lengths. It should be noted that these calculations were performed with p-t-butyl substituents replaced by hydrogens. The process of ring inversion in biscal is now described using a schematic drawing of biscal as shown in Figure 4.

![Figure 4. Schematic of biscal showing second calix[4]arene as an R group](image)

As can be seen, the second calix[4]arene can be described as a methylene substituent R and the remaining calixarene can be considered in isolation as regards ring inversion. By convention the
calix[4]arene undergoing ring inversion is the left hand calixarene of Figure 5 with the R substituent forming the right hand calixarene. It is clear that the four phenyl rings making up the calix[4]arene undergoing inversion are not equal. There are four phenyl rings to select from as regards which one inverts first. After this point there are three remaining options for which phenyl ring inverts second and so on. This gives rise to 4! or 24 permutations for the conversion from the anti- biscal shown in Figure 2 to the syn- biscal shown in Figure 3. Consideration of the system symmetry aids in reducing the number of permutations, and thus transition states. For example, inverting phenyl ring A first will be identical to inverting phenyl ring D first. Equally inverting phenyl ring B first will be identical to inverting ring C first. Therefore immediately it can be seen that all of the permutations involving phenyl rings C and D inverting first can be discarded as duplicates.

Further permutations can be discarded by considering matched paths. Matched paths can be understood by considering what happens when both phenyl rings A and then B have been inverted. Inverting phenyl ring A and then phenyl ring B is a matched path of inverting phenyl ring B followed by phenyl ring A and only one of these needs to be considered within the context of finding the transition state when, for example, phenyl ring C is inverted third. Eliminating matched paths such as this reduces the problem to fourteen full inversion pathways requiring elucidation.

Within this report, the convention for naming the inversion pathways are as follows: starting with the anti- biscal shown in Figure 5 (called start), one possible inversion pathway could involve initially inverting phenyl ring A via transition state A_TS leading to intermediate A_prod. Subsequent inversion of phenyl ring C could occur via transition state AC_TS leading to intermediate AC_prod. This could then be followed by inversion phenyl ring D via transition
state ACD_TS and subsequent intermediate ACD_prod and finally phenyl ring B to obtain the syn- biscal shown in Figure 6 via transition state ACDB_TS. This pathway is named ACDB and is shown in Figure 7 where Figure 7(a) shows the energy values associated with the use of B3LYP/6-31G(d,p), Figure 7(b) shows the energy values associated with the use of B3LYP/6-311G(d,p) and Figure 7(c) shows the energy values associated with the use of B3LYP/6-311G(d,p) with corrections added for GD3BJ Empirical Dispersion. Partial inversion pathways are similarly named - for example to obtain the 1,3-alternate structure AC_prod by the above method, this partial pathway would be called AC and so on. In this way we differentiate between the inversion pathway and the intermediates and transition states of which that pathway is constructed.

**Figure 5.** Calculated anti- biscal structure. H atoms have been removed for clarity (oxygen atoms are shown in red)

**Figure 6.** Calculated syn- biscal structure. H atoms have been removed for clarity (oxygen atoms are shown in red)
Figure 7. **ACDB** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol\(^{-1}\).

Comparison of selected calculated structures was made between AM1 and SVWN, BP86 and B3LYP functionals (using the 6-31G(d,p) basis set) using B3LYP/6-311G(d,p)/GD3BJ empirical dispersion calculation as the benchmark to show the effect of using improved functionals and basis sets. The **BD** and **BDC** barriers are presented as examples here (see Figure 8 and Figure 9 where Figure 8(a) and Figure 9(a) show the energy values associated with the use of B3LYP/6-31G(d,p), Figure 8(b) and Figure 9(b) show the energy values associated with the use of B3LYP/6-311G(d,p) and Figure 8(c) and Figure 9(c) show the energy values associated with the use of B3LYP/6-311G(d,p) with corrections added for GD3BJ Empirical Dispersion) with the structures of **B_prod**, **BD_TS**, **BD_prod**, **BDC_TS** and **BCD_prod** shown in Figure 10 and Figure 11. The energy barriers for **BD** and **BDC** are shown in Table 2.
Table 2. Comparison of semi-empirical and DFT calculations of selected activation barriers (6-31G(d,p) basis set for DFT functionals unless mentioned - all values kcal mol\(^{-1}\) and are referenced from the energy of the anti- structure, named start, shown in Figure 10)

<table>
<thead>
<tr>
<th></th>
<th>AM1</th>
<th>SVWN</th>
<th>BP86</th>
<th>B3LYP</th>
<th>B3LYP/6-311G(d,p)</th>
<th>B3LYP/6-31G(d,p) and GD3BJ empirical dispersion</th>
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</thead>
<tbody>
<tr>
<td><strong>B_prod</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>energy</td>
<td>5.62</td>
<td>14.75</td>
<td>9.03</td>
<td>8.49</td>
<td>7.87</td>
<td>6.93</td>
</tr>
<tr>
<td><strong>BD_TS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>energy</td>
<td>21.30</td>
<td>41.20</td>
<td>34.11</td>
<td>34.07</td>
<td>33.10</td>
<td>30.63</td>
</tr>
<tr>
<td><strong>BD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>activation</td>
<td>15.68</td>
<td>26.45</td>
<td>25.08</td>
<td>25.58</td>
<td>25.23</td>
<td>23.70</td>
</tr>
<tr>
<td>barrier</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BD_prod</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>energy</td>
<td>10.82</td>
<td>24.60</td>
<td>16.37</td>
<td>16.03</td>
<td>14.83</td>
<td>12.58</td>
</tr>
<tr>
<td><strong>BDC_TS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>energy</td>
<td>17.60</td>
<td>33.39</td>
<td>26.01</td>
<td>25.55</td>
<td>23.83</td>
<td>22.14</td>
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<tr>
<td><strong>BDC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>activation</td>
<td>6.78</td>
<td>8.79</td>
<td>9.64</td>
<td>9.52</td>
<td>9.00</td>
<td>9.56</td>
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<td>barrier</td>
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</table>

As can be seen, AM1 results are substantially different for both BD and BDC barriers and appear to substantially under estimate the inversion energy compared to the B3LYP/6-31G(d,p)/GD3BJ dispersion results. Of the DFT functionals, SVWN shows greatest deviation particularly with the BD barrier results. To reach BD_TS from B_prod, the D phenyl ring must be inverted. This requires the breaking of two hydrogen bonds. It would therefore seem
reasonable that functionals which did not contain appropriate dispersion corrections would deviate from those which did. In this case, all DFT functionals show deviation from the B3LYP/6-311G(d,p)/GD3BJ dispersion result although DFT results were considerably more precise than AM1. The BDC activation energy on the other hand involved inversion of the C phenyl ring which had no neighbouring hydrogen bonds left to break. Unsurprisingly, lower activation energies are observed and the deviation of other DFT functionals with B3LYP/6-311G(d,p)/GD3BJ dispersion is much reduced as dispersion becomes less important for this ring inversion. These results indicate the care required when choosing DFT functionals to make calculations of this nature when hydrogen bond breaking is present.

The stability levels of each of the conformations paco, 1,2-alternate and 1,3-alternate conformations are shown in Table 3. There are two possible paco conformations, B_prod and A_prod, (see Figure 10 and Figure 12) which are found to be 8.70 and 6.93 kcal mol\(^{-1}\) for B3LYP/6-311G(d,p)/GD3BJ dispersion respectively. As expected, B_prod is a more stable species than A_prod as a result of higher steric hindrance between the upper rim of the inverted phenyl ring A with the upper rim of the second calixarene moiety. Increasing the basis set unsurprisingly lowers the overall energy with the addition of GD3BJ dispersion allowing a better description of the hydrogen bonding present in the system. It is therefore the B3LYP/6-311G(d,p)/GD3BJ dispersion results which are described in the rest of this work.
Table 3. Calculated energies of major stable intermediates – paco, 1,2-alternate and 1,3-alternate. (All energies in kcal mol\(^{-1}\) and are quoted relative to the anti- biscal start structure)

<table>
<thead>
<tr>
<th>Structure</th>
<th>B3LYP 6-31G(d,p)</th>
<th>B3LYP 6-311G(d,p)</th>
<th>B3LYP 6-311G(d,p) and dispersion</th>
<th>Barrier to conformer B3LYP 6-311G(d,p)/GD3BJ dispersion</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti- biscal (start)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>paco 1 (A_prod)</td>
<td>10.96</td>
<td>10.33</td>
<td>8.70</td>
<td>20.78</td>
</tr>
<tr>
<td>paco 2 (B_prod)</td>
<td>8.49</td>
<td>7.87</td>
<td>6.93</td>
<td>15.84</td>
</tr>
<tr>
<td>1,2-alternate 1 (AB_2_prod)</td>
<td>15.83</td>
<td>15.06</td>
<td>13.43</td>
<td>20.78</td>
</tr>
<tr>
<td>1,2-alternate 2 (AD_3_prod)</td>
<td>13.84</td>
<td>13.02</td>
<td>12.00</td>
<td>20.78</td>
</tr>
<tr>
<td>1,2-alternate 3 (BC_3_prod)</td>
<td>10.66</td>
<td>9.82</td>
<td>9.23</td>
<td>15.84</td>
</tr>
<tr>
<td>1,3-alternate 1 (AC_prod)</td>
<td>16.07</td>
<td>14.87</td>
<td>12.62</td>
<td>21.72</td>
</tr>
<tr>
<td>1,3-alternate 2 (BD_prod)</td>
<td>16.03</td>
<td>14.83</td>
<td>12.58</td>
<td>30.63</td>
</tr>
<tr>
<td>syn- biscal (end)</td>
<td>3.46</td>
<td>3.98</td>
<td>3.81</td>
<td>19.31</td>
</tr>
</tbody>
</table>

The energy barrier to the two paco structures, A_prod and B_prod, was found to be 20.78 and 15.84 kcal mol\(^{-1}\) respectively, represented by A_TS and B_TS (Figure 10 and Figure 12). Both paco routes involve the inversion of either ring A or B, requiring the breaking of two hydrogen bonds and the overcoming of angle strain around the methylene bridges of the inverting phenyl rings. However, because the route to inversion of phenyl ring A requires the additional penalty of overcoming steric hindrance with the second calixarene, the formation of paco variant B_prod experiences a lower energy barrier. Because B_prod is also more stable thermodynamically than A_prod as described above, the B_prod paco variant will subsequently be predicted to be the more prevalent form as a result of both thermodynamic and kinetic considerations.
Three possible 1,2-alternate structures exist - AB$_2$\_prod, AD$_3$\_prod and BC$_3$\_prod, (structures shown in Figure 10, Figure 11 and Figure 12) and are shown to have stabilization energies of 13.43, 12.00 and 9.23 kcal mol$^{-1}$ respectively. BC$_3$\_prod involves inverting two phenyl rings which are furthest away from the second calixarene and therefore this would be expected to be the most stable 1,2-alternate conformer. AB$_2$\_prod shows phenyl ring D encroaching on the second calixarene at an angle which brings the hydrogens of ring D close to the second calixarene. AD$_3$\_prod inverts both phenyl rings A and D and does not have this problem. Therefore AB$_2$\_prod is the least stable 1,2-alternate conformer. The barriers to the three 1,2-alternate structures AB$_2$\_prod, AD$_3$\_prod and BC$_3$\_prod, are 20.78, 20.78 and 15.84 kcal mol$^{-1}$ respectively. The reason for this is that the rate determining step for the attainment of 1,2-alternate conformers is the initial phenyl ring inversion which will be A or B as this represents the largest number of hydrogen bonds requiring breaking. The most favoured 1,2-alternate form is therefore predicted to be BC$_3$\_prod on both thermodynamic and kinetic grounds as explained above. Although AB$_2$\_prod and AD$_3$\_prod forms are equally kinetically accessible, as indicated above, thermodynamically AD$_3$\_prod was found to be more stable for reasons described above and we therefore predict that AB$_2$\_prod will be the least favoured form on both thermodynamic and kinetic grounds.

Two 1,3-alternate conformers, BD$_\text{prod}$ and AC$_\text{prod}$ (as shown in Figure 11 and Figure 12), are seen to have almost identical stabilisation energies of 12.62 and 12.58 kcal mol$^{-1}$ respectively. This is to be expected as both are considered matched paths of each other by symmetry hence validating our argument above of omitting matched path duplicates. The
barriers to the two 1,3-alternate structures, \textbf{AC\textsubscript{prod}} and \textbf{BD\textsubscript{prod}}, are 21.72 and 30.63 kcal mol\textsuperscript{-1} respectively. Because both 1,3-alternate structures, \textbf{AC\textsubscript{prod}} and \textbf{BD\textsubscript{prod}} have the same energy, as explained above, it is \textbf{AC\textsubscript{prod}} which is expected to be the most prevalent form, driven by kinetic considerations.

Finally, the fully inverted \textit{syn}-biscal conformation shown as structure \textbf{end} in Figure 6 and Figure 10, shows a stabilisation energy of 3.81 kcal mol\textsuperscript{-1} which reveals that the \textit{syn}-conformation is only slightly less stable thermodynamically than the \textit{anti}-conformer. The \textit{syn}-conformer is therefore predicted to be the most stable species which can bind in a multidentate fashion to the same metal atom and from a purely thermodynamic argument it could be predicted that most cluster structures will display this double cone feature. It should however be stated that the 1,2-alternate and 1,3-alternate structures are also relatively stable with respect to the \textit{anti}-conformer and it is expected that clusters containing these conformations of biscal will be possible. Of course the thermodynamic picture must be supplemented with elucidation of the barrier to all of these conformations. Only at that point can useful predictions be made about which biscal structure is likely to be most prevalent in crystal clusters.

The lowest energy pathway to full ring inversion was discovered to be \textbf{BADC} with energy barriers of 22.36, 21.64 and 19.31 kcal mol\textsuperscript{-1} for B3LYP/6-31G(d,p), B3LYP/6-311G(d,p) and B3LYP/6-311G(d,p) with GD3BJ empirical dispersion respectively. The transition state diagram for this pathway is shown in Figure 13 where Figure 13(a) shows the energy values associated with the use of B3LYP/6-31G(d,p), Figure 13(b) shows the energy values associated with the use of B3LYP/6-311G(d,p) and Figure 13(c) shows the energy values associated with the use of
B3LYP/6-31G(d,p) with corrections added for GD3BJ Empirical Dispersion. The mechanism detailing the transition states and intermediates is provided in Figure 10.

Figure 8. **BDAC** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol⁻¹.
Figure 9. **BDCA** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol\(^{-1}\).
Figure 10. Inversion mechanism for lowest energy pathway – BADC showing key structures
Figure 11. Key structures during biscal annular ring inversion
Figure 12. Key structures during biscal annular ring inversion (continued)
Figure 13. BADC inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol\(^{-1}\).

Working through the mechanism for the BADC pathway it can be seen that the start structure displays methylene bridge angles of 114° with the exception of 110° at the bridge to the second calixarene. Both calix[4]arenes are seen to be adopting a stable position where they are sitting on the same plane anti- to each other. On rotation of phenyl ring B, transition state B_Ts is seen to introduce both hydrogen bond breaking and a significant increase in angle strain at B-A and B-C methylene bridges over 120.9° and 123.5° respectively. The energy barrier of 15.84 kcal mol\(^{-1}\) is too great to be accounted for solely due to the hydrogen bonds breaking and so it is concluded that the barrier to rotation here is equally as a result of methylene bridge angle strain on either side of the rotating phenyl ring. Interestingly, the appearance of a single transition state suggests hydrogen bond breaking and angle strain increase is a concerted process with no intermediate identified to separate the two processes. B_prod shows that both methylene bridges are still
experiencing angle strain but it is considerably relieved in both cases. An energy stabilisation to 6.93 kcal mol\(^{-1}\) is found. \textbf{B\_prod} is as described above, one of the two possible \textit{paco} structures. Having fully inverted ring B, ring A is then inverted. The transition state \textbf{BA\_TS}, is reached at 16.07 kcal mol\(^{-1}\). This transition state is caused by hydrogen bond breaking between the phenolic oxygen atoms of A and D and also an increase in angle strain across the methylene bridges between A and B and also between B and C. This increase in strain is smaller than that experienced for the \textbf{B\_TS} structure and hence this barrier is smaller than that experienced for the inversion of B. Again, hydrogen bond breaking and angle strain increase appears to be a concerted process rather than stepwise.

\textbf{BA\_prod} shows relief of the angle strain across the A-B methylene bridge to 115.7\(^{\circ}\). This is a small reduction in angle strain and results in a very small energetic stabilisation to 14.59 kcal mol\(^{-1}\).

Further rotation of the phenyl ring A results in further stabilisation of angle strain between A and B but crucially causes a deviation of dihedral angle between the calixarene moieties from 180\(^{\circ}\) (for the \textit{anti-} conformer) to 163.2\(^{\circ}\). This small change in dihedral angle causes the two calixarene moieties to come too close to each other resulting in a low barrier transition state at 17.43 kcal mol\(^{-1}\) (\textbf{BA\_2\_TS}).

At \textbf{AB\_2\_prod}, the dihedral angle between the calixarenes has been restored to around 180\(^{\circ}\). The angle strain has decreased again between A and B, between C and D and also at the bridge to the second calixarene with an additional restoration of the hydrogen bonding between phenyl rings A and B. However there is an increase in angle strain around the B-C rings which cancels some of the energy stabilisation. Net stabilisation of energy to 13.42 kcal mol\(^{-1}\) (\textbf{AB\_2\_prod}) is observed. Note that \textbf{AB} and \textbf{BA} are matched paths and therefore \textbf{BA\_2\_prod} is the same as
**AB_2_prod** and only the latter label is used for both pathways. At this stage, both A and B rings are fully inverted and the **AB_2_prod** structure is one of the three 1,2-alternate conformers. Some sign of the rotating calixarene coming out of the plane of the second calixarene is observed.

Inverting ring D next results in a significant deviation of the dihedral angle between the calix moieties to 145.1° and an increase in angle strain at the methylene bridge between A and D to 117.6°. This is on top of the breaking of the hydrogen bond between D and C. This results in the **ABD_TS** transition state at 18.98 kcal mol⁻¹. The rotating calixarene is now seen to be coming significantly out of the plane of the second calixarene.

Further rotation of ring D relieves the angle strain at the A-D bridge and also recovers the dihedral angle deviation somewhat. Although there is a concomittant increase in angle strain at the D-C bridge to 119.2°, the overall effect is a net stabilisation to 13.87 kcal mol⁻¹ (**ABD_prod**). At this point, the rotating calixarene structure is almost perpendicular to the second calixarene, settling somewhere around 110°, as expected, to ensure minimal torsion between the calixarenes and minimal ring strain at the A-D methylene bridge.

Further rotation of D results in a small increased angle strain at the D-C bridge to 121.7° resulting in a transition state at 15.94 kcal mol⁻¹ (**ABD_2_TS**). Beyond the transition state, there is relief of the C-D and B-C angle strain along with an increase in the angle at the A-D bridge and restoration of the hydrogen bonding between phenyl rings A and D. The net effect is an energy stabilisation to 9.69 kcal mol⁻¹ (**ABD_2_prod**).

The final inversion involves rotation of the C ring. Although this results in relief of the A-D bridge angle strain to 111.6°, a concomittant large increase in angle strain of the B-C and D-C
bridges to 121.6° and 123.6° respectively results in a transition state at 19.31 kcal mol⁻¹ (ABDC_TS).

Finally, further rotation of C sees the angle strains at B-C and D-C bridges relieved to 113.7° and 114.2° respectively and the full restoration of all four hydrogen bonds between the phenyl rings, resulting in a energy stabilisation to 3.81 kcal mol⁻¹. This structure is the syn- conformer, called end, and is of slightly higher energy than the anti- conformer, or start structure, due to the rotated calixarene occupying a position almost at 90° out of the plane of the second calixarene. This distortion from the plane is necessary to prevent untenable angle strain around the D-A methylene bridge which connects the two calixarene moieties. The result is a structure where the OH atoms from both calixarene moieties come very close together in a "clam"-like geometry which forms a pocket for the binding of metal atoms. In this way, the initial inversion of biscal is complete allowing subsequent formation of polymetallic clusters.

Although ABDC_TS is the highest energy point on the ABDC pathway and therefore represents the overall energy barrier for this pathway, the rotation of the C ring to get to this point on the surface is not the rate determining step. As seen, it requires just 9.62 kcal mol⁻¹ from the previous intermediate structure ABD_2_prod. Instead the rate determining step is that required to fully invert the B ring at the start to attain the B_TS structure. As explained earlier, this is because of the combination of breaking two hydrogen bonds and having to overcome angle strain deviations of 11.5° on the B-C bridge in one concerted mechanistic step.

All other full ring inversion pathways are detailed in Figure 14 to Figure 23 where, for each figure, (a) shows the energy values associated with the use of B3LYP/6-31G(d,p), (b) shows the energy values associated with the use of B3LYP/6-311G(d,p) and (c) shows the energy values
associated with the use of B3LYP/6-311G(d,p) with corrections added for GD3BJ Empirical Dispersion. Full structures of all intermediate and transition states shown in Figure 10, Figure 11 and Figure 12.

Figure 14. ABCD Path 1 inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol\(^{-1}\).
Figure 15. **ABCD Path 2** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol\(^{-1}\).

Figure 16. **ABDC** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol\(^{-1}\).
Figure 17. **ACBD** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol\textsuperscript{-1}.
Figure 18. **ADBC** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol\(^{-1}\).

Figure 19. **ADCB** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol\(^{-1}\).
Figure 20. **BACD** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol$^{-1}$. 
Figure 21. **BCAD** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol$^{-1}$.

Figure 22. **BCDA Path 1** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol$^{-1}$. 
Figure 23. **BCDA Path 2** inversion pathway. (a) B3LYP/6-31G(d,p) (black). (b) B3LYP/6-311G(d,p) (red). (c) B3LYP/6-311G(d,p) and GD3BJ Empirical Dispersion (blue). Energy values in kcal mol$^{-1}$.

All pathways which begin by rotation of the A ring are seen to have this initial rotation as the rate determining step. Indeed, with the exception of pathways **BCDA Path 2**, **BDAC** and **BDCA**, which experience the rotation of ring D as the rate determining step, this is also true of pathways with an initial rotation of the B ring. Energy barriers and rate determining step details are provided in Table 4. That pathways **BDCA** and **BDAC** experience the inversion of D as the rate determining step should not be a surprise. The rotation of ring D after ring B is made energetically more difficult by the fact that D is engaged in two hydrogen bonds and needs to overcome the angle strain and steric hindrance from the second calixarene. For both **BDAC** and **BDCA**, this rate determining step is also responsible for the highest energy transition state -
BD_TS, with the product from this barrier being BD_prod - one of the two 1,3-alternate conformers.

Table 4. Pathway rate determining step and barrier energies (B3LYP/6-311G(d,p)/GD3BJ dispersion and energies in kcal mol\(^{-1}\))

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Overall Barrier</th>
<th>Inversion</th>
<th>Rate Determining Step</th>
<th>Rate Determining Step Barrier</th>
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</thead>
<tbody>
<tr>
<td>ABCD Path 1</td>
<td>21.58</td>
<td>Inversion of ring A</td>
<td>20.78</td>
<td></td>
</tr>
<tr>
<td>ABCD Path 2</td>
<td>21.58</td>
<td>Inversion of ring A</td>
<td>20.78</td>
<td></td>
</tr>
<tr>
<td>ABDC</td>
<td>20.78</td>
<td>Inversion of ring A</td>
<td>20.78</td>
<td></td>
</tr>
<tr>
<td>ACBD</td>
<td>21.72</td>
<td>Inversion of ring A</td>
<td>20.78</td>
<td></td>
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<tr>
<td>ACDB</td>
<td>25.26</td>
<td>Inversion of ring A</td>
<td>20.78</td>
<td></td>
</tr>
<tr>
<td>ADBC</td>
<td>20.78</td>
<td>Inversion of ring A</td>
<td>20.78</td>
<td></td>
</tr>
<tr>
<td>ADCB</td>
<td>20.78</td>
<td>Inversion of ring A</td>
<td>20.78</td>
<td></td>
</tr>
<tr>
<td>BACD</td>
<td>25.50</td>
<td>Inversion of ring B</td>
<td>15.84</td>
<td></td>
</tr>
<tr>
<td>BADC</td>
<td>19.31</td>
<td>Inversion of ring B</td>
<td>15.84</td>
<td></td>
</tr>
<tr>
<td>BCAD</td>
<td>21.58</td>
<td>Inversion of ring B</td>
<td>15.84</td>
<td></td>
</tr>
<tr>
<td>BCDA Path 1</td>
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<td>15.84</td>
<td></td>
</tr>
<tr>
<td>BCDA Path 2</td>
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<td>Inversion of ring D</td>
<td>39.11</td>
<td></td>
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<tr>
<td>BDAC</td>
<td>30.63</td>
<td>Inversion of ring D</td>
<td>23.70</td>
<td></td>
</tr>
<tr>
<td>BDCA</td>
<td>30.63</td>
<td>Inversion of ring D</td>
<td>23.70</td>
<td></td>
</tr>
</tbody>
</table>

By far the most inaccessible pathway to full inversion is BCDA Path 2. An RDS of 39.11 kcal mol\(^{-1}\) and an overall barrier of 50.30 kcal mol\(^{-1}\) is experienced via the BCD_2_TS transition state.
structure. As seen, in Figure 11, BCD_2_TS shows a high degree of distortion in the inverting calixarene. In addition to the A-B bridge displaying angle strain at 119.1°, a worse problem exists at the D-C bridge where the angle strain reaches 136.9°. This is because when ring D is inverted, ring C has already been inverted by around 90°. In essence, inverting ring C through to structure BC_prod shows angle strain at 120.7° on the D-C bridge. Inverting ring D at this point adds considerably to that angle strain. This could be considered proof that a concerted ring inversion involving more than one phenyl ring at the same time would simply fail to be of lower energy than a stepwise rotation of one ring at a time on angle strain grounds.

Finally, solvent calculations were performed to investigate long range solvent effects. Geometry optimisations using both PCM31 and conductor CPCM32 solvent models at B3LYP/6-31G(d,p) were used on two separate transition state structures and associated intermediates - A_TS and ABDC_TS. Therefore, the start, A_TS, A_prod, ABD_2_prod, ABDC_TS and end structures were investigated and compared with B3LYP/6-31G(d,p) gas phase calculations. PCM calculations were performed both with and without SMD33. Because biscal complexes are generally synthesised in solvent mixtures of DMF and methanol, both solvents were used. The results for methanol are shown in Table 5 and the results for DMF are shown in Table 6. Gas phase calculations are provided for comparison.

For methanol calculations, all three solvent calculations show some energy stabilisation for the ABDC_TS transition state of around 1-2 kcal mol\(^{-1}\). PCM with SMD and CPCM also show some stabilisation of the ABD_2_prod intermediate of around 0.75 kcal mol\(^{-1}\). CPCM calculations also display around 1 kcal mol\(^{-1}\) of energy stabilisation on the end structure. All other solvent calculations are in agreement with the gas phase calculations.
Table 5. Calculated energies from methanol solvent calculations on a variety of intermediate and transition state structures. (All energies in kcal mol\(^{-1}\) and are quoted relative to the \textit{anti-} biscal \textit{start} structure. All calculations use B3LYP/6-31G(d,p))

<table>
<thead>
<tr>
<th>Structure</th>
<th>Gas Phase</th>
<th>PCM</th>
<th>PCM and SMD</th>
<th>CPCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>start</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A_TS</td>
<td>23.22</td>
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<tr>
<td>A_prod</td>
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<td>11.77</td>
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<td>10.98</td>
<td>11.05</td>
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<tr>
<td>ABDC_TS</td>
<td>20.69</td>
<td>19.90</td>
<td>18.68</td>
<td>19.50</td>
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<tr>
<td>end</td>
<td>3.46</td>
<td>2.98</td>
<td>3.20</td>
<td>2.47</td>
</tr>
</tbody>
</table>

Table 6. Calculated energies from DMF solvent calculations on a variety of intermediate and transition state structures. (All energies in kcal mol\(^{-1}\) and are quoted relative to the \textit{anti-} biscal \textit{start} structure. All calculations use B3LYP/6-31G(d,p))

<table>
<thead>
<tr>
<th>Structure</th>
<th>Gas Phase</th>
<th>PCM</th>
<th>PCM and SMD</th>
<th>CPCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>start</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A_TS</td>
<td>23.22</td>
<td>23.48</td>
<td>23.39</td>
<td>23.19</td>
</tr>
<tr>
<td>A_prod</td>
<td>10.96</td>
<td>10.73</td>
<td>10.81</td>
<td>10.55</td>
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<tr>
<td>ABD_2_prod</td>
<td>11.77</td>
<td>11.41</td>
<td>10.99</td>
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<tr>
<td>ABDC_TS</td>
<td>20.69</td>
<td>19.85</td>
<td>19.48</td>
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</tr>
<tr>
<td>end</td>
<td>3.46</td>
<td>2.91</td>
<td>3.28</td>
<td>2.46</td>
</tr>
</tbody>
</table>
For DMF calculations an almost identical pattern is observed with comparable results with methanol. The result for PCM with SMD however does show closer agreement with the gas phase calculation for the ABDC_TS structure showing a stabilisation of 1 kcal mol\(^{-1}\) compared to almost 2 kcal mol\(^{-1}\) for methanol.

The solvent stabilisation effects seen are fairly minor and suggest that long range solvent effects are not important for ring inversion.

**Summary and Conclusions**

In summary, pathway BADC appears to be the global minimum pathway with an energy barrier of 19.31 kcal mol\(^{-1}\) and a rate determining step of inversion of ring B (15.84 kcal mol\(^{-1}\) barrier). All of the other inversion pathways however are easily attainable, with the exception of pathway BCDA Path 2, BDAC and BCDA with all pathways showing some very low barriers between intermediate steps. In light of this it is not surprising to find rapid interconversion between the various conformations of biscal. The exceptions to this - pathways BCDA Path 2, BDAC and BDAC were analysed and found to contain particularly high angle strain problems resulting in their higher energy barriers. BDCD and BDAC were shown to be energetically problematic on inversion of ring D with BCDA Path 2 experiencing severe angle strain as a result of attempting to invert both rings C and D effectively at the same time. The syn- conformer was found to be just 3.81 kcal mol\(^{-1}\) above the energy for the anti- conformer suggesting a very thermodynamically stable syn- conformer.

Other than the syn- structure, various other common and stable conformers paco, 1,2-alternate and 1,3-alternate structures were identified and their stability determined. The most
A thermodynamically stable and kinetically accessible paco conformer was predicted to be \textbf{B\textsubscript{prod}} with a barrier of 15.84 kcal mol\textsuperscript{-1} and a stability of 6.93 kcal mol\textsuperscript{-1}. In a similar way, \textbf{AD\textsubscript{3\_prod}} was predicted to be the most stable and accessible 1,2-alternate conformer with a barrier of 20.78 kcal mol\textsuperscript{-1} and a stability of 12.00 kcal mol\textsuperscript{-1}. Finally, the 1,3-alternate conformer predicted to be the most stable and accessible was \textbf{AC\textsubscript{prod}} with a barrier of 21.72 kcal mol\textsuperscript{-1} and a stability of 12.58 kcal mol\textsuperscript{-1}.

Although most barriers are above the thermally averaged 0.5 kcal mol\textsuperscript{-1} expected to be required for accessibility at room temperature, in fact as explained earlier\textsuperscript{7}, it is expected that biscal rings will readily interconvert between various conformers as for calix[4]arene. As such, it is perhaps not surprising to find that room temperature crystallisation of metal complexes is challenging, as stable conformations are required. Large combinatorial matrices can be required, which are often expensive in terms of both effort and materials. Successful nucleation can be affected by movement of the molecules involved in the crystallisation and it may be that the rapid inversion property of the calixarenes is a barrier to this. It might be useful therefore to consider attempting crystallisations at temperatures below which the calixarene is known to maintain a single conformation. Consideration could then be given to techniques for forcing biscal to adopt a particular conformation at a temperature low enough to then prevent further ring inversion. Variable temperature NMR experiments on biscal would be required in order to determine what that temperature might be for biscal.

It is also evident from a synthetic point of view, that because paco, 1,2-alternate and 1,3-alternate conformations are readily accessible biscal conformations, clusters involving biscal conformations other than the double cone (\textbf{end} structure) could be readily achievable simply by varying the amount of base used to deprotonate the biscal lower rim hydroxyl groups. For
example, a base to biscal stoichiometric ratio of 8:1 would be recommended for clusters involving the double cone conformation whilst ratios of 1:1 to 7:1 would be required for other cluster structures. In this way base could be used to control cluster synthesis with our calculations predicting that all common cluster conformations could be achieved thermodynamically, including non-cone conformations appearing simultaneously on both calixarene moieties.

Finally, solvent optimisation calculations were performed for both methanol and DMF using PCM (with and without SMD) and CPCM solvent models on selected transition states and intermediates. No significant energy differences were found in comparison to gas phase calculations with solvent calculations showing slight energy stabilisation in most cases. This would suggest that long-range solvent effects have minimal impact on the inversion mechanism.

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Table of Contents Graphic

Mechanism?
Inversion Energy?

anti-biscalixarene syn-biscalixarene