Combined NMR spectroscopy and molecular mechanics studies on the stable structures of calix[*n*]arenes

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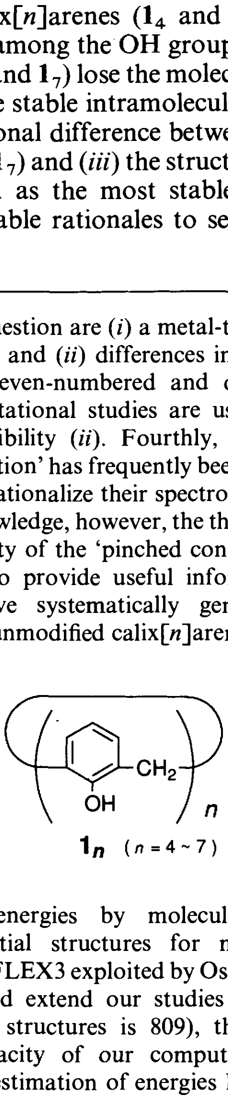
All possible conformations of unmodified calix[*n*]arenes ($\mathbf{1}_n$: n = 4–7) were systematically generated by CONFLEX3 using corresponding model compounds $\mathbf{2}_n$: the numbers of the trial conformations and the final conformations are 110 and 5 for $\mathbf{2}_4$, 645 and 23 for $\mathbf{2}_5$, 4438 and 133 for $\mathbf{2}_6$ and 31620 and 809 for $\mathbf{2}_7$. These initial structures for $\mathbf{1}_n$ were optimized by MM3(92): the numbers of the energy minima are 4 for $\mathbf{1}_4$, 10 for $\mathbf{1}_5$, 90 for $\mathbf{1}_6$ and 651 for $\mathbf{1}_7$. The most stable structures screened out of these conformational isomers were compared with those predicted by ^{1}H NMR spectroscopic studies and with those determined by X-ray crystallographic studies. It was shown that (*i*) the small-ring calix[*n*]arenes ($\mathbf{1}_4$ and $\mathbf{1}_5$) keep the high molecular symmetry because stable intramolecular hydrogen bonds among the OH groups can be formed in the regular cone conformer whereas the large-ring calix[*n*]arenes ($\mathbf{1}_6$ and $\mathbf{1}_7$) lose the molecular symmetry and tend to adopt a 'pinched' conformation because the formation of the stable intramolecular hydrogen bonds inevitably induces ring deformation, (*ii*) there exists no special torsional difference between even-numbered calix[*n*]arenes ($\mathbf{1}_4$ and $\mathbf{1}_6$) and odd-numbered calix[*n*]arenes ($\mathbf{1}_5$ and $\mathbf{1}_7$) and (*iii*) the structures obtained from X-ray analysis and NMR spectroscopic studies can be generated as the most stable structures in the computational studies. The results have enabled us to give reasonable rationales to several controversial problems that have been troubling calixarene chemists.

Computational studies of conformational isomerism in calix[*n*]arenes and their analogues have been of much concern recently.[1–6] This stems from two major interests, *i.e.*, (*i*) the conformational isomerism is closely related to the unique metal and molecular recognition properties of calix[*n*]arenes $\mathbf{1}_n$ and (*ii*) the computational approach is considerably simplified because of the high symmetry. For example, calix[4]arene derivatives actually consist of a 16-membered ring but involve only four stable and significant conformers (cone, partial cone, 1,2-alternate and 1,3-alternate) because of the rigid metacyclophane framework.[7–9] These particular characteristics make the computational approach to the conformational studies extremely simple and reliable. A few but essential observations for unmodified calix[*n*]arenes, however, still remain unexplained. Firstly, it is known that cone conformers of tetra-*O*-alkylcalix[4]arenes adopt C_{2v} symmetry as the most stable conformation and undergo rapid C_{2v}–C_{2v} interconversion which can be observed by ^{1}H NMR spectroscopy at −85 °C.[10] It is uncertain, however, whether unmodified cone-calix[4]arene-25,26,27,28-tetraol also adopts C_2 symmetry.† Secondly, it is known that the ^{1}H NMR spectrum of cone-calix[6]arene-37,38,39,40,41,42-hexaol gives three pairs of doublets for the ArCH$_2$Ar methylene protons in a 1:1:1 integral intensity ratio.[8] This implies that cone-calix[6]arene-37,38,39,40,41,42-hexaol contains three non-equivalent methylene groups. The reasonable structure to explain this symmetry has been found in the crystal state by the X-ray analysis,[11c] but it is not yet sure whether cone-calix[6]arene-37,38,39,40,41,42-hexaol also adopts the similar structure in solution. Thirdly, in calix[*n*]arene syntheses even-numbered calix[*n*]arenes (n = 4, 6 and 8) can be synthesized in good yields whereas odd-numbered calix[*n*]arenes (n = 5 and 7) are obtained in low yields as '*by-products*' of even-numbered calix[*n*]arenes.[8,12] The reason for this is not yet understood. Two possible solutions to this question are (*i*) a metal-template effect on the cyclization process and (*ii*) differences in the thermodynamic stability between even-numbered and odd-numbered calix[*n*]arenes. Computational studies are useful to evaluate the feasibility of possibility (*ii*). Fourthly, the presence of the 'pinched conformation' has frequently been proposed for larger calix[*n*]arenes to rationalize their spectroscopic properties. To the best of our knowledge, however, the theoretical background for the favourability of the 'pinched conformation' has never been presented. To provide useful information about these questions we have systematically generated all possible conformations of unmodified calix[*n*]arenes ($\mathbf{1}_n$: n = 4–7) and estimated their energies by molecular mechanics. For generation of initial structures for molecular mechanics calculations CONFLEX3 exploited by Osawa *et al.*[13] was used. Although we could extend our studies up to $\mathbf{1}_7$ (the total number of initial structures is 809), the application to $\mathbf{1}_8$ exceeded the capacity of our computational system. For optimization and estimation of energies MM3(92),[14] which is known to give the most reliable results for the conformational studies of calix[*n*]arenes,[15] was used.



$\mathbf{1}_n$ (n = 4 ~ 7)

Results and discussion

Computational methods

The primary problem towards the evaluation of stable conformers in flexible molecules is to choose an appropriate method for generating all possible conformations. This choice is a very important factor in managing the evaluation efficiently

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† When the direction of the OH groups is taken into account, $\mathbf{1}_4$ is classified as being of C_2 symmetry.

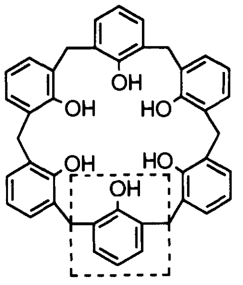
Table 1 Total numbers of initial structures and optimized structures

	Initial structure[a]		Optimized Structure[b]
$\mathbf{1}_n$	Trial conformation	Final conformation	Energy minimum
$n = 4$	110	5	4
$n = 5$	645	23	10
$n = 6$	4 438	133	90
$n = 7$	31 620	809	651

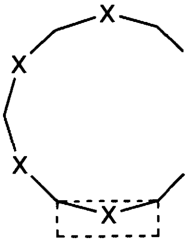
[a] Systematically generated by CONFLEX3 with MM2(77) force field in the first step. [b] Finely optimized by MM3(92) in the third step.

and without mistake. The methods offered so far are classified into two categories, a random search method and a systematic search method.[16] We decided to use CONFLEX3[13] which belongs to the latter category for several positive reasons: (*i*) it is known that this algorithm is very suitable for conformation generation in cycloalkanes because of its exhaustive conformational space search principle in the low energy region where chemically significant conformers exist,[17] (*ii*) as the duplication of the same conformer (the redundancy problem) can be avoided by the original pre-check mechanism, the CONFLEX3 search is fast and efficient (this becomes particularly important in large molecules) and (*iii*) the program includes MM2(77) as an optimizer, which is useful as a pre-treatment process for further refinement with MM3(92).[14]

Previously, we estimated the conformational structures and relative stabilities of calix[4]arene derivatives with MM3(89) and MM3(92) force fields.[15] In the calix[4]arene family, the basic skeleton ([1_4]metacyclophane framework) is rigid and generates only four conformers: cone, partial cone, 1,2-alternate and 1,3-alternate. In the calix[6]arene family, on the other hand, the flexible skeleton can generate a number of conformers. In fact, it is expected that the total number of possible conformers increases exponentially with increasing *n*. To solve this troublesome problem we employed a simplification procedure consisting of the following three steps. In the first step, we regarded $\mathbf{2}_n$ as a simplified skeleton of $\mathbf{1}_n$ and generated all possible conformers for $\mathbf{2}_n$ with CONFLEX3 computations. Here, the atom X in $\mathbf{2}_n$ is an imaginary atom that is originally defined so as to represent the geometric character of a phenyl unit. In $\mathbf{1}_n$, carbon and oxygen atoms in the CH_2–Ar–CH_2 unit lie in approximately the same plane, so that they can be expressed by a single descriptor X as in $\mathbf{2}_n$: hence, the plane formed from C–X–C in $\mathbf{2}_n$ corresponds to the phenyl plane in $\mathbf{1}_n$. We found that this simplification enabled us to manage the following calculations within the capacity of our computer system. All candidate structures were checked to exclude duplicate conformers and then optimized with the MM2(77) force field contained within the program of the CONFLEX3 computation system. All parameters for the atom X used in MM2(77) calculations were set taking those of type 6 (oxygen) atoms into account. We found five stable conformers for $\mathbf{2}_4$, 23 stable conformers for $\mathbf{2}_5$, 133 stable conformers for $\mathbf{2}_6$ and 809 stable conformers for $\mathbf{2}_7$ in the 40 kcal mol^{-1} energy region from the most stable conformer (Table 1).



$\mathbf{1}_6$



$\mathbf{2}_6$

In the second step, the original $\mathbf{1}_n$ structures were reconstructed from selected $\mathbf{2}_n$ using the average bond lengths[18] and the torsional parameters obtained in the previous step. To define the structure of $\mathbf{1}_n$ the dihedral angles of X–C–X–C and C–X–C–X in $\mathbf{2}_n$ were applied to the certain part in the Z-matrix that defines the geometry of all atoms in $\mathbf{1}_n$. After small modifications on the data format with a molecular modelling system (MOL-GRAPH[19]) all initial structures of $\mathbf{1}_n$ were settled for the subsequent refinement with MM3(92). In the third step, energy optimizations with the MM3(92) force field were executed for all structures of $\mathbf{1}_n$ generated through the previous steps. In these calculations all aromatic carbons in the phenyl units were treated as those in a conjugated π-system. The atom type number for phenolic OH hydrogens was set at 73. The search of the energy minima was carried out using a full-matrix Newton–Raphson minimization method, followed by checking of the eigenvalues of each Hessian matrix.

Numbers of initial structures and optimized structures

The total numbers of trial conformations and final conformations for $\mathbf{2}_n$ generated by CONFLEX3 are recorded in Table 1. Extrapolation of the relationship between *n* and these numbers suggests that one has to take *ca.* 220 000 trial conformations and *ca.* 4800 final conformations into account for $\mathbf{2}_8$, which exceeds the practical computational limitation. The numbers of the local minimum structures are 4 for $\mathbf{1}_4$, 10 for $\mathbf{1}_5$, 90 for $\mathbf{1}_6$ and 651 for $\mathbf{1}_7$. The eigenvalues (the number is $3N - 6$ where N is the number of all atoms) obtained by full-matrix Newton–Raphson optimizations are all positive, indicating that these structures are assignable to the locally energy-minimized structures (local minima). On the other hand, some of the transition states which are shown by involvement of one negative eigenvalue and $3N - 7$ positive eigenvalues, were also found.

In Fig. 1, the steric energy differences from the lowest minimum are shown for all optimized structures. It is seen from Fig. 1 that the number of possible conformations is rather limited in $\mathbf{1}_4$ and $\mathbf{1}_5$ and the energy difference among conformers is relatively large. In contrast, the number of possible conformations increases exponentially in $\mathbf{1}_6$ and $\mathbf{1}_7$ and many conformers densely exist in a narrow energy region. The results imply that the parent [1_n]metacyclophane skeleton conspicuously increases the conformational freedom with the increase in *n*. It is also noteworthy that the energy differences between the most stable local minimum (corresponding to the global minimum) and the second stable local minimum are relatively large (2–5 kcal mol^{-1}). This tendency is accounted for by the stabilization effect characteristic of the intramolecular hydrogen bonds: that is, the slight conformational change induces the large damage on the hydrogen bonding interaction. This problem will be discussed later again.

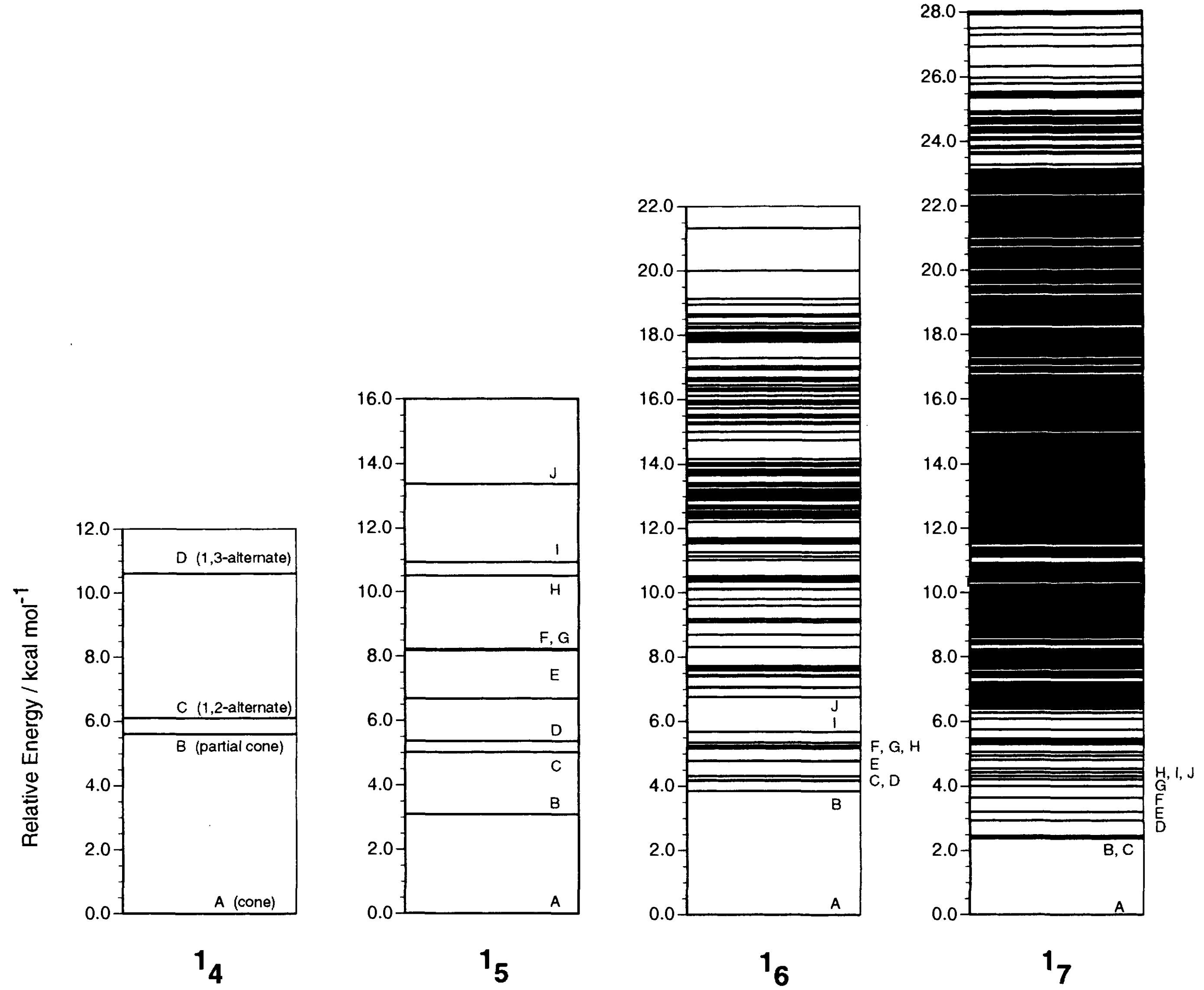


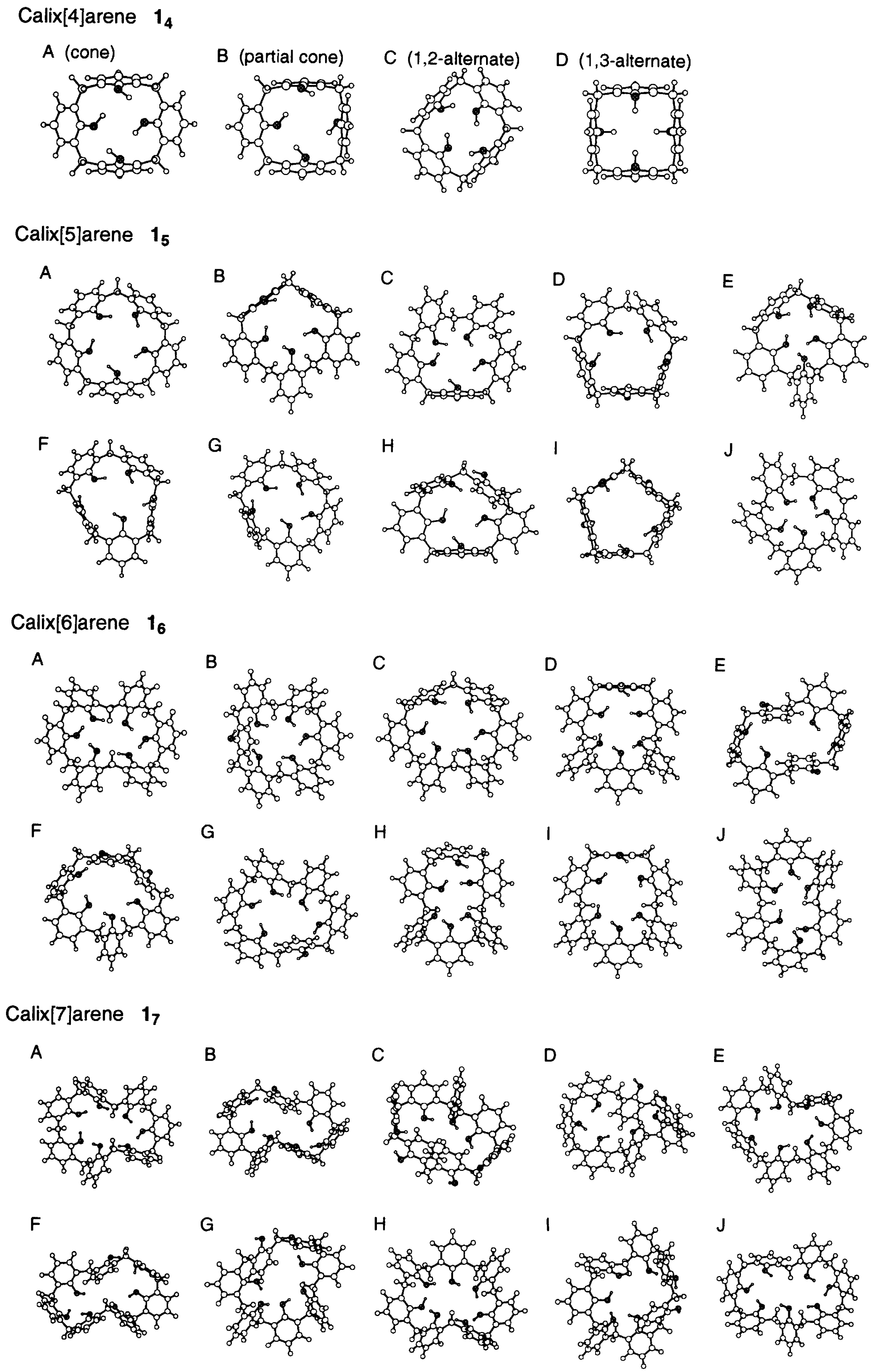
Fig. 1 Steric energy levels of optimized structures for 1_n

Comparison of energy terms which govern the relative stability of optimized structures

In Fig. 2, 4–10 optimized structures from the most stable structure (in the order A, B, C, . . .) for each calix[*n*]arene are shown. In the most stable structures (structure A in Fig. 2) all OH groups form neat hydrogen bonds with neighbouring OH groups with a regular distance and a regular angle. In relatively unstable conformers the intramolecular hydrogen bonds are loosened or partially cleaved, for example, by deformation of the calix[*n*]arene ring and inversion of the phenyl unit. The most stable structures A for 1_4 and 1_5 adopt a cone-shaped trapezium with a smaller lower-rim edge and a larger upper-rim edge whereas those for 1_6 and 1_7 adopt a double-cone pinched conformation. The results indicate that as suggested previously, smaller calix[*n*]arenes tend to adopt a regular cone conformation whereas larger calix[*n*]arenes tend to adopt a pinched conformation.

In 1_4 and 1_5 all bridge-methylene carbons ($ArCH_2Ar$) exist in the same plane for the most stable structures, resulting in a regular cone conformation. In 1_6, in contrast, the plane α composed of four bridge-methylene carbons connecting benzenes a, b and c kept the 74.6° dihedral angle to the plane β composed of four bridge-methylene carbons connecting benzenes d, e and f (Fig. 3). In 1_7 we find three planes α, β and γ, the dihedral angle being 168.0° for α and β and 77.4° for β and γ. When 1_6 and 1_7 are forced to adopt a cone-shaped trapezium as 1_4 and 1_5, the distance between OH groups becomes too long to form the stable intramolecular hydrogen bonds (Fig. 4). These results imply that the ring systems in 1_6 and 1_7 are less symmetrical than those in 1_4 and 1_5 of which the latter pair have bond lengths and bond angles of regular values so that the OH groups can form stable intramolecular hydrogen bonds.

To obtain further insights into the stabilization factors we compared energy terms for the most stable structures A with those for the regular C_n-symmetrical structures (Table 2). In 1_4 and 1_5 the structures A are more or less similar to the regular C_4- and C_5-symmetrical structures, so that a pronounced difference in the energy terms does not exist between these two structures. In 1_6 and 1_7, on the other hand, the energy terms for structures A are very different from those for the regular C_6- and C_7-symmetrical structures. As seen in Table 2, most energy terms (except the compression term) for structures A are more advantageous. In particular, a large energy difference is observed for the 'van der Waals other' term (-3.0 kcal mol^{-1} for 1_6 and -12.6 kcal mol^{-1} for 1_7) and the 'torsional' term (-8.6 kcal mol^{-1} for 1_6 and -16.7 kcal mol^{-1} for 1_7). Clearly, these two terms are the major factors that stabilize the pinched conformation in 1_6 and 1_7. The 'van der Waals other' term

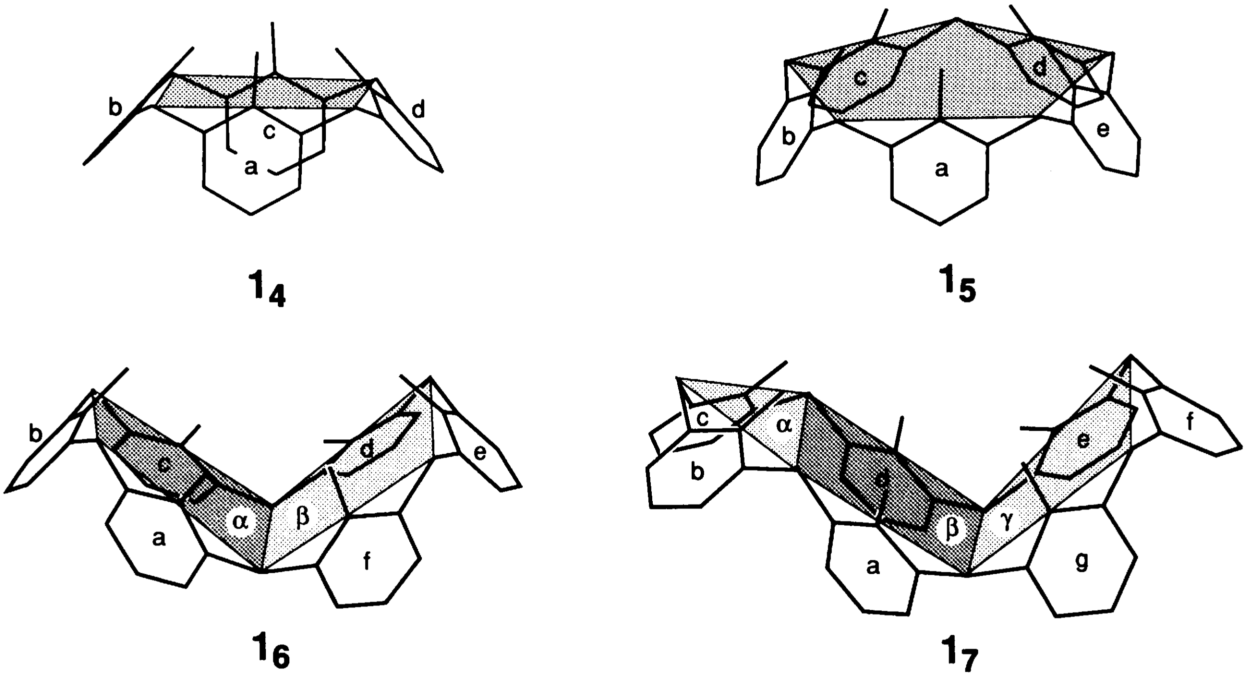

Calix[4]arene $\mathbf{1}_4$

Calix[5]arene $\mathbf{1}_5$

Calix[6]arene $\mathbf{1}_6$

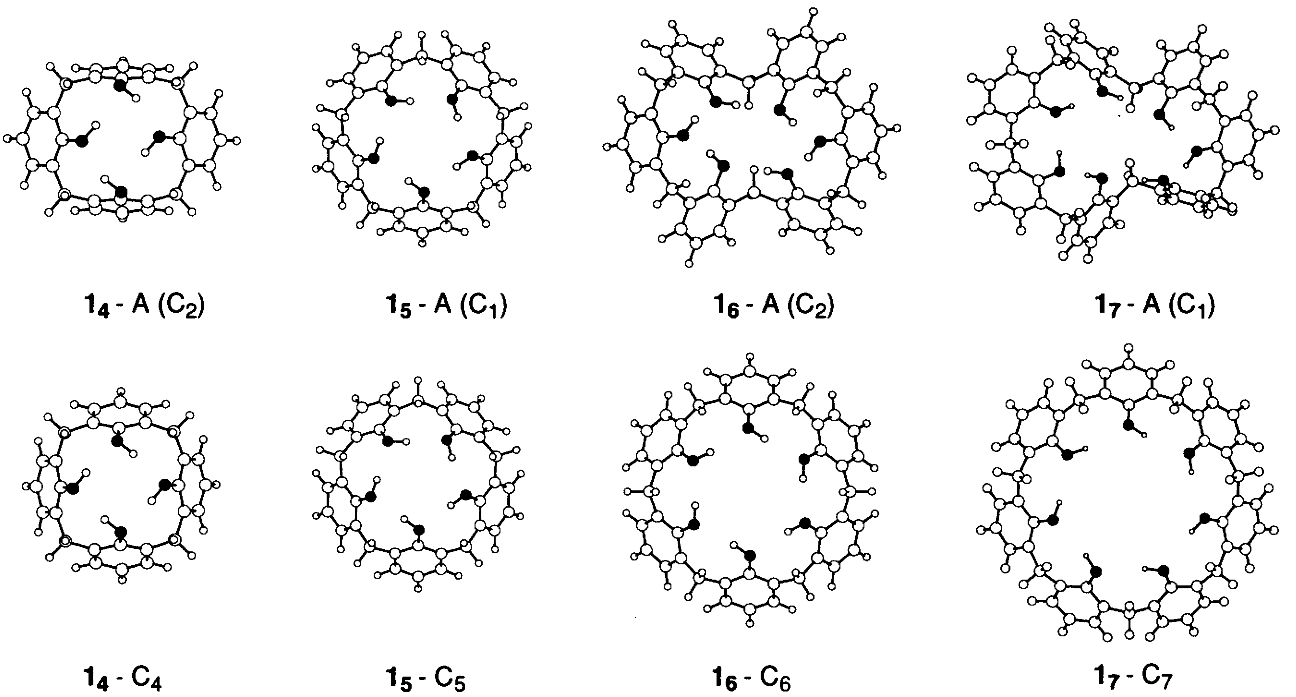
Calix[7]arene $\mathbf{1}_7$

Fig. 2 MM3(92)-optimized structures of $\mathbf{1}_n$ in the order A, B, C, . . from the most stable structure A



1_4 **1_5** **1_6** **1_7**

Fig. 3 Planes composed of bridge-methylene carbons in most stable $\mathbf{1}_4$, $\mathbf{1}_5$, $\mathbf{1}_6$ and $\mathbf{1}_7$



$\mathbf{1}_4$ - A (C_2) $\mathbf{1}_5$ - A (C_1) $\mathbf{1}_6$ - A (C_2) $\mathbf{1}_7$ - A (C_1)

$\mathbf{1}_4$ - C_4 $\mathbf{1}_5$ - C_5 $\mathbf{1}_6$ - C_6 $\mathbf{1}_7$ - C_7

Fig. 4 Most stable structure A and enforced cone structures which destabilize the intramolecular hydrogen-bonding interaction

means the contribution of non-bonded interaction energy between all pairs of atoms not bound to each other except for the vicinal atom pair (*i.e.*, the 1,4-position). In MM3(92), the estimation function that reflects the stabilization effect arising from the hydrogen bonding interaction was for the first time included in this term. In the C_6-symmetrical structure of $\mathbf{1}_6$, -13.6 kcal mol^{-1} of the 'van der Waals other' term (total energy, -17.1 kcal mol^{-1}) is attributed to the stabilization effect of the intramolecular hydrogen bonding interaction between OH groups. In the most stable structure A of $\mathbf{1}_6$, -14.0 kcal mol^{-1} of the 'van der Waals other' term (total energy, -20.1 kcal mol^{-1}) is attributed to the stabilization effect of the intramolecular hydrogen bonding interaction between OH groups: that is, the most stable structure A gains a stabilization energy of -0.4 kcal mol^{-1} from the intramolecular hydrogen bonding interaction compared with the C_6 structure. Similarly, the computational data indicate that the most stable structure A gains a stabilization energy of -0.2 kcal mol^{-1} from the relief of steric repulsion between the OH groups and bridge-methylene groups compared with the C_6 structure.[15c] In fact, the average O–O distance in the most stable structure A of $\mathbf{1}_6$ (3.09 Å) is shorter than that in the regular C_6-symmetrical structure (3.25 Å). The results consistently support the view that the pinched conformation is more energetically favourable to the formation of the stable hydrogen bonding network than the regular C_6-symmetrical conformation. The 'torsional' term reflects the

Table 2 Comparison of energy terms (kcal mol^{-1}) between the most stable structures (A: the symmetry is given in the parentheses) and the regular cone structures (C_n-symmetry) for $\mathbf{1}_n$

	$\mathbf{1}_4$		$\mathbf{1}_5$		$\mathbf{1}_6$		$\mathbf{1}_7$	
Energy term	A (C_2)	$C_4{}^a$	A (C_1)	$C_5{}^a$	A (C_2)	$C_6{}^a$	A (C_1)	$C_7{}^a$
Steric energy	10.2	10.8	10.6	10.8	12.8	25.1	12.7	47.5
Compression	3.4	3.6	3.6	3.7	4.8	4.0	5.4	4.9
Bending	5.2	5.2	6.2	6.3	9.4	9.3	9.5	13.3
Bend–bend	−0.1	−0.1	−0.1	−0.1	−0.1	−0.0	−0.1	0.0
Stretch–bend	−0.7	−0.7	−0.7	−0.7	−0.8	−0.7	−1.0	−0.9
Van der Waals 1,4	25.7	25.6	32.5	32.4	38.6	39.7	45.2	46.6
other	−13.0	−12.8	−16.4	−16.3	−20.1	−17.1	−24.2	−11.6
Torsional	−25.0	−25.0	−32.5	−32.6	−40.1	−31.5	−46.9	−30.2
Dipole–dipole	14.7	15.0	18.0	18.0	21.0	21.5	24.7	25.3

^{a} Symmetry for C_n-symmetrical calix[*n*]arene. The structure is not necessarily the energy minimum.

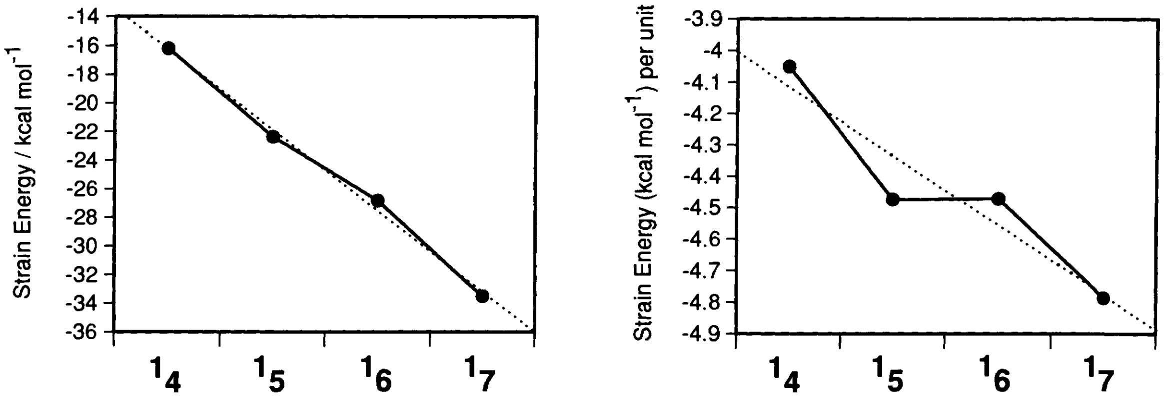


Fig. 5 Total strain energy and strain energy per phenyl unit

torsional energy arising from the dihedral angles in the mother [1_n]metacyclophane skeleton and the phenolic hydroxy groups. The energy difference in this term between these two structures is −8.6 kcal mol^{-1}: −3.2 kcal mol^{-1} of this difference is attributed to distortion around OH groups. This means that a conformational change from the regular C_6-symmetrical structure to the pinched structure can reduce the steric crowding.

In the C_7-symmetrical structure of $\mathbf{1}_7$, −11.7 kcal mol^{-1} of the 'van der Waals other' term (total energy, −11.6 kcal mol^{-1}) is attributed to the stabilization effect of the intramolecular hydrogen bonding interaction between OH groups. In the most stable structure A of $\mathbf{1}_7$, −16.5 kcal mol^{-1} of the 'van der Waals other' term (total energy, −24.2 kcal mol^{-1}) is attributed to the stabilization effect of the intramolecular hydrogen bonding interaction between OH groups. The most stable structure A of $\mathbf{1}_7$ gains the stabilization energy of −4.8 kcal mol^{-1} from the intramolecular hydrogen bonding interaction compared with the C_7 structure. Similarly, the most stable structure A gains the stabilization energy of −1.4 kcal mol^{-1} from the relief of steric repulsion between OH groups and bridge-methylene groups compared with the C_7 structure. These values are much greater than those for $\mathbf{1}_6$, indicating that the regular C_7-symmetrical structure is considerably destabilized. This is also supported by the O–O distance (3.47 Å), which is much longer than that for the regular C_6-symmetrical structure of $\mathbf{1}_6$ (3.25 Å). The energy difference in the 'torsional' term between the structure A and the regular C_7-symmetrical structure of $\mathbf{1}_7$ is −16.7 kcal mol^{-1}: −6.3 kcal mol^{-1} of this difference is attributed to distortion around the OH groups. Thus, the regular C_7-symmetrical structure is very destabilized also in this term.

The foregoing computational studies thus establish that the pinched conformation in $\mathbf{1}_6$ and $\mathbf{1}_7$ arises because of the formation of efficient intramolecular hydrogen bonds and the reduction of steric crowding around the OH groups.

Comparison of strain energy for the most stable structures

To give a possible answer to the question of why the yield of odd-numbered calix[*n*]arenes is particularly low we here compare the strain energy of $\mathbf{1}_4$–$\mathbf{1}_7$.‡ The strain energy can be calculated from the steric energy, bond enthalpy and strainless bond enthalpy in the optional procedure for the calculation of heat of formation in MM3(92). To compare $\mathbf{1}_4$–$\mathbf{1}_7$ with the different number of atoms we normalized this value to that for one phenyl unit. Fig. 5 shows the total strain energy and that per phenyl unit plotted against $\mathbf{1}_n$. It is seen from Fig. 5 that the total strain energy decreases almost linearly with the increase in *n* and the strain energy per phenyl unit decreases in $\mathbf{1}_5$ and $\mathbf{1}_7$ more than in $\mathbf{1}_4$ and $\mathbf{1}_6$. The results imply that from an energetics viewpoint there is no reason why odd-numbered calix[*n*]arenes are exceptionally destabilized. Conceivably, the low yields observed in the preparations of odd-numbered calix[*n*]arenes may be ascribed to the cyclization step (where metal cations, present as MOH, play crucial roles) and not to the thermodynamic stability of the final products.

Comparison with the ^{1}H NMR spectral data and X-ray crystallographic data

To compare the stable structures obtained from the computational study with those suggested from ^{1}H NMR spectroscopy we measured the temperature-dependent ^{1}H NMR spectra of $\mathbf{1}_n$. As shown in Fig. 6, the ArCH$_2$Ar methylene protons in $\mathbf{1}_5$, $\mathbf{1}_6$ and $\mathbf{1}_7$, the splitting pattern of

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‡ Two controversial rationales have been presented for this question, namely, the thermodynamic control which is governed by the stability of the final products and the kinetic control which is governed by the transition-state energy. The present study was done to examine the former rationale.

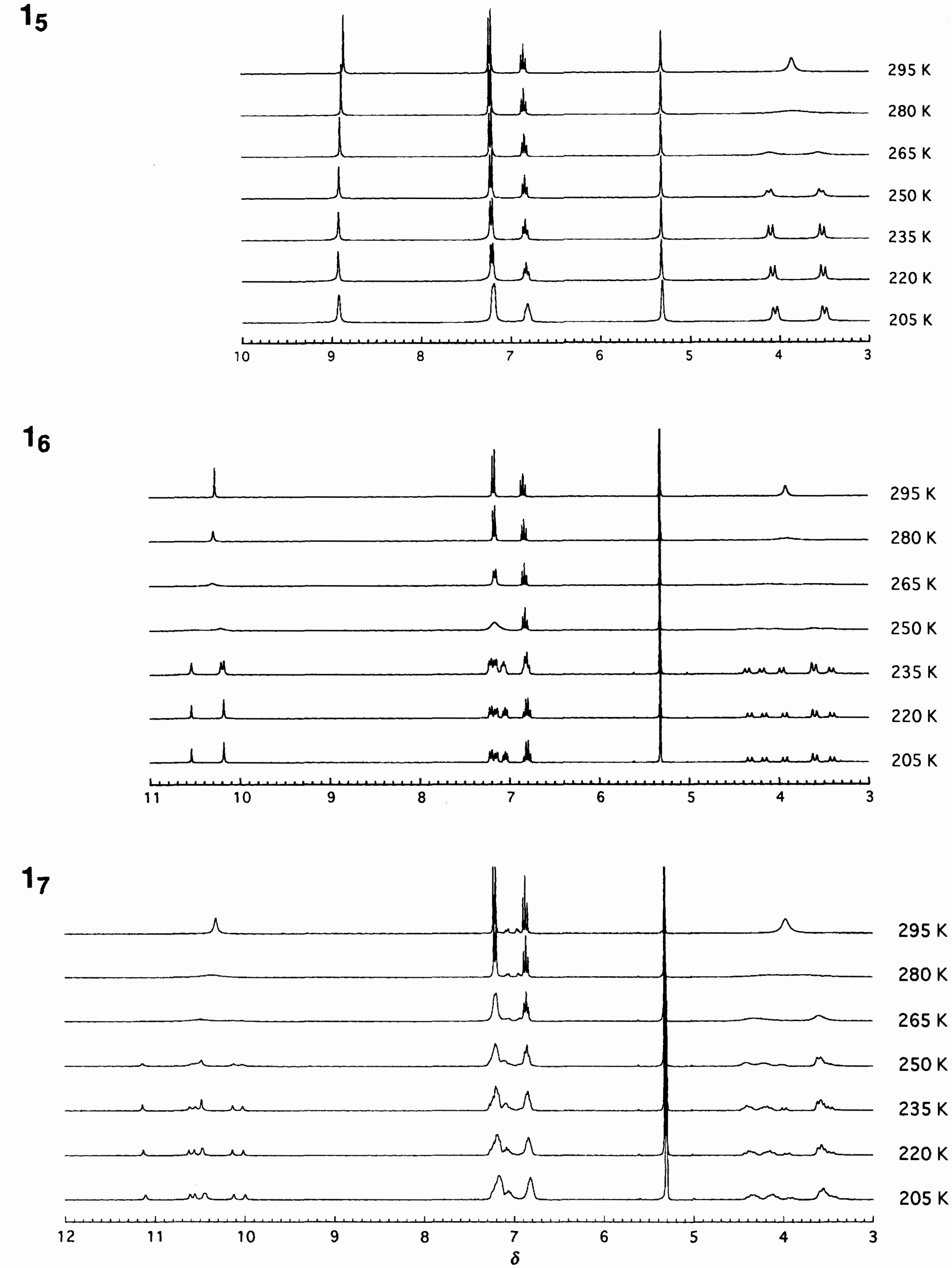

Fig. 6 Temperature-dependent ^{1}H NMR spectra of $\mathbf{1}_5$, $\mathbf{1}_6$ and $\mathbf{1}_7$ (300 MHz, solvent CD_2Cl_2)

which is useful for the assignment of the favourable conformation, appear as a broad singlet at room temperature but are gradually separated into resolved peaks on lowering of the measurement temperature. The partial ^{1}H NMR spectra for the $ArCH_2Ar$ methylene protons, aromatic protons and phenolic OH protons at low temperature region are shown in

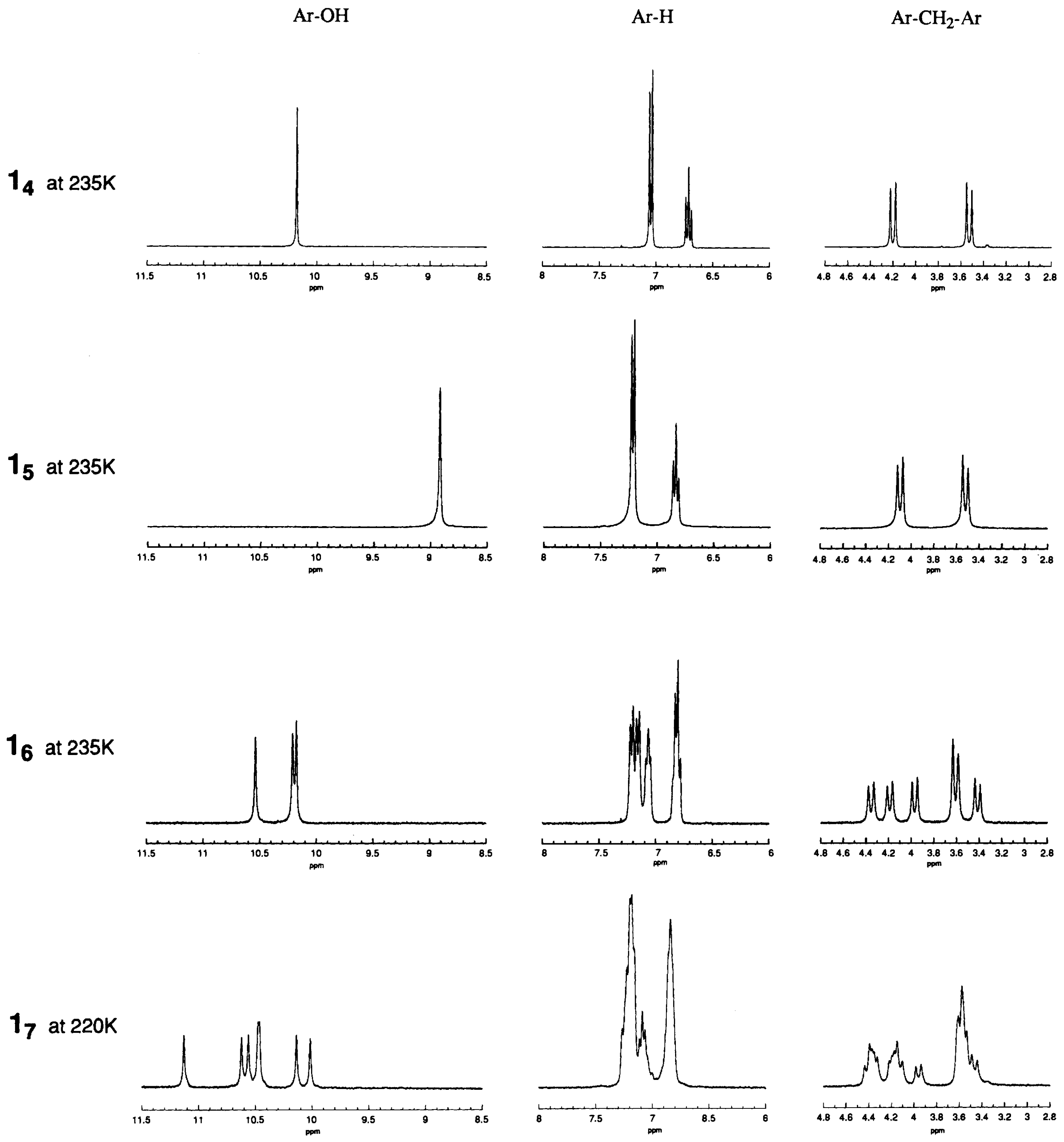

Fig. 7 Partial ^{1}H NMR spectra of $\mathbf{1}_n$ in the low-temperature region (300 MHz, solvent CD_2Cl_2)

Fig. 7.§ The spectral pattern for $\mathbf{1}_5$ is very similar to that for $\mathbf{1}_4$ except that δ_{OH} shifts to higher magnetic field. This indicates that, as suggested by the computational studies, $\mathbf{1}_5$ adopts a cone conformation with C_5 (or nearly C_5) symmetry but the intramolecular hydrogen bonding interaction among the OH groups is weaker than that in $\mathbf{1}_4$. The ^{1}H NMR spectrum of $\mathbf{1}_6$ is characterized by three pairs of doublets for the $ArCH_2Ar$ methylene protons and three singlets for the ArOH protons in a 1:1:1 integral intensity ratio. The downfield shift of δ_{OH} compared with that of $\mathbf{1}_4$ indicates that the intramolecular hydrogen bonding interaction among the OH groups is as strong as that in $\mathbf{1}_4$. In other words, $\mathbf{1}_5$ still tries to retain the regular cone conformation but the hydrogen bonds are considerably destabilized whereas $\mathbf{1}_6$ gives up trying to retain the regular cone conformation and opts for the pinched conformation to acquire stable hydrogen bonds. This view is also supported by IR spectroscopic measurements (KBr): the ν_{OH} bands for $\mathbf{1}_4$ (3156 cm^{-1}), $\mathbf{1}_6$ (3158 cm^{-1}) and $\mathbf{1}_7$ (3173 cm^{-1}) appear at lower frequency than that for $\mathbf{1}_5$ (3289 cm^{-1}). The splitting pattern of $\mathbf{1}_6$ is reasonably explained by C_2 symmetry

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§ We also measured NMR spectra of $\mathbf{1}_n$ in various concentrations (2 – 20 × 10^{-3} mol dm^{-3}) at low temperature. However, the δ_{OH} values of all signals were scarcely affected by the changes in concentration, indicating that the change induced by molecular aggregation is negligible.

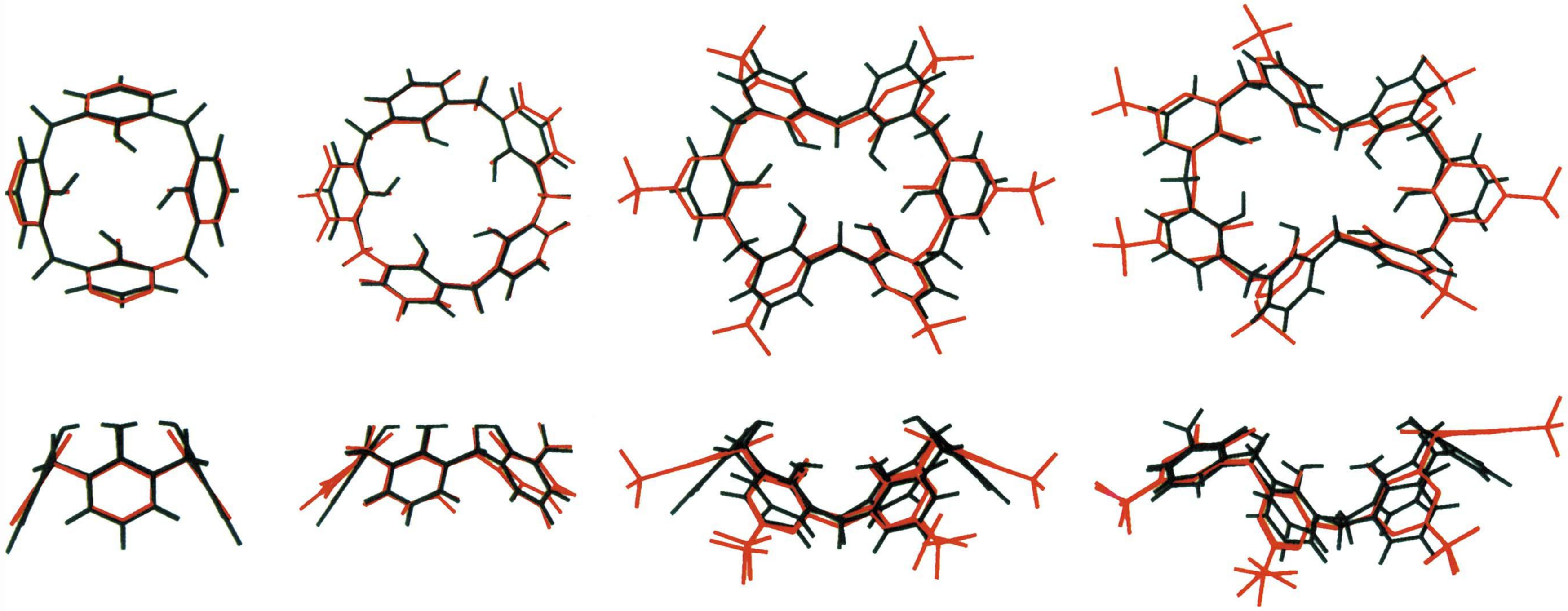

Fig. 8 Superimposed views of crystallographic structures (red) and MM3(92)-optimized structures (green) of $\mathbf{1}_n$. The root-mean-square distances of the geometry of corresponding bridge-methylene carbons are 0.02 Å for $\mathbf{1}_4$, 0.14 Å for $\mathbf{1}_5$, 0.33 Å for $\mathbf{1}_6$ and 0.49 Å for $\mathbf{1}_7$.

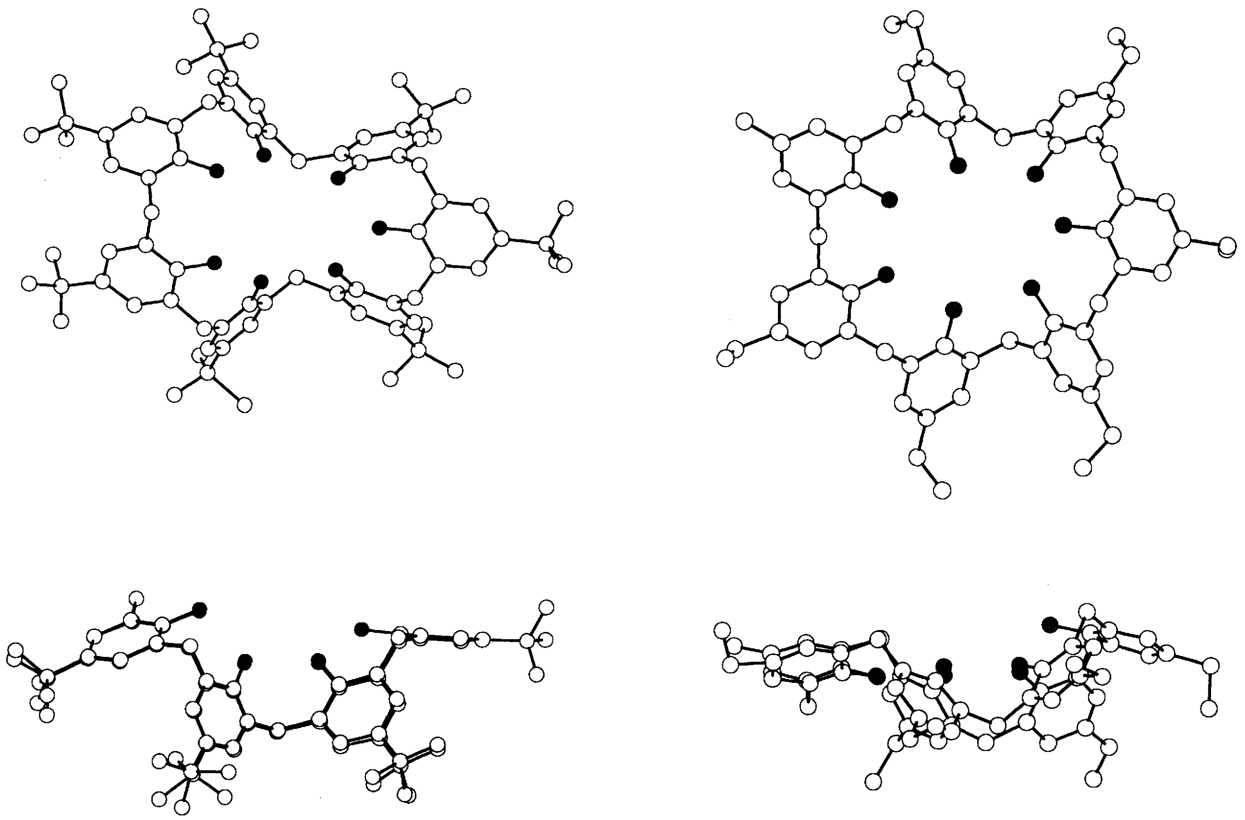

Fig. 9 X-Ray structures for $\mathbf{1}_7$: Andreetti's (left) and Perrin's (right)

Table 3 Molecular symmetries of $\mathbf{1}_n$

$\mathbf{1}_n$	^{1}H NMR	MM3(92)
$n = 4$	C_4	C_2 (nearly C_4)
$n = 5$	C_5	C_1 (nearly C_5)
$n = 6$	C_2	C_2
$n = 7$	C_1	C_1

involving three pairs of non-equivalent phenyl units. The result is successfully reproduced by the computational studies as seen for the most stable structure A (Table 2). The ^{1}H NMR spectrum of $\mathbf{1}_7$ gives multiplet peaks for the ArCH$_2$Ar methylene protons and seven singlet peaks for the ArOH protons, indicating that none of the seven phenyl units is equivalent in $\mathbf{1}_7$. One can thus conclude that $\mathbf{1}_7$ adopts C_1 symmetry.

In conclusion we summarize the symmetries of $\mathbf{1}_n$ obtained from the computational studies and from the ^{1}H NMR spectral measurements in Table 3. Strictly speaking, MM3(92)-optimized structures of $\mathbf{1}_4$ and $\mathbf{1}_5$ adopt C_2- and C_1-symmetry, respectively, however, they are close to C$_4$- and C$_5$- symmetry, respectively. In total, the computational results show good coincidence with the ^{1}H NMR spectroscopic results.

Next, we compare the MM3(92)-optimized structures with those obtained from X-ray crystallographic studies.[11] We summarize selected plane angles and interatomic distances in Table 4 and illustrate superimposed structures in Fig. 8. It is seen from Fig. 8 that in general the MM3(92)-optimized structures are very similar to those found in the crystals but the rings in the X-ray structures have a tendency to be somewhat more flattened. This difference makes the O–O interatomic distance shorter by 0.3–0.5 Å (Table 4). Careful examination of Table 4 reveals that the O–O interatomic distances in $\mathbf{1}_5$ are larger than those in $\mathbf{1}_4$ and $\mathbf{1}_6$. As shown above by IR and ^{1}H NMR spectral evidence the intramolecular hydrogen bonding interaction between OH groups in $\mathbf{1}_5$ is weaker than those in $\mathbf{1}_4$ and $\mathbf{1}_6$. Hence, the energetic unfavourability of the hydrogen bonding interaction in $\mathbf{1}_5$ is consistently supported by the X-ray, spectroscopic and computational studies.

A survey of the past references informs us that two different X-ray structures have been found for $\mathbf{1}_7$. Both structures feature the pinched conformation with C_1 symmetry (Fig. 9). The structure reported by Andreetti *et al.*[11d] is consistent with the most stable structure A. On the other hand, the structure reported by Perrin *et al.*[11e] corresponds to the 19th most stable structure, the steric energy of which is higher by 5.4 kcal mol^{-1} than that of the most stable structure A. As shown in Fig. 9, seven OH groups in Andreetti's version of $\mathbf{1}_7$ form intramolecular hydrogen bonds on the same side whereas in Perrin's two of the seven phenol groups are inverted. This difference is reflected by the steric energy difference due mainly to the 'van der Waals other' term and 'bending' term. We are not yet sure why such an unstable $\mathbf{1}_7$ was obtained in Perrin's system, but presumably it is attributed to the crystal packing effect on the flexible calix[7]arene unless intermolecular hydrogen bonds are formed.

The root-mean-square distance of the geometry of corresponding bridge-methylene carbon can be calculated from the superimposed structures in Fig. 8 and reflects the difference between the MM3(92)-optimized structure and the X-ray structure. As recorded in the caption to Fig. 8, this value increases with increasing n. In $\mathbf{1}_6$ and $\mathbf{1}_7$, the X-ray structures are relatively symmetrical because of the presence of 'pseudo-planes' whereas the phenyl rings in the MM3(92)-optimized structures are inclined independently so that the OH groups can form stable intramolecular hydrogen bonds. This situation reduces the molecular symmetry in $\mathbf{1}_6$ and $\mathbf{1}_7$. The multiple peaks observed in ^{1}H NMR spectroscopy support the view that

Table 4 Structural parameters of X-ray crystallographic and MM3-optimized structures

	1$_4$			**1**$_5$			**1**$_6$			**1**$_7$				
	X-Ray[11a]	MM3 C_2	MM3 C_4	X-Ray[11b]	MM3 C_1	MM3 C_5	X-Ray[11c]	MM3 C_2	MM3 C_6	X-Ray[11d]	MM3 C_1-1	X-Ray[11e]	MM3 C_1-2	MM3 C_7
Plane angle[a]/deg														
α–β							78.4	74.6		178.4	168.0	96.6	76.3	
β–γ										80.8	77.4	91.5	74.2	
Plane angle[b]/deg														
Ph(a)	54.3	77.1	63.7	40.0	65.6	55.4	54.8	44.5	48.6	72.8	48.0	55.9	53.1	45.4
Ph(b)	54.3	48.4	63.7	52.7	48.7	55.4	16.4	45.4	48.6	40.2	38.7	−21.7	−29.6	45.4
Ph(c)	54.3	77.1	63.7	42.1	56.1	55.4	63.6	53.1	48.6	34.5	43.2	−32.8	−42.5	45.4
Ph(d)	54.3	48.4	63.7	53.3	61.4	55.4	62.9	44.5	48.6	66.3	62.0	57.5	50.5	45.4
Ph(e)				53.8	45.9	55.4	24.0	45.4	48.6	68.4	57.6	48.4	37.7	45.4
Ph(f)							52.3	53.1	48.6	−3.4	29.0	24.8	44.4	45.4
Ph(g)										75.6	74.7	46.2	47.1	45.4
Plane angle[c]/deg														
Ph(a)							42.3	30.1 α-a		51.8	31.5	31.1	33.5 β-a	
Ph(b)							55.7	82.5 α-b		64.5	55.1	−42.9	−48.5 α-b	
Ph(c)							54.3	40.2 α-c		60.8	55.0	−47.9	−66.0 α-c	
Ph(d)							53.6	30.1 β-d		46.0	46.4	29.2	33.7 β-d	
Ph(e)							63.0	82.5 β-e		61.8	77.4	43.2	27.8 γ-e	
Ph(f)							39.2	40.2 β-f		41.5	42.4	64.5	77.6 γ-f	
Ph(g)										60.6	74.5	28.0	42.7 γ-g	
Distance[d]/Å														
O(a)	2.65	2.98	3.05	2.83	3.12	3.12	2.57	3.26	3.25	2.78	3.17	2.61	2.91	3.47
O(b)	2.66	3.12	3.05	2.83	3.13	3.12	2.52	2.92	3.25	3.51	3.12	2.52	3.02	3.47
O(c)	2.65	2.98	3.05	2.84	3.13	3.12	2.61	3.09	3.25	2.76	3.11	2.59	3.19	3.47
O(d)	2.66	3.12	3.05	2.86	3.12	3.12	2.62	3.26	3.25	2.96	3.18	2.62	3.09	3.47
O(e)				2.85	3.16	3.12	2.61	2.92	3.25	2.79	3.13	2.56	3.26	3.47
O(f)							2.65	3.09	3.25	2.60	2.97	2.74	3.02	3.47
O(g)										2.85	3.14	2.72	3.07	3.47
Average	2.66	3.05	3.05	2.84	3.13	3.12	2.60	3.09	3.25	2.89	3.12	2.62	3.08	3.47

[a] Dihedral angle between the 'reference planes' in Fig. 3. [b] Dihedral angle between the phenyl plane and the 'mean plane' of bridging methylene carbons. [c] Dihedral angle between the phenyl plane and the 'reference plane': α, β or γ. [d] Interatomic distance between the neighbouring phenolic oxygen atoms, *e.g.*, O(a) denotes the distance between oxygen(a) and oxygen(b).

$\mathbf{1}_6$ and $\mathbf{1}_7$ in solution are more or less close to those predicted on the basis of the computational studies.

Conclusions

The present computational studies combined with the NMR spectroscopic studies have enabled us to give reasonable explanations to several essential problems that have been troubling calixarene chemists for a long time, namely, *(i)* a C_2-symmetrical conformation (but not a C_4-symmetrical one) appears to be the most stable $\mathbf{1}_4$ structure, *(ii)* the low-symmetrical structures of $\mathbf{1}_6$ and $\mathbf{1}_7$, noted in the NMR spectroscopic studies, are reasonably regenerated as the most stable structures by the computational studies and the ring deformation is induced by the predominant effect of the intramolecular hydrogen bond formation over the maintenance of the regular ring structure, *(iii)* from a thermodynamic view point, odd-numbered calix[*n*]arenes (n = 5 and 7) are not particularly destabilized compared with even-numbered calix[*n*]arenes (n = 4 and 6) and *(iv)* the presence of a 'pinched' conformation is also supported from the computational studies. The high reproducibility of the theoretical calculations with MM3(92) indicates that this algorithm is superior to others in the conformational analysis of the cyclophane family.[20] We believe that the conclusions obtained in this paper should prove very useful in the prediction of favourable calix[*n*]arene conformations which play basic roles in the design of functionalized calix[*n*]arenes with high metal and molecular recognition ability.

Experimental

Instruments

CONFLEX3 and MM3(92) calculations were performed on a UNIX workstation system: SUN 4/2GX–IRIS 4D/35G. A molecular modelling system MOL-GRAPH was used to analyse the geometry of the optimized structures. The NMR spectrometer used was a Bruker ARX300. The IR spectra were measured with a Shimazu FTIR-8100M infrared spectrophotometer.

Materials

Compounds $\mathbf{1}_n$ were prepared according to the references: $\mathbf{1}_4$,[8] $\mathbf{1}_5$,[12a,b] $\mathbf{1}_6$[8] and $\mathbf{1}_7$.[12c,d]

References

1 H. H. Minn, S. K. Chang and K. T. No, *Theor. Chim. Acta*, 1989, **75**, 233.

2 S. Shinkai, K. Iwamoto, K. Araki and T. Matsuda, *Chem. Lett.*, 1990, 1263.

3 P. D. J. Grootenhuis, P. A. Kollman, L. C. Groenen, D. N. Reinhandt, G. J. van Hummel, F. Ugozzoli and G. D. Andreetti, *J. Am. Chem. Soc.*, 1990, **112**, 4165; S. Fischer, P. D. J. Grootenhuis, L. C. Groenen, W. P. van Hoorn, F. C. J. M. van Veggel, D. N. Reinhandt and M. Karplus, *J. Am. Chem. Soc.*, 1995, **117**, 1611.

4 J. Roger, F. Bayard and C. Decoret, *J. Chim. Phys.*, 1990, **87**, 1695.

5 S. Miyamoto and P. A. Kollman, *J. Am. Chem. Soc.*, 1992, **114**, 3668.

6 E. Dohan and S. E. Biali, *J. Org. Chem.*, 1991, **56**, 7269.

7 C. D. Gutsche, *Acc. Chem. Res.*, 1983, **16**, 161.

8 For reviews see (*a*) C. D. Gutsche, *Calixarenes*, Royal Society of Chemistry, Cambridge, 1989; (*b*) J. Vicens, V. Böhmer (eds.), *Calixarenes*, Kluwer, Dordrecht, 1991. See also the references cited therein.

9 S. Shinkai, *Bioorg. Chem. Front.*, 1990, **1**, 161; S. Shinkai, *Tetrahedron*, 1993, **49**, 8933.

10 A. Ikeda, H. Tsuzuki and S. Shinkai, *J. Chem. Soc. Perkin Trans. 2*, 1994, 2073.

11 References for the X-ray crystallographic structures of calixarenes; (*a*) calix[4]arene: R. Ungaro, A. Pochini, G. D. Andreetti and V. Sangermano, *J. Chem. Soc.*, *Perkin Trans. 2*, 1984, 1979; (*b*) calix[5]arene: M. Coruzzi, G. D. Andreetti, V. Bocchi, A. Pochini and R. Ungaro, *J. Chem. Soc.*, *Perkin Trans. 2*, 1982, 1133; (*c*) *p*-Bu^t-calix[6]arene: G. D. Andreetti, F. Ugozzoli, A. Casnati, E. Ghidini, A. Pochini and R. Ungaro, *Gazz. Chim. Ital.*, 1989, **119**, 47; (*d*) *p*-Bu^t-calix[7]arene: G. D. Andreetti, F. Ugozzoli, Y. Nakamoto and S. Ishida, *J. Incl. Phenom.*, 1991, **10**, 241; (*e*) *p*-Et-calix[7]arene: M. Perrin, S. Lecoco and Z. Asfari, *C. R. Acad. Sci.*, *Ser. 2*, 1990, **310**, 515.

12 Synthesis of calix[5]arene: (*a*) A. Ninagawa and H. Matsuda, *Makromol. Chem.*, *Rapid Commun.*, 1982, **3**, 65; (*b*) D. R. Stewart and C. D. Gutsche, *Org. Prep. Proced. Int.*, 1993, **25**, 137. Synthesis of calix[7]arene: (*c*) Y. Nakamoto and S. Ishida, *Makromol. Chem.*, *Rapid Commun.*, 1982, **3**, 705; (*d*) Z. Asfari and J. Vicens, *Makromol. Chem.*, *Rapid Commun.*, 1989, **10**, 181.

13 CONFLEX ver. 3.2: CONFormation generator for FLEXible molecules; *JCPE* P 040, developed by H. Goto and E. Osawa. See also, *JCPE* P 012 and *QCPE* Program No. 592.

14 N. L. Allinger, Y. H. Yuh and J.-H. Lii, *J. Am. Chem. Soc.*, 1989, **111**, 8551, 8566, 8576. The MM3(89) and MM3(92) programs for the UNIX system were obtained from Technical Utilization Corporation, Inc., 235 Glen Village Court, Powell, OH 43065 USA. See the manual and references cited therein.

15 (*a*) T. Harada, J. M. Rudzinski and S. Shinkai, *J. Chem. Soc.*, *Perkin Trans. 2*, 1992, 2109; (*b*) T. Harada, J. M. Rudzinski, E. Osawa and S. Shinkai, *Tetrahedron*, 1993, **49**, 5941; (*c*) T. Harada, F. Ohseto and S. Shinkai, *Tetrahedron*, 1994, **50**, 13377.

16 (*a*) P. A. Kollman and K. M. Merz, Jr., *Acc. Chem. Res.*, 1990, **23**, 246; (*b*) D. M. Ferguson, W. A. Glauser and D. J. Raber, *J. Comput. Chem.*, 1989, **10**, 903; (*c*) M. Saunders, *J. Comput. Chem.*, 1991, **12**, 645; (*d*) J. M. Goodman and W. C. Still, *J. Comput. Chem.*, 1991, **12**, 1110; (*e*) G. M. Crippen, *J. Comput. Chem.*, 1992, **13**, 351; (*f*) H. Goto, E. Osawa and M. Yamato, *Tetrahedron*, 1993, **49**, 387; (*g*) H. Goto and E. Osawa, *J. Mol. Struct.*, 1993, **285**, 157.

17 H. Goto and E. Osawa, *J. Chem. Soc.*, *Perkin Trans. 2*, 1993, 187.

18 F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc.*, *Perkin Trans. 2*, 1987, S1.

19 MOL-GRAPH™ is a molecular design support system from DAIKIN Co. Ltd., 1994.

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