Conformational behaviour of methyl *p-tert*-butylcalix[6]arene ester: interconversions among 1,2,3-alternate conformations

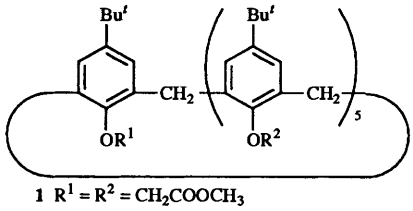
Sangdoo Ahn,[a] Jo Woong Lee *,[a] and Suk-Kyu Chang[b]

[a] *Department of Chemistry, Seoul National University, Seoul 151-742, Korea*
[b] *Department of Chemistry, Chung-Ang University, Seoul 156-756, Korea*

The conformational characteristics of methyl hexa(*p-tert*-butyl)hexabenzenacyclododecaphane (*p-tert*-butylcalix[6]arene) ester 1 have been studied by means of ^1H and ^{13}C NMR spectroscopy. Methyl ester 1, in its solution state, was found to adopt one of several equivalent 1,2,3-alternate conformations that can undergo mutual interconversions over the observed range of temperatures (233–303 K). Thermodynamic and kinetic parameters for these interconversions in several organic solvents were successfully obtained by complete lineshape analysis of temperature dependent ^1H NMR spectra of 1. The results seem to suggest that the conformational interconversions in methyl ester 1 take place predominantly in such a manner that only a pair of benzene rings exchange their up–down orientations at a time. In contrast to 1, its homologues, ethyl and propyl ester 2 and 3, were found to have no such preferential conformations. To gain further insight into the role of the methyl group substituted into 2, we examined a methyl and ethyl mixed ester 4 and found this compound preferentially adopted the symmetrical 1,2,3-alternate conformation rather than other asymmetrical conformations.

Calixarenes have been attracting much research interest as a versatile platform for the design of novel supramolecular systems.[1] One particularly interesting feature of these compounds is that they can assume unique conformations which are known to have profound effects on their interactions with guests.[1,2] One such notable example may be found in the unique ionophoric properties of some alkyl calix[4]arene esters and calix-crown ethers.[2,3] Much is known about the conformational behaviour of calix[4]arenes;[4] however, unfortunately, this is not the case for calix[6]arenes.[5,6] The latter compounds are known to be conformationally more flexible and have a higher degree of functionality than the former, which makes them suitable for the design of more elaborate biomimetic supramolecular systems.

Most NMR studies on conformational properties of calixarenes have been limited to the investigation of bridging methylene protons ($ArCH_2Ar$) and/or the splitting patterns, chemical shifts, coalescence temperature, *etc.* of carbon resonances.[2,4,7,8] Shinkai and co-workers have investigated the conformational properties of *p-tert*-butylcalix[4]arenes by simulating temperature dependent spectral changes observed for bridging methylene protons.[1b] However, no such studies have been reported thus far for their calix[6]arene counterparts. In this paper we report some unique conformational characteristics of the methyl ester of hexa(*p-tert*-butyl)hexabenzenacyclododecaphane **1** revealed by its EXSY spectra and temperature dependent spectral changes observed for *p-tert*-butyl and aromatic protons in several organic solvents. And for the purpose of understanding the effect of methyl substitution on the conformational behaviour we have also examined the mono-methyl penta-ethyl ester **4** and compared its conformational characteristics with those of **1** and **2**.



1 $R^1 = R^2 = CH_2COOCH_3$

2 $R^1 = R^2 = CH_2COOCH_2CH_3$

3 $R^1 = R^2 = CH_2COOCH_2CH_2CH_3$

4 $R^1 = CH_2COOCH_3$, $R^2 = CH_2COOCH_2CH_3$

Results and discussion

The ^1H NMR spectrum of **1** consists of five broad singlets at room temperature because its rate of conformational interconversion (due mainly to oxygen-through-the-annulus rotation) is very fast on the NMR timescale. Upon cooling, each of these singlets is seen to split into multiple peaks, giving a characteristic pattern typical of a 1,2,3-alternate conformation below 243 K as already reported elsewhere.[6,8] That is, the aromatic protons give rise to three singlets with 1 : 1 : 1 intensity ratio while the bridging $ArCH_2Ar$ methylene proton line splits into a pair of doublets plus a singlet located between them. Also, each of the proton resonances observed for OCH_2CO_2, CO_2CH_3 and the *p-tert*-butyl group is found to split into two singlets with a 2 : 1 intensity ratio. That the ester **1** assumes a 1,2,3-alternate conformation in the solution state can further be confirmed by its ^{13}C NMR spectral splitting patterns at low temperature (Fig. 1). Each of the carbons at the *o*- and *m*-positions in the benzene ring (*i.e. e* and *d* carbons) gives rise to three lines with a 1 : 1 : 1 intensity ratio while each of the remaining carbons, except the quaternary *p-tert*-butyl carbon, produces two lines with 2 : 1 intensity ratio as expected for a 1,2,3-alternate conformation in calix[6]arene. The low temperature ^1H NMR spectra in several other organic solvents, *e.g.* CD_2Cl_2, [$^2H_8$]THF and [$^2H_6$]acetone, are found to differ slightly from each other; however, the general splitting patterns exhibited by its $CDCl_3$ solution are retained and are well consistent with a 1,2,3-alternate conformation.

At temperatures above 243 K, the bridging $ArCH_2Ar$ methylene proton signals are found to intermix with those arising from OCH_2CO_2 and CO_2CH_3 protons, but the aromatic and *p-tert*-butyl proton regions remain unperturbed. ^1H NMR lineshape analysis of the aromatic and *p-tert*-butyl proton regions can be performed by making use of the modified Bloch equations[9] for exchanging systems of three equally populated sites and two 2 : 1 populated sites, respectively. The ^1H NMR lineshape analysis for **1** at various temperatures yields the dynamic and activation parameters for the conformational

Table 1 Activation parameters for methyl ester **1** obtained from lineshape analysis[a]

Solvent	E_a/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1}K^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta G^{\ddagger}_{298}$/kJ mol^{-1}
CD_2Cl_2	57.3	5.9	54.8	53.1
[$^2H_8$]THF	53.1	−10.0	50.6	53.5
[$^2H_8$]Toluene	53.9	−1.7	51.4	51.8
[$^2H_5$]Pyridine	49.3	−14.6	46.8	51.0
[$^2H_6$]Acetone	47.2	−34.7	44.7	55.2
$C_2D_2Cl_4$	57.7	−4.6	55.2	56.4

[a] For toluene and pyridine solutions, only the aromatic region could be simulated because of too small a splitting in *p-tert*-butyl proton signals.

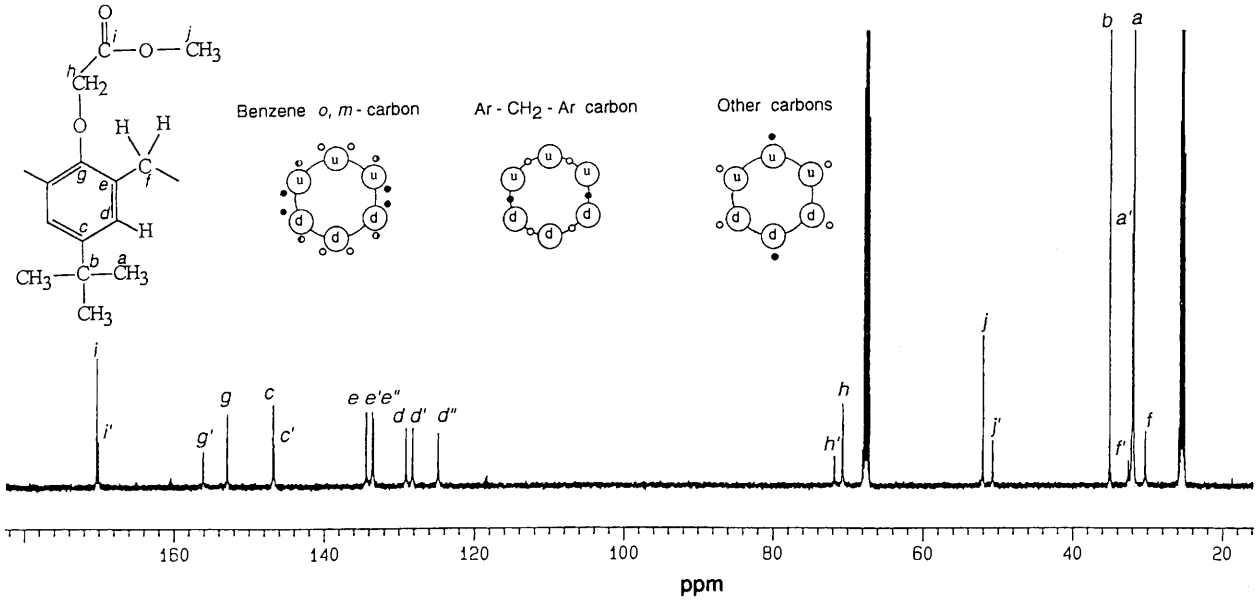
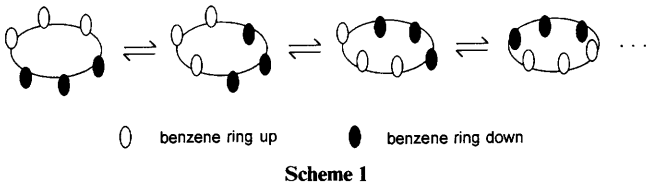


Fig. 1 ^{13}C NMR spectrum of **1** in [$^2H_8$]THF at 238 K (500 MHz). At this temperature, the conformational interconversion is slow enough for us to be able to identify each peak readily. The small (hollow and filled) circles represent the carbon atoms at the positions indicated and the carbons denoted by the same type of circles represent those located at the isochronous sites.

interconversion such as mean lifetime (τ), E_a, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$. As we see from Fig. 2, excellent agreements are attained between calculated and observed spectra with the corresponding Arrhenius plots showing good linearity ($R^2 > 0.99$). The activation parameters can be estimated from the Arrhenius and Eyring equations by making use of the exchange mean lifetimes determined from the lineshape fittings and the results are summarized in Table 1. The successful reproduction of temperature dependent NMR spectra by employing only one parameter indicates the occurrence of interconversion among equivalent 1,2,3-alternate conformations,[1b, 4a] which in turn strongly suggests that the conformation of **1** maintains a 1,2,3-alternate form although the rate of interconversion among these forms may vary over the observed temperature range.[7] These observations and steric considerations lead us to the conclusion that the interconversions proceed predominantly in such a manner that only one pair of benzene rings exchange their up–down orientations at a time with the overall concentration of 1,2,3-alternate conformers remaining unaltered (*cf.* Scheme 1). The 2D-EXSY spectra observed at



Scheme 1

238 K provide further evidence for this conclusion. At this temperature, a well resolved spectral pattern of a 1,2,3-alternate

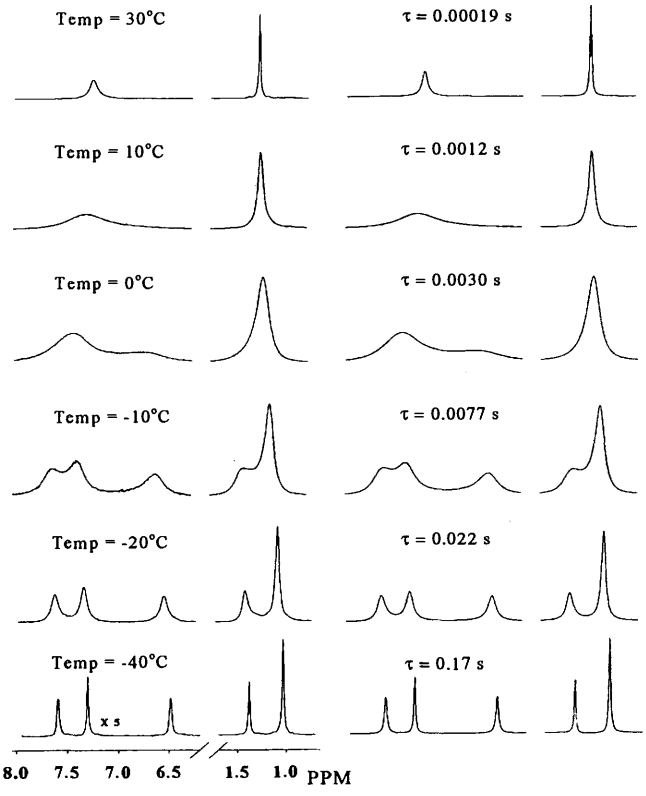


Fig. 2 Temperature dependent partial ^1H NMR spectra of **1** in CD_2Cl_2 (200 MHz). Observed (left) and simulated spectra (right) with indicated lifetime τ.

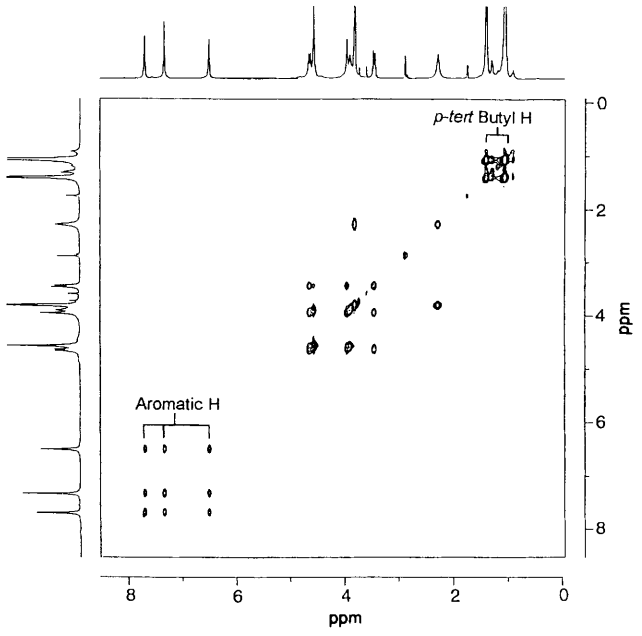


Fig. 3 2D-EXSY spectrum of **1** in [$^2H_8$]THF at 238 K (500 MHz). Cross peaks correspond to the exchange between the relevant sites.

conformation can clearly be recognized in the ^1H NMR spectrum (Fig. 3). The presence of cross peaks between the relevant signals in 2D-EXSY spectra confirms that the interconversions among various 1,2,3-alternate conformations actually take place as shown in Scheme 1.

To obtain additional information on the conformational properties we performed a lineshape analysis of the NMR spectra of **1** obtained in several other organic solvents and the resulting activation parameters are summarized in Table 1. As we see from this tabulated data, $\Delta H^{\ddagger}$ is relatively larger than $\Delta S^{\ddagger}$ (mostly small negative values), which implies that the process is dominated by the enthalpy contribution and does not induce any drastic environmental changes. The free energy changes for conformational interconversions at 298 K in the various solvents employed are estimated to be in the range of 51.0 to 56.4 kJ mol^{-1} which are comparable with those for the underivatized parent hexa(*p-tert*-butyl)hexabenzenacyclododecaphane itself (55.6 kJ mol^{-1} in $CDCl_3$),[10] but lower than those for calix[4]arene.[1b] Introduction of the relatively bulky methoxycarbonylmethoxy groups into the calix[6]arene backbone is thought to result in a reduction in conformational freedom, more than compensating for the increase in conformational freedom caused by removal of the hydrogen bonding interactions between the phenol groups of underivatized calix[6]arene.[7] The conformational behaviour of **1** can be seen to depend moderately on solvent properties. For $C_2D_2Cl_4$, which has a relatively large viscosity (more than twice that of the other solvents employed), the largest E_a and $\Delta G^{\ddagger}$ values are obtained, whereas a relatively large negative value of $\Delta S^{\ddagger}$ is observed for polar solvents such as acetone and pyridine. At the present stage, however, we find it difficult to correlate the solvent effects on the conformational interconversion of **1** quantitatively with any known solvent properties.

In contrast to the methyl ester **1**, its higher homologues, ethyl and propyl ester derivatives of calix[6]arene **2** and **3**, which have more prominent ionophoric properties,[1] were not found to exhibit the same conformational behaviour. Even at low temperatures we could find no prevailing conformation favoured by esters **2** and **3**. The mono-methyl penta-ethyl ester **4** (Fig. 4) shows a very complicated ^1H spectrum with each peak being much sharper compared with the ester **1**, which means that the conformation adopted by **4** is relatively more rigid. Besides, this spectrum is consistent with the fact that the free ester **4** can adopt the symmetrical 1,2,3-alternate conformation

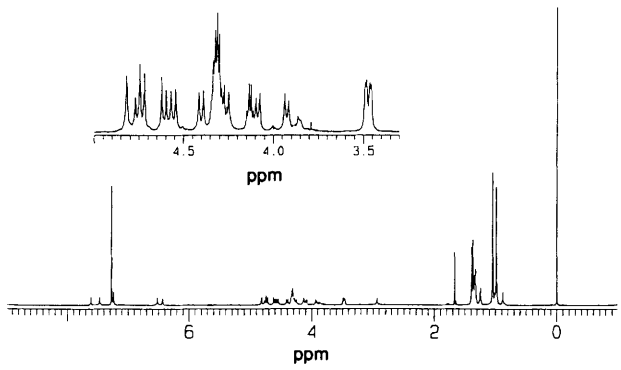


Fig. 4 ^1H NMR spectrum of **4** in $CDCl_3$ at 280 K (600 MHz). At this temperature, the conformational interconversion is slow and peaks are sharp enough for the splitting patterns to be analysed.

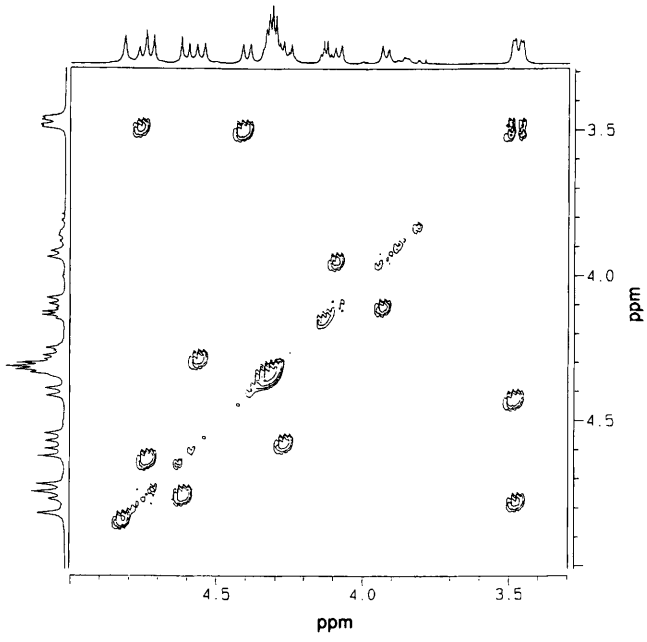
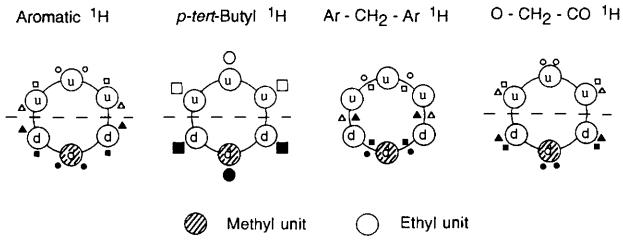


Fig. 5 Partial 2D-COSY spectrum of **4** in $CDCl_3$ at 280 K (600 MHz). Only bridging methylene and CH_2COO protons regions are shown.



Scheme 2 The small symbols (circles, triangles and rectangles) represent the proton atoms at the positions indicated and the protons denoted by the same type of symbols represent those located at the isochronous sites

shown in Scheme 2. For this conformation the ^1H NMR lines of aromatic and *p-tert*-butyl protons will split into two sets of three singlets with the same intensities and two sets of two singlets each with a 2:1 intensity ratio, respectively, while the bridging methylene and O–CH_2–CO_2 protons can give rise to three sets of doublets and two sets of doublets in addition to a singlet, respectively. This can be confirmed by COSY spectra of the ester **4** (shown in Fig. 5) showing the cross peaks among the relevant signals arising from bridging methylene and O–CH_2–CO_2 protons. Upon complexation with the ethylammonium ion, however, the spectrum of **4** is simplified as shown in Fig. 6, indicating that the complex formed has a cone conformation

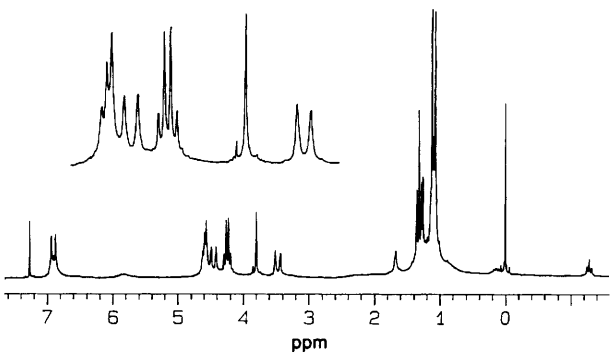
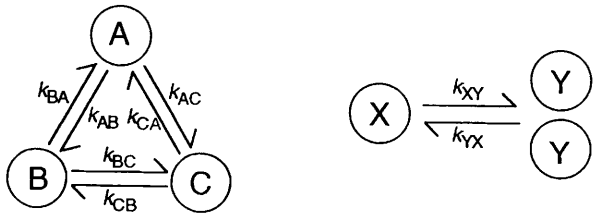


Fig. 6 ^{1}H NMR spectrum of the complex of **4** with ethylammonium picrate in $CDCl_3$ at 298 K (200 MHz). This spectrum resembles that for the complex of **2** with the same guest.



Scheme 3

like the complexes of esters **1**, **2** and **3** with the same ion.[11] From the results obtained in the present study we may conclude that the methyl ester moiety exerts some crucial effect on the conformational behaviour of calix[6]arene ester derivatives, but further investigations are deemed necessary to understand exactly how this comes about.

Experimental

General

The esters **1**, **2** and **3** were prepared following the reported standard procedure.[12] All the deuteriated solvents for our experiment were purchased from Aldrich and/or Sigma Chemical Co. and used without further purification. Temperature dependent ^{1}H NMR experiments for lineshape analysis and 2D experiments were performed on a Varian VXR-200S and Bruker AMX-500/DMX-600 NMR spectrometers, respectively. All the peaks could be identified readily by means of hetero-COSY and 2D-EXSY experiments.

$1^5,3^5,5^5,7^5,9^5,11^5$-Hexa(*tert*-butyl)-$1^2,3^2,5^2,7^2,9^2$-penta(ethoxycarbonylmethoxy)-11^2-(methoxycarbonylmethoxy)-1,3,5,7,9,11-hexa[1,3]benzenacyclododecaphane 4

A mixture of hexa(*p-tert*-butyl)hexabenzenacyclododecaphane (1 mmol), K_2CO_3 (2 mmol) and methyl bromoacetate (3 mmol) in dry THF was refluxed under N_2 for 18 h. After evaporation of the solvent, the residue was extracted with CH_2Cl_2. Purification was achieved by column chromatography followed by recrystallization from CH_2Cl_2–MeOH solution to give a pure derivative of mono-methyl ester hexa(*p-tert*-butyl)hexabenzenacyclododecaphane (58%). A mixture of this mono-methyl ester derivative (1 mmol), K_2CO_3 (8 mmol) and ethyl bromoacetate (in excess, *ca.* 10 mmol) in dry acetone was refluxed under N_2 for 48 h. After evaporation of the solvent, the residue was extracted with CH_2Cl_2. The organic layer was washed with water and then dried with $MgSO_4$. The crude product was purified by recrystallization from CH_2Cl_2–MeOH to afford **4**; yield 82%; mp 258–260 °C; ν_{max}/cm^{-1} 1752 (C=O stretching) (Found: C, 72.5; H, 8.1. $C_{89}H_{118}O_{18}$ requires C, 72.43; H, 8.06); δ_H(600 MHz, $CDCl_3$, 280 K) 7.61, 7.47, 7.27, 7.24, 6.52, 6.44 (each 2 H, s, ArH), 4.82–4.25 (12 H, m, OCH_2), 4.77–3.46 (12 H, three d, $ArCH_2Ar$), 4.32, 4.12 (8 H, 2 H, m, q, CO_2CH_2), 2.94 (3 H, s, CO_2CH_3), 1.39, 1.37, 1.05, 1.01 [9 H, 9 H, 18 H, 18 H, s, $C(CH_3)_3$] and 1.33 and 1.24 (12 H, 3 H, m, t, CH_2CH_3).

Calculations

In general, the NMR lineshape of a multisite exhange system may be reproduced from the modified Bloch equation including relaxation and exchange effects.[9] For methyl ester **1** in a 1,2,3-alternate conformation we may treat the aromatic and *p-tert*-butyl protons as the intramolecular exchanging systems of three equally populated sites and two 2:1 populated sites, respectively (see Scheme 3). In Scheme 3 it may be assumed that the lifetimes of three sites (A, B, and C) and that of site X are all equal, while the lifetime of site Y is twice as long. Therefore, the exchange process in these spin systems may be described in terms of only one rate constant k, since we may write $k_{AB} = k_{BC} = \ldots = k_{YX} = k$ and $k_{XY} = 2k$. The calculations have been performed on IBM PC 486-DX2 using a least-squares fitting program employing the Marquadt algorithm[13] and the results are shown in Fig. 2 and Table 1.

Acknowledgements

This research was supported financially by the Basic Science Research Institute Program, Ministry of Education, Korea, 1994, project no. BSRI-94-3414. S. K. C. is also grateful for financial support from Chung-Ang University (1995).

References

1 (*a*) C. D. Gutsche, *Calixarenes*, Royal Society of Chemistry, Cambridge, 1989; (*b*) Eds. J. Vicens and V. Böhmer, *Calixarenes: A Versatile Class of Macrocyclic Compounds*, Kluwer, Dordrecht, 1991.
2 K. Iwamoto and S. Shinkai, *J. Org. Chem.*, 1992, **57**, 7066.
3 R. Ungaro, A. Casnati, F. Ugozzoli, A. Pochini, J.-F. Dozol, C. Hill and H. Rouquette, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1506.
4 (*a*) K. Araki, S. Shinkai and T. Matsuda, *Chem. Lett.*, 1989, 581; (*b*) L. C. Groenen, J.-D. van Loon, W. Verboom, S. Harkema, A. Casnati, R. Ungaro, A. Pochini, F. Ugozzoli and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1991, **113**, 2385; (*c*) S. Shinkai, K. Araki, M. Kubota, T. Arimura and T. Matsuda, *J. Org. Chem.*, 1991, **56**, 295; (*d*) J. Blixt and C. Detellier, *J. Am. Chem. Soc.*, 1994, **116**, 11 957.
5 (*a*) M. A. Molins, P. M. Nieto, C. Sanchez, P. Prados, J. de Mendoza and M. Pons, *J. Org. Chem.*, 1992, **57**, 6924; (*b*) P. Neri, M. Foti, G. Ferguson, J. F. Gallagher, B. Kaitner, M. Pons, M. A. Molins, L. Giunta and S. Pappalardo, *J. Am. Chem. Soc.*, 1992, **114**, 7814.
6 J. P. M. van Duynhoven, R. G. Janssen, W. Verboom, S. M. Franken, A. Casnati, A. Pochini, R. Ungaro, J. de Mendoza, P. M. Nieto, P. Prados and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1994, **116**, 5814.
7 S. Kanamathareddy and C. D. Gutsche, *J. Org. Chem.*, 1994, **59**, 3871.
8 S.-Y. Han, M.-H. Kang, Y. Jung and S.-K. Chang, *J. Chem. Soc., Perkin Trans. 2*, 1994, 835.
9 (*a*) J. Sandström, *Dynamic NMR Spectroscopy*, Academic Press, London, 1981; (*b*) L. M. Jackman and F. A. Cotton, *Dynamic Nuclear Magnetic Resonance Spectroscopy*, Academic Press, London, 1975.
10 C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.*, 1985, **107**, 6052; 6059.
11 S. Ahn, S.-K. Chang, T. Kim and J. W. Lee, *Chem. Lett.*, 1995, 297.
12 F. Arnaud-Neu, E. M. Collins, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, B. L. Ruhl, M. J. Schwing-Weill and E. M. Seward, *J. Am. Chem. Soc.*, 1989, **111**, 8681.
13 W. H. Press, B. P. Flannery, S. A. Teukolsfy and W. T. Vetterling, *Numerical Recipes: The Art of Scientific Computing*, Cambridge University Press, Cambridge, 1986.

Paper 5/03070F
Received 15*th May* 1995
Accepted 22*nd August* 1995