JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 2, 531–539 (1989)

INFLUENCE OF AROMATIC SUBSTITUENTS ON THE CONFIGURATION AND CONFORMATION OF CALIX[4]ARENEOCTOLS

G. MANN, F. WEINELT AND S. HAUPTMANN
Chemistry Section, Karl-Marx-Universität, Leipzig, GDR

ABSTRACT

Acid-catalysed condensation of resorcinol with aromatic aldehydes results in 2,8,14,20-tetrasubstitued calix[4]areneoctols. Sixteen compounds of this type containing different aromatic substituents were synthesized. The ring closure step, under the conditions of the reaction, is a reversible process. Four configurations are possible for every constitution, viz. *cccc*, *cctt*, *ccct*, and *ctct*, but only *cccc* and *cctt* were formed in detectable amounts. In seven cases the thermodynamically more stable *cccc* isomers (**1a–5a, 7a, 8a**) and also the kinetically controlled *cctt* isomers (**1b–5b, 7b, 8b**) could be isolated. The configurations of the compounds were assigned by temperature-dependent ^{1}H NMR analysis. The conformational motions of the macrocyclic ring permit only the *cccc* isomers to show coalescence for the signals of the aromatic H^b protons. The coalescence temperature was determined for isomers **1a** ($\Delta G^{\neq}_{384} = 83{\cdot}5$ kJ mol^{-1}) and **3a** ($\Delta G^{\neq}_{369} = 83{\cdot}7$ kJ mol^{-1}). For steric reasons the 'chair–chair' conformers **B** and the 'quasi-boat–chair' conformers **F** are favoured. ^{1}H and ^{13}C NMR shifts show that compounds **1a–5a** and **1b–5b** have a quasi-axial arrangement of the aromatic substituents, whereas **6–9** have a quasi-equatorial arrangement of the substituents.

INTRODUCTION

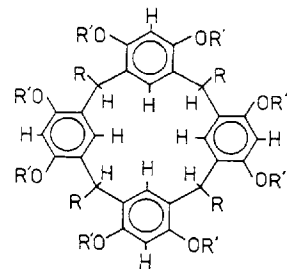
The configuration and conformation of alicyclic compounds have great importance with regard to their physical behaviour and their reactivity. Conformational processes in molecules which are used as abiotic receptor models and enzyme models play a decisive role in the understanding of their host–guest chemistry.[1] Since 1970 a class of metacyclophanes called calixarenes have been investigated by several groups.[2–4] The synthesis of compounds derived from resorcinol was described by Baeyer in 1872,[5] by Michael and Ryder in 1886[6] and by Liebermann and Lindenbaum in 1904.[7] By determination of molecular weights, Niederl and Vogel[8] succeeded in formulating the correct constitutional formula of the reaction products between aliphatic aldehydes and resorcinol.

On analysing the cyclic condensation products of benzaldehyde and 4-bromobenzaldehyde with resorcinol, Erdtman *et al.*[9] found two isomeric compounds in both cases. The stereostructure of these isomers was assigned by Högberg,[10] who analysed their selective formation and DNMR behaviour.

A representative example of cavitands based on resorcinol is the sodium tetraphenolate of 2,8,14,20-tetramethylcalix[4]areneoctol, which complexes methylammonium compounds.[11]

0894–3230/89/070531–09$05.00

Received 10 March 1988
Revised 20 September 1988



Formula A

Our work is concerned with the analysis of the influence of different aromatic substituents on the configuration and conformation of the macrocyclic ring of calix[4]areneoctols. We have adopted the term 'calixarene' introduced by Gutsche[2] for condensation products from resorcinol and aldehydes because of their [1$_n$]metacyclophane structure. This ring system was selected because such compounds have a symmetrical strucure, which permits this 16-membered ring to be compared with cyclooctane. Because two stable stereoisomers are formed from each constitution, it was of interest to establish the proportions which result under different conditions and the products of isomerization. All compounds have to be converted into the butyrates in order to increase their solubility and to investigate the pure isomers and their conformational mobility by means of DNMR spectrocopy.

RESULTS

Different substituted benzaldehydes and equimolar amounts of resorcinol were condensed in ethanolic hydrochloric acid at boiling temperature. The precipitated calixarenes were isolated and converted into the corresponding butyrates. The synthesized compounds are listed in Table 1.

With compounds **1**–**5**, **7** and **8** two isomers, **a** and **b**, could be isolated, but with **6** and **9** only one isomer was obtained. The **b** isomers could be converted into the **a** isomers. For example, **1b** is formed in more than 30% yield at 15 °C after a reaction time of 10 min. After 10 h at 78 °C only isomer **1a** is obtained. Consequently, the **a** isomers are thermodynamically controlled whereas the **b** isomers are kinetically favoured.

Table 1. Melting points of calix[4]arene-4,6,10,12,16,18,22,24-octol butyrates

Compound	R^d	R^e	R^f	R^g	R^h	Melting point	
						a(*cccc*)	**b**(*ccct*)
1	H	H	$OCOC_3H_7$	H	H	186–187	284–285
2	$OCOC_3H_7$	H	H	H	H	251–252	203–204
3	H	OCH_3	$OCOC_3H_7$	H	H	128–129	206–207
4	$OCOC_3H_7$	OCH_3	H	H	H	241–245	224–225
5	$OCOC_3H_7$	Br	H	Br	H	225–228	232–235
6	H	H	NO_2	H	H	310 (decomp.)	
7	NO_2	H	H	H	H	380 (decomp.)	360 (decomp.)
8	H	NO_2	H	H	H	255–256	237–238
9	$OCOC_3H_7$	NO_2	H	NO_2	H	260 (decomp.)	
10	H	H	H	H	H	252–254	212–215[10]

Table 2. ^{1}H NMR chemical shifts (ppm) of compounds **1–10** (298 K, acetone-d_6, 300 MHz)

Compound	H^a	H^b	H^c	H^d	H^e	H^f	H^g	H^h
1a[a]	5·49 s	6·10 s 6·28 s	6·95 s 6·97 s	6·68–6·93	6·68–6·93		6·68–6·93	6·68–6·93
1b[a]	5·61 s	6·08 s 6·39 s	6·97 s 7·12 s	6·78–6·87	6·78–6·87	–	6·78–6·87	6·78–6·87
2a	5·51 s	5·66 s 6·06 s	6·95 s 6·98 s	6·43 d (^3J = 8 Hz)	7·09 m (^3J = 8 Hz) (^4J = 2 Hz)	6·83–6·88	6·83–6·88	–
2b	5·65 s	5·66 s 6·25 s	6·94 s 6·99 s	6·43 d (^3J = 8 Hz)	7·02 m (^3J = 8 Hz) (^4J = 2 Hz)	6·79–6·84	6·79–6·84	–
3a[a]	5·52 s	6·18 s 6·26 s	6·95 s 6·99 s	6·22 d (^3J = 8 Hz)	6·81 d (^3J = 8 Hz)	–	–	6·50 s
3b[b]	5·62 s	6·22 s 6·44 s	7·00 s 7·04 s	6·37 d (^3J = 8 Hz)	6·78 d (^3J = 8 Hz)	–	–	6·44 s
4a	5·47 s	5·89 s 6·15 s	6·93 s 6·94 s	6·83–6·90	6·83–6·90	6·04 q (^3J = 9 Hz) (^4J = 3 Hz)	–	–
4b	5·59 s 6·29 s	5·85 s 7·00 s	6·91 s	6·74–6·84	6·74–6·84	6·06 q (^3J = 7 Hz) (^4J = 2 Hz)	–	–
5a	5·49 s	5·73 s 6·09 s	7·02 s 7·08 s	6·58 d (^4J = 2 Hz)	–	7·72 d (^4J = 2 Hz)	–	–
5b	5·44 s	5·52 s 6·01 s	6·92 s 6·94 s	6·61 d (^4J = 2 Hz)	–	7·57 d (^4J = 2 Hz)	–	–
6[a]	5·86 s	5·61 s 6·38 s	7·04 s 7·20 s	7·15 d (^3J = 10 Hz)	7·90 d (^3J = 10 Hz)	–	7·90 d (^3J = 10 Hz)	7·15 d (^3J = 10 Hz)
7a	6·32 s	5·66 s 6·29 s	7·07 s 7·33 s	6·82 q (^3J = 7 Hz) (^4J = 2 Hz)	7·47–7·54	7·47–7·54	7·73 d (^3J = 7 Hz)	–
7b	6·41 s	5·62 s 6·47 s	7·04 s 7·20 s	6·78 q (^3J = 8 Hz) (^4J = 2 Hz)	7·33–7·40	7·33–7·40	7·69 d (^3J = 8 Hz)	–
8a	5·77 s	5·56 s 6·31 s	7·06 s 7·11 s	7·26 (br)	7·43 d (^3H = 8 Hz)	8·01 q (^3J = 8 Hz) (^4J = 2 Hz)	–	7·71 (br)
9[a]	5·91 s	5·47 s 6·32 s	7·13 s 7·17 s	7·71 d (^4J = 3 Hz)	–	8·69 d (^4J = 3 Hz)	–	–
10a[a]	5·47 s	6·04 s 6·26 s	7·05 s 7·10 s	6·76–6·84	6·95–7·14	6·95–7·14	6·95–7·14	6·76–6·84
10b[a]	5·60 s	5·99 s 6·42 s	7·05 s 7·19 s	6·75–6·86	6·96–7·10	6·96–7·10	6·96–7·10	6·75–6·86

[a] 80 MHz.

Table 2 gives the results of the ^{1}H NMR examination of compounds **1–9** at ambient temperature with the notation of the protons according to Figure 1.

In all compounds H^a protons provide singlets only. The four H^b protons and the four H^c protons show two singlets (H^{b1}, H^{b2}, H^{c1}, H^{c2}) of equal intensity, as was found for **10a** and **10b**.

The synthesized compounds were examined with respect to their dynamic behaviour by means of ^{1}H NMR spectroscopy at 293–410 K using $CDBr_3$ as solvent. Compounds **1a**, **3a** and **10a** show coalescence for the H^b protons: **1a**, T_c = 384 K, $\Delta G^{\neq}$ = (83·5 ± 0·6) kJ mol^{-1}; **3a**, T_c = 369 K, $\Delta G^{\neq}$ = 83·7 ± 1·0) kJ mol^{-1}; **10a**, T_c = 397 K, $\Delta G^{\neq}$ = (85·4 ± 0·5) kJ mol^{-1} (lit.,[10] T_c = 375 K, $\Delta G^{\neq}$ = 79·4 kJ mol^{-1}).

Direct two-dimensional ^{1}H–^{13}C NMR correlation spectra were recorded for **4a** and **7a** in

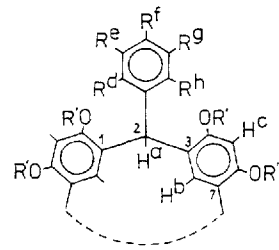


Figure 1. Notation of positions and substituents in 2,8,14,20-tetraaryl-substituted calix[4]arene-4,6,10,12,16,18,22,24-octols

Table 3. Results of direct $^{1}H-^{13}C$ NMR correlation for **4a** and **7a** (values in ppm; solvent, acetone-d_6; ambient temperature)

Compound	H^{b_1}	C^{b_1}	H^{b_2}	C^{b_2}
4a	5·89	131·10	6·15	130·79
7a	5·66	128·93	6·29	131·84

order to assign the signals of the carbon-atoms bound to the H^b protons. The chemical shifts are listed in Table 3.

Coupling constants $^{1}J_{C-H^a}$ were determined for **1b** (^{1}J = 129·8 Hz) and **5a** (^{1}J = 130·1 Hz). The calculated percentage *s* character is 26% for C^a atoms, which is in good agreement with the theoretical value of 25% for sp^3-hybridized carbon.[12] Obviously the macrocyclic ring system is free from strain.

DISCUSSION

The constitution of the macrocycle permits the existence of four diastereomers, *cccc*, *cctt*, *ctct* and *ccct*, with respect to the substituents R (Figure 2).

The ^{1}H NMR spectra of all the isolated compounds indicate that the four substituents R and the H^a protons are in equivalent positions, but the resorcinol moieties are only equivalent in pairs. Symmetry considerations indicate that only *cccc* and *cctt* isomers correspond to the observed ^{1}H NMR spectra. The assignation was found by means of temperature-dependent ^{1}H NMR spectroscopy, because only the *cccc* isomer is able to coalesce as a consequence of conformational motions of the macrocyclic ring and exchange the arrangements of the two pairs of resorcinol rings (H^b and H^c protons). Such an exchange is not possible for *cctt* isomers, because in this case the two pairs of resorcinol rings are always in different chemical environments with respect to substituents R. Coalescence was found for the **a** isomers only, which consequently possess *cccc* configuration. A comparison of differences in the chemical shifts of H^b protons shows that the isomers **1a**, **3a** and **10a**, which coalesce, have smaller differences $\Delta\delta H^b$ ($\delta H^{b_2} - \delta H^{b_1}$) than the isomers **1b**, **3b** and **10b**, respectively (Table 4). Therefore, the thermodynamically more stable compounds **2a**, **4a** and **5a** are assigned also to a *cccc* configuration, although coalescence was not observed at temperatures up to 410 K. Isomers **3b** and **10a** exhibit an equal $\Delta\delta H^b$ value (0·22 ppm) but only **10a** coalesces. This means that the kinetically controlled ring closure reaction results in *cctt* isomers.

Condensation of resorcinol and 4-nitro- and 2-hydroxy-3,5-dinitrobenzaldehyde gave only

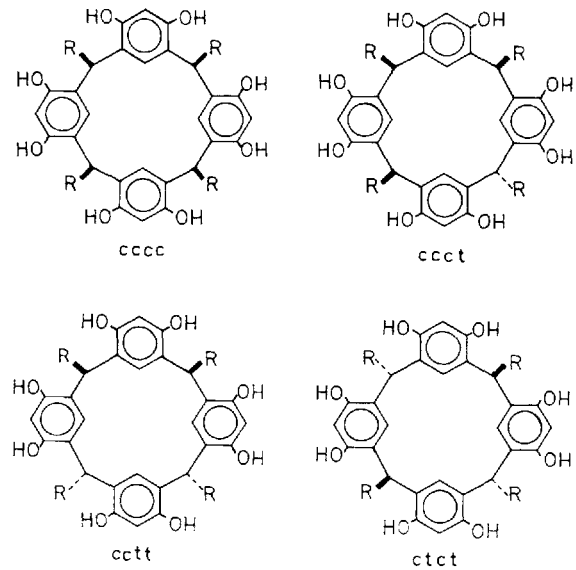


Figure 2. Configurational isomers of substituted calix[4]arenes

Table 4. $\Delta\delta H^b$ values (ppm)

	1	2	3	4	5	7	8	10
a (*cccc*)	0·18	0·40	0·08	0·26	0·36	0·73	0·75	0·22
b (*cctt*)	0·31	0·59	0·22	0·44	0·49	0·85	0·91	0·43

one isomer. We assume that only the *cctt* isomers were obtained as a consequence of a very slow isomerization rate, as was observed with compounds **7a/7b** and **8a/8b**.

Conformations of the 16-membered ring system of calix[4]arene were described by means of the symmetrical forms given in Figure 3. The analogy with cyclooctane is obvious. Every second carbon atom of cyclooctane is exchanged by a resorcinol moiety.

The preferred spatial arrangements of the calix[4]arenes were established by means of δH^b and $\Delta\delta H^b$ values from the ^1H NMR spectra. At a constant temperature and concentration using the same solvent, these values are influenced by the average position of H^b protons relative to the macrocycle, by the statistical distribution of possible conformers, including twisted conformers, and by the aromatic substituents.

The mobility of the macrocyclic ring system is small owing to the spatial extent of the aromatic substituents R. From consideration of molecular models it is seen that these substituents are normally arranged quasi-axially (Figure 4). This is supported by x-ray crystallographic analysis of calix[4]arene with 4-bromopenyl substituents, in which a quasi-axial arrangement of R was found.[9,13]

The ^1H NMR spectra of the nitro derivatives 6–9 show the largest $\Delta\delta H^b$ values of all isomers. The low-field H^b resonances are shifted to lower field in comparison with **2**, **4** and **5**. Calculation of ring current effects[14,15] on H^b protons with quasi-axial and quasi-equatorial arrangements of the aryl substituents show that H^b protons must have shifts, to lower field in the case of quasi-equatorial arrangements. This was observed in the ^1H NMR spectra of the

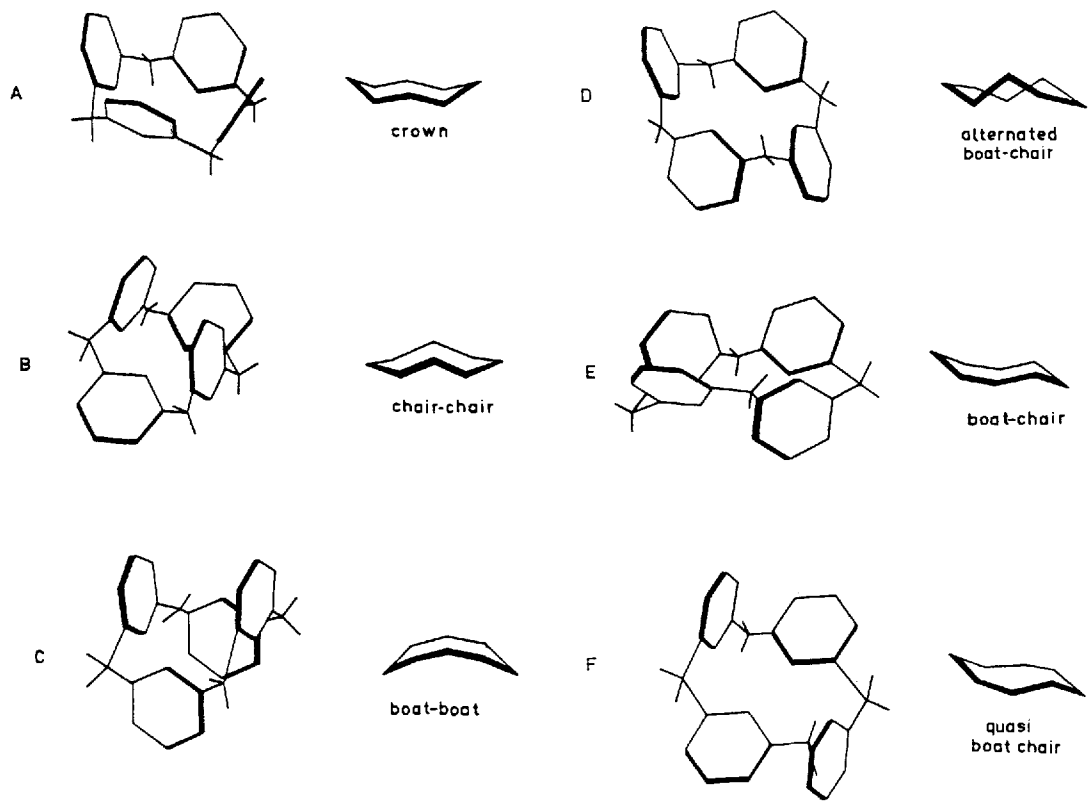


Figure 3. Conformations of calix[4]arenes and the corresponding cyclooctane

nitro derivatives. The quasi-equatorial arrangement of substituents R in these compounds is also supported by broadened signals for H^d and H^h protons in the 300 MHz ^1H NMR spectra of the nitro derivatives **8a** and **8b** as a result of hindered rotation of the aromatic substituents. Further support for our assumption is given by the ^{13}C NMR spectra. Whereas δC^{b_1} of **4a** is greater than δC^{b_2}, the opposite applies with **7a**.

Using ring current theory, it should be possible to predict the chemical shifts for H^b protons in the different conformations, which depend on their position relative to the neighbouring aromatic rings. In order to obtain approximate information about the conformation of the

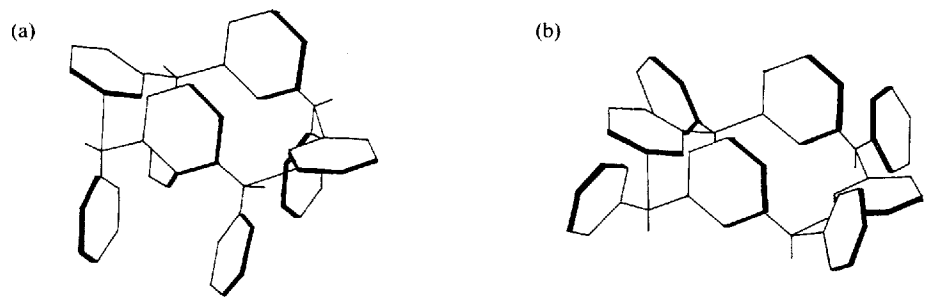


Figure 4. Conformations of tetraaryl-substituted calix[4]arenes: (a) R quasi-axial; (b) R quasi-equatorial

macrocycle, a computer simulation was made of δH^b chemical shift differences for the conformations **A** to **E** using interesting angles ω between the planes of moved opposite resorcinol rings and the plane of the macrocyle. The results are shown in Figure 5 for quasi-axial substituents R. Two conformational changes were examined, **A–B–C** and **E–F–E**. Free rotation of R around C—C single bonds was assumed.

It can be seen that in the range $+10^\circ$ to $+90^\circ$ the $\Delta\delta H^b$ values of the *cccc* isomers are smaller

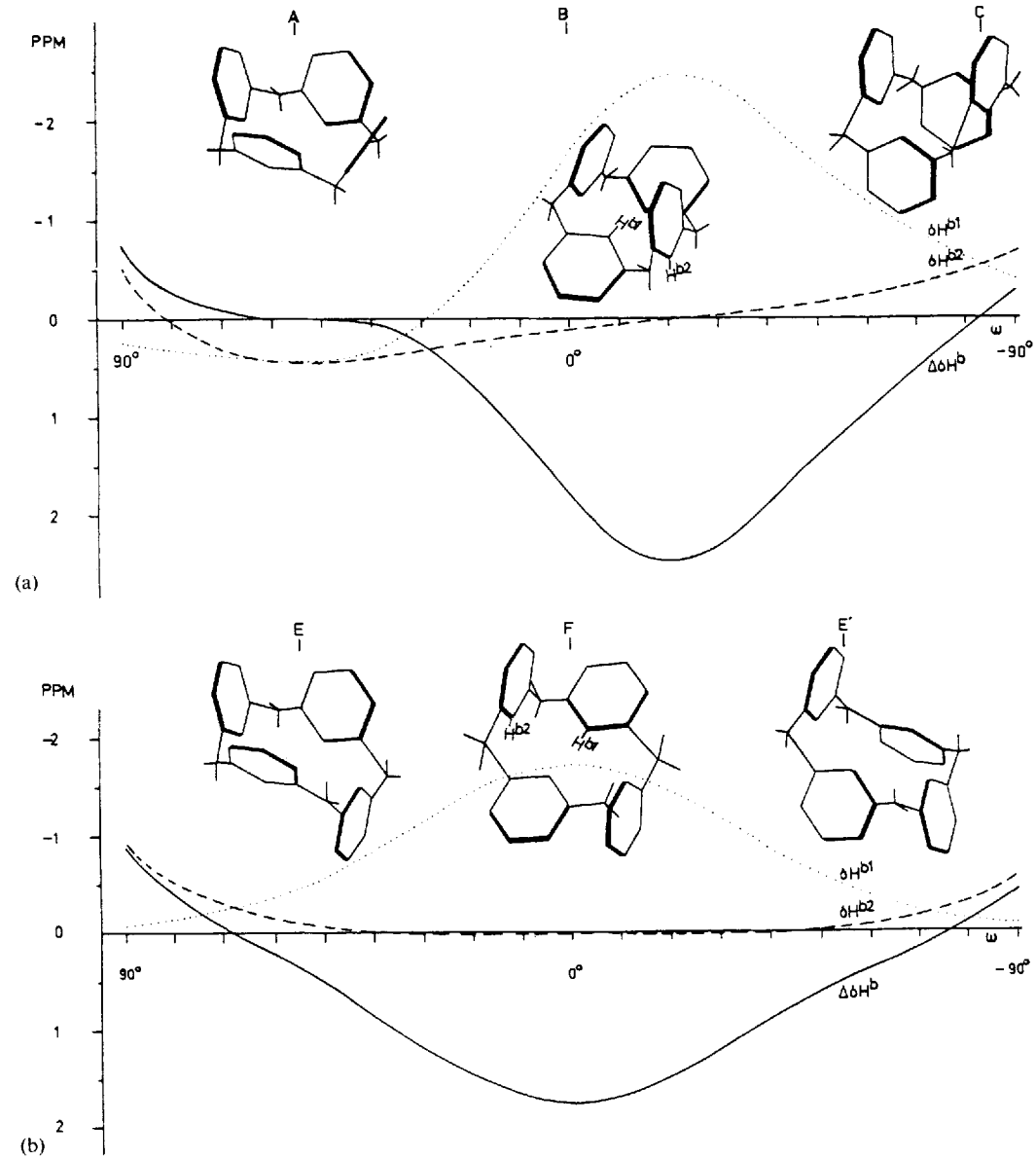


Figure 5. Computer-simulated δH^b chemical shift differences as a function of the conformation of calix[4]arenes. ω, Intersecting angle between the planes of the moved resorcinol rings and the plane of the macrocycle with aryl substituents quasi-axial. (a) Conformational change **A** → **B** → **C** simulated for a *cccc* configuration; (b) conformational change **E** → **F** → **E** simulated for a *cctt* configuration

than those of the *cctt* isomers. This means *cccc* isomers possess a conformation between **A** and **B**. The larger $\Delta\delta H^b$ values correspond to conformation **B**.

Compounds **2a**, **4a** and **5a** with *ortho*-butyryloxy substituents exhibit high-field shifted H^b signals and larger $\Delta\delta H^b$ values than **1a**, **3a** and **10a**. Obviously the *ortho* substituents cause a higher probability of conformation **B** as a result of steric hindrance. The situation with *cctt* isomers is analogous. This means the *ortho*-substituted compounds **2b**, **4b** and **5b** have a higher probability of conformation **F**. The possibility of twisted conformations in the different isomers must be noted. Twisting of the ring system is more probable with *cctt* isomers on account of minor transannular repulsion.

EXPERIMENTAL

Calix[4]areneoctols

A solution of 0·05 mol of resorcinol and 0·05 mol of aromatic aldehyde in 40 ml of methanol is refluxed and 13 ml of concentrated hydrochloric acid are added rapidly. The reaction mixture is stirred for between 5 min and 96 h (Table 5). The precipitate is washed with methanol and dried.

Table 5. Reaction times for synthesis of different calix[4]arenes

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
a (*cccc*)	10 h	10 h	10 h	20 h	10 h	–	100 h	100 h	–
b (*cctt*)	5 min	5 min	5 min	30 min	1 h	1 h	1 h	5 h	1 h

Butyrates of calix[4]arenes

A 0·01 mol amount of calixarene was suspended in 0·06 mol of butyric anhydride, 1 ml of pyridine was added and the mixture was heated at 80 °C. When all the calixarene had dissolved the mixture was allowed to stand for 2 h. The excess of solvent was removed and the residue was recrystallized from ethanol–acetone until the melting point was constant.

NMR spectra

^1H NMR and ^{13}C NMR spectra were recorded on Tesla BS 487 C and Bruker MSL 300 spectrometers at ambient temperature in acetone-d_6. Chemical shifts are reported as δ values in ppm relative to TMS as internal standard. Temperature-dependent ^1H NMR spectra were recorded in $CDBr_3$ at 293–410 K.

In order to calculate ring current effects on the chemical shifts of the four H^b protons, the four bridge atoms of the macrocycle were placed on one level. Resorcinol moieties and phenyl substituents were contracted into points (centres of the aromatic rings). The points of the resorcinol rings and bridge carbon atoms were connected, resulting in an eight-membered ring system. The points of the aromatic rings are origins for the calculation of cylinder coordinates of H^b protons. Conformational motion of the macrocycle was simulated by movement of two opposite points of resorcinol rings through the plane of the macrocycle. The differences in chemical shifts were calculated for quasi-axial and quasi-equatorial phenyl substituents.

REFERENCES

1. K. Odashima and K. Koga, *Organic Chemistry*, Vol. 45, Academic Press, New York (1983), p. 629.
2. C. D. Gutsche, *Top. Curr. Chem.*, **123**, 1 (1985).
3. S. Shinkai, T. Arimura, H. Satok and O. Manabe, *J. Chem. Soc., Chem. Commun.*, 1495 (1987).
4. V. Böhmer, L. Merkel and U. Kunze, *J. Chem. Soc., Chem. Commun.*, 896 (1987).
5. A. Baeyer, *Ber. Dtsch. Chem. Ges.*, **5**, 25 (1872).
6. A. Michael and J. P. Ryder, *Ber. Dtsch. Chem. Ges.*, **19**, 1388 (1886).
7. C. Liebermann and S. Lindenbaum, *Ber. Dtsch. Chem. Ges.*, **37**, 1171 (1904).
8. J. B. Niederland, H. J. Vogel, *J. Am. Chem. Soc.*, **62**, 2512 (1940).
9. H. Erdtman, S. Högberg, S. Abrahamson and B. Nilsson, *Tetrahedron Lett.*, 1679 (1968).
10. A. G. S. Högberg, *J. Am. Chem. Soc.*, **102**, 6046 (1980).
11. H. J. Schneider, D. Güttes and U. Schneider, *Angew. Chem.*, **98**, 635 (1986).
12. M. D. Newton, J. M. Schulman and M. M. Manus, *J. Am. Chem. Soc.*, **96**, 17 (1974).
13. B. Nilsson, *Acta Chem. Scand.*, **22**, 732 (1968).
14. C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
15. R. B. Mallion, *J. Chem. Soc.*, 681 (1971).