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EXTENSION OF THE HYDROPHOBIC CAVITY OF CALIX[4]ARENE BY "UPPER RIM" FUNCTIONALIZATION

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Abstract - The hydrophobic cavity of calix[4]arene (1) has been extended by "upper rim" functionalization with different alkyl groups. Using p-chloromethylcalix[4]arene (2) as the intermediate, the synthesis of ethyl (4) and p-benzylcalix[4]arenes (5 a-c) was performed. By reaction of 1 with cyclohexene p-cyclohexylcalix[4]arene (6) was obtained. The crystal structure of p-ethylcalix[4]arene (4) was solved.

Solid state molecular inclusion of neutral molecules in calix[4]arenes is strongly affected by the nature of alkyl substituent on the aromatic nuclei ("upper rim") of these macrocyles.[1] A more extensive and systematic study of this influence has not yet been carried out because the direct one-pot synthesis of p-alkylcalix[4]arenes via the base-catalyzed phenol-formaldehyde condensations is successful only for "phenols carrying p-substituents very similar in structure to tert-butyl".[2] An alternative is to use the easily prepared calix[4]arene (1)[3] as the starting material. Due to its phenolic nature, electrophilic substitution should be the easiest way to introduce substituents onto the aromatic nuclei of calix[4]arene. However these reactions usually do not proceed in a smooth fashion on this substrate so many times calix[4]arene ethers have to be used.[4] Only by a careful choice of the electrophile and the reaction conditions sometimes it is possible to perform successfully reactions on unprotected calix[4]arene. Electrophilic carbons introduced on calix[4]arene have been acyl groups, both by Friedel-Crafts reactions and Fries rearrangements,[5] aminomethyl groups by Mannich reactions[6] and chloromethyl groups by Friedel-Crafts reactions.[7] Other carbon functionalities have been introduced by a Claisen rearrangement route followed by chemical modification of the allyl moiety.[8]

For these reasons we have explored new synthetic procedures to functionalize calix[4]arene (1). As a first strategy to extend the hydrophobic cavity we employed p-chloromethylcalix[4]arene (2) as intermediate, prepared as previously reported[7] from 1, and the results are reported in Table 3. We have already synthesized p-methylcalix[4]arene (3) in good yield by reduction of this product with $LiAlH_4$.[7]

p-Ethylcalix[4]arene (4)

This product was obtained in 35% yield from p-chloromethylcalix[4]arene by reaction with an excess of methyllithium.

The crystal structure of this compound (4) was determined by X-ray diffraction on a colourless single crystal obtained from chloroform.

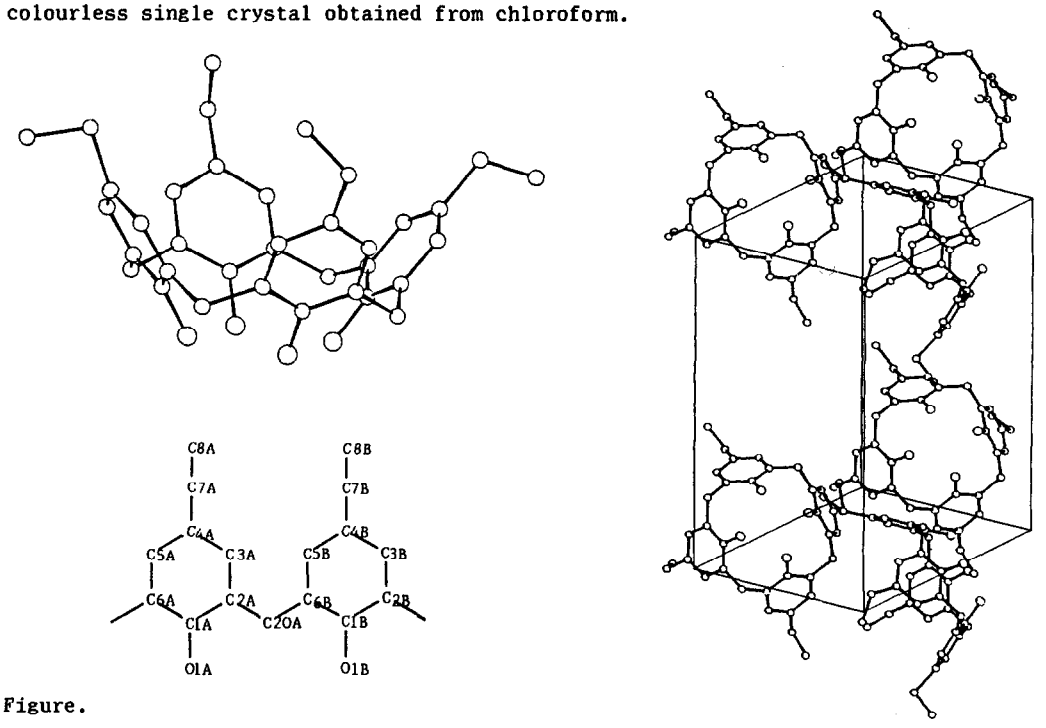


Figure.
Molecular structure, crystal packing and atomic numbering of p-ethylcalix[4]arene (4)

A perspective view of the molecule with the atomic numbering is shown in the figure. The molecule exists in the cone conformation mainly determined by the cyclic array of intramolecular hydrogen bonds. The most relevant parameters concerning the hydrogen bonds are summarized in Table 1. The conformation of the macrocycle is quite similar to that observed in the empty form of p-(1,1,3,3-tetramethylbutyl)calix[4]arene (LOC).[9] Taking as a reference plane the weighted least-squares plane through the four CH_2 bridges, the dihedral angles formed by the four phenolic rings with respect to it are: A-R 124.0(2), B-R 126.9(1) C-R 120.2(1), D-R 124.2(1)°, quite similar to those observed in the LOC compound and slightly different from the value of 123(1)° observed in the p-t-butylcalix[4]arene 1:1 toluene complex.[10] The conformation of the macrocycle may be more conveniently described by the torsion angles involving the four C atoms of the methylene bridges, whose calculated values are reported in Table 2, to be compared with the values of 88.9(4), -89.4(5)° found in the p-t-butylcalix[4]arene 1:1 toluene complex. Similarly to what is observed in the LOC compound, the orientation of the ethyl

chains with respect to the intramolecular cavity are : A endo, B exo, C endo, D exo as shown by the torsion angle reported in Table 2. However the two ethyl chains which point towards the interior of the macrocycle are not long enough to occupy completely the intramolecular cavity although in the present case no guest molecules have been found. The C...C contact between the two endo CH_3 groups is 8.779(5) Å.

It is interesting to note that the molecular packing (see Figure) reaches a density of 1.189 g cm^{-3}, significantly higher than the value of 1.055 g cm^{-3} found in the LOC compound. Since both compounds crystallize in the same space group we may conclude that longer p-substituent alkyl chains fill the available space less efficiently despite their greater flexibility.

Table 1. Cyclic intramolecular H bonds.

Donor-H(A)	Donor...Acceptor(A)	H...Acceptor(A)	Donor-H...Acceptor
O1A-H1A	O1A...O1D	H1A...O1D	O1A-H1A...O1D
0.66(9)	2.678(7)	2.03(9)	168(7)
O1B-H1B	O1B...O1A	H1B...O1A	O1B-H1B...O1A
0.71(6)	2.663(5)	1.00(6)	156(6)
O1C-H1C	O1C...O1B	H1C...O1B	O1C-H1C...O1B
0.62(7)	2.666(7)	2.10(7)	154(7)
O1D-H1D	O1D...O1C	H1D...O1C	O1D-H1D...O1C
0.76(6)	2.702(7)	2.01(6)	169(7)

Table 2. Selected torsion angles(°). Torsion angles involving the ethyl p-substituents.

	A	B	C	D
C3-C4-C7-C8	-102.7(8)	84.4(7)	-39(1)	74(1)

Torsion angles involving the methylene bridges.

C3A-C2A-C20A-C6B	90.3(6)	C2A-C20A-C6B-C5B	-92.4(6)
C3B-C2B-C20B-C6C	90.3(6)	C2B-C20B-C6C-C5C	-85.2(6)
C3C-C2C-C20C-C6D	85.2(6)	C2C-C20C-C6D-C5D	-88.4(3)
C3D-C2D-C20D-C6A	89.1(7)	C2D-C20D-C6A-C5A	-89.2(6)

p-Benzylcalix[4]arenes (5a-c)

p-Benzylcalix[4]arene obtained in good yields (see Scheme) by a Friedel-Crafts alkylation of benzene with p-chloromethylcalix[4]arene (2). BF_3 was found to be a better catalyst than $AlCl_3$ and $SnCl_4$.

Bulkier groups were also introduced on the "upper rim" of 2 by reaction with mesitylene, providing p-(2',4',6'-trimethylbenzyl)calix[4]arene (5b) in very good yields. Whereas the reaction with 2,5-dimethylphenol gave p-(4'-hydroxy-3',5'-dimethylbenzyl)calix[4]arene (5c).

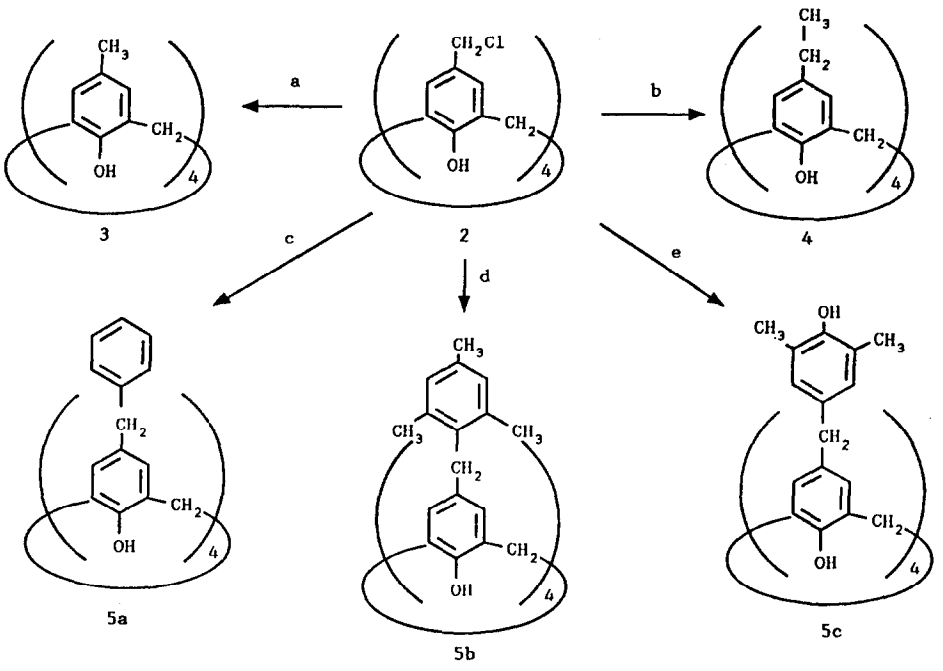


Table 3.

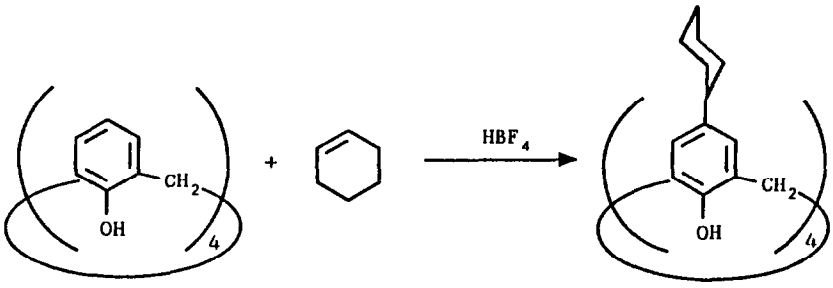
	Reagent	Catalyst	Solvent	Time (h)	Temp.	Product	Yield (%)
a)	$LiAlH_4$ [7]	-	THF	12	r.t.	3	83
b)	CH_3Li	-	DME	48	r.t.	4	35
c)	Benzene	BF_3	Benzene	18	r.t.	5a	50
d)	Mesitylene	BF_3	Mesitylene	24	r.t.	5b	60
e)	2,6-Dimethylphenol	BF_3	Chloroform	1	r.t.	5c	30

p-Cyclohexylcalix[4]arene (6)

Calix[4]arenes bearing long and flexible alkyl groups in the para position, such as 1,1,3,3-tetramethylbutyl, give self-complexation because the groups are folded inside the cavity of the calix, preventing the inclusion of other guest species.[9]

In order to avoid this phenomenon, the more rigid cyclohexyl group which is known to

prefer a linkage to the aromatic nuclei in equatorial position,[11] was chosen. p-Cyclohexylcalix[4]arene (6) was obtained by reaction of cyclohexene with calix[4]arene (1) in the presence of fluoboric acid.



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CONCLUSIONS

We have obtained by functionalization of calix[4]arene some new interesting calix[4]arenes with extended hydrophobic cavities. All these products are conformationally mobile in solution as evidenced by the two broad doublets for axial and equatorial protons of the CH_2 bridges. Only product 5b shows two well resolved doublets. As previously reported,[12] in fact, the mobility of these products is only slightly affected by the nature of of p-alkyl groups. It has also been shown that p-chloromethylcalix[4]arene (2) is an interesting and useful intermediate in calixarene chemistry complementary with p-(trimethylammoniummethyl)calix[4]arene, reported by Gutsche and co-workers.[6]

EXPERIMENTAL

^1H and ^{13}C NMR Spectra were recorded at 100 MHz using Bruker AC100 Instrument in $CDCl_3$ with TMS as internal standard. Chemical shifts are expressed in ppm. Melting points were taken on a Electrothermal apparatus in a capillary and have not been corrected. Mass spectra were recorded using Finnigan Mat 8400. All reactions were performed under nitrogen.

Chemicals. 5,11,17,23-Tetra(chloromethyl)-25,26,27,28-tetrahydroxycalix[4]arene (2) was prepared according to the literature.[7] ACS Grade reagents were used without further purification. All solvents were dried with line molecular sieves 4 Å and stored on the same sieves. Thin layer chromatography analysis were performed on precoated silica gel plates (Merck DC-Alutolien Kieselgel $60F_{254}$). Flash column chromatography was performed using Merck silica gel 230-400 mesh.

5,11,17,23-Tetraethyl-25,26,27,28-tetrahydroxycalix[4]arene (4).

A solution of p-chloromethylcalix[4]arene (2) 1 g, 1.6 mmol) dissolved in dry toluene (40 ml) was added dropwise in about 30 min to a solution of CH_3Li (1,6 N solution in ethyl ether, 57 ml, 91 mmol) in dry dimethoxyethane (100 ml) cooled at 0°C. The cooling bath was removed and the reaction mixture stirred at room temperature for 24

h. The resulting orange and homogeneous reaction mixture was then quenched with methanol. A 5% HCl solution was then added and the reaction mixture was extracted with chloroform; the organic layer was washed twice with distilled water, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography using chloroform:hexane=1:1 as eluent. Solvent evaporation from the combined chromatographic fractions gave 0.305 g (35% yield) of a white solid. Recrystallization from chloroform gave transparent crystals (m.p. 333°C with dec.); ^{1}H NMR ($CDCl_3$) δ 1.37 (t, 12H, CH_2-C$\underline{H}_3$), 2.44 (q, 8H, -C$\underline{H}_2$-CH_3, J = 8 Hz), 3.51 (bs, 4H, H_{eq}), 4.14 (bs, H_{ax}), 6.65 (s, 8H, ArH), 10.20 (s, 4H, OH). ^{13}C NMR ($CDCl_3$) 15.54 (q, $\underline{C}H_3$-CH_2), 27.95 (t, $\underline{C}H_2$-CH_3), 31.97 (t, Ar-$\underline{C}H_2$-Ar), 128.16 (s, Ar-ortho), 128.20 (d, Ar-meta), 137.62 (s, Ar-para), 146.75 (s, Ar-O). m/e (%) 537(100), 269(30), 147(50), 119(30). Anal. Calcd for $C_{36}H_{40}O_4$: C, 80.56; H, 7.51. Found: C, 80.31; H, 7.40.

5,11,17,23-Tetrabenzyl-25,26,27,28-tetrahydroxycalix[4]arene (5a). 1 g (1.6 mmol) of 2 was dissolved in 50 ml of benzene and 1.1 ml (16 mmol) of $BF_3.(C_2H_5)_2O$ were added dropwise in 5 min. The reaction mixture was stirred at room temperature for 5 h. The resulting yellow solution was quenched with H_2O, the organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated in *vacuo*. The residue was purified by column chromatography using chloroform:hexane = 1:1 as eluent and gave 630 mg (50% yield) of pure compound m.p. 64-67°C (dec.). ^{1}H NMR ($CDCl_3$) δ 3.40 (bs, 4H, Ar-CH_2-Ar eq.), 3.77 (s, 8H, Ar-CH_2-Ph) 4.15 (bs, 4H, Ar-C$\underline{H}_2$-Ar ax), 6.78 (s, 8H, Ar-H), 7.1-7.3 (m, 20H, $-C_6H_5$), 10.19 (s, 4H, O$\underline{H}$). ^{13}C NMR ($CDCl_3$) 31.80 (t, Ar-$\underline{C}H_2$-Ar), 41.03 (t, Ar-$\underline{C}H_2$-Benzene), 126.05, 128.24, 128.42, 128.94, 129.38, 134.55, 147.17 (arom-C). m/z (%) 784(100), 708(20), 424(20), 91(95), 85(45), 71(55). Anal. Calcd for $C_{56}H_{48}O_4$: C, 85.68; H, 6.16. Found: C, 85.45; H, 6.02.

5,11,17,23-Tetra-(2',4',6'-trimethylbenzyl)-25,26,27,28-tetrahydroxycalix[4]arene (5b). 1 g of (2) (1.6 mmol) and 1.1 ml (16 mmol) of $BF_3.(C_2H_5)_2O$ were dissolved in 50 ml of 1,3,5-trimethylbenzene in nitrogen atmosphere and stirred at room temperature for 24 h. The reaction was quenched with water, the organic layer separated washed twice with water and dried with anhydrous Na_2SO_4 and the solvent evaporated. Purification by column chromatography (hexane:ethyl acetate = 1:1) gave 900 mg (60% yield) of compound 5b m.p. 237-239°C. ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 24H, $ArCH_3$), 2.27 (s, 12H, $ArCH_3$), 3.29 (bd, 4H, $ArCH_2Ar$ eq.), 3.77 (s, 8H, $ArCH_2$ mes.), 4.09 (bd, 4H, $ArCH_2Ar$ ax, J = 13.4), 6.61 (s, 8H, ArH), 6.66 (s, 8H, ArH), 10.23 (s, 4H, ArOH). m/z(%) 953(100), 133(98). Anal. Calcd for $C_{68}H_{72}O_4$: C, 85.67; H, 7.61. Found: C, 85.50; H, 7.48.

5,11,17,23-Tetra(3',5'-dimethyl-4'-hydroxybenzyl)-25,26,27,28-tetrahydroxycalix[4]arene (5c). 1 g (1.6 mmol) of 2,6-dimethylphenol was dissolved in 100 ml of chloroform. After complete dissolution, 1.1 ml (16 mmol) of $BF_3.(C_2H_5)_2O$ were added in 3 min. The reaction mixture was stirred at room temperature for 1 h and quenched with water. After separation the organic layer was washed with water, dried over anhydrous Na_2SO_4 and the solvent evaporated. Purification by column chromatography (hexane:ethylacetate = 1:1) gave 460 mg (30% yield) of compound (5c) m.p. >300°C (dec). ^{1}H NMR ($CDCl_3$) δ 2.35 (s,

24H, $\underline{CH}_3$-Ar), 3.35 (bs, 4H, Ar-CH_2-Ar eq), 3.79 (s, 4H, Ar-$\underline{CH}_2$-phenol), 4.10 (bs, 4H, Ar-$\underline{CH}_2$-Ar ax), 4.76 (bs, 4H, Ar$\underline{OH}$). ^{13}C NMR ($CDCl_3$) δ 15.86 (q, $\underline{CH}_3$-Ar), 31.75 (t, Ar-$\underline{CH}_2$-Ar), 40.23 (t-Ar-$\underline{CH}_2$ phenol), 122.87, 128.19, 128.92, 129.26, 132.60, 135.17, 146.91, 150.37 (arom-C). m/z (%) 961(80), 826(20), 149(40), 135(100), 122(40), 107(40), 97(60), 91(40). Anal. Calcd for $C_{64}H_{64}O_8$: C, 79.97; H, 6.71. Found: C, 79.78; H, 6.65.

5,11,17,23-Tetracyclohexyl-25,26,27,28-tetrahydroxycalix[4]arene (6). 425 mg (1 mmol) of calixarene 1 and 660 mg (8 mmol) of cyclohexene were dissolved in 25 ml of CH_2Cl_2, then 1.63 g (10 mmol) of fluoboric acid 54% in ethyl ether were added. The reaction mixture was stirred at room temperature for 12 h and quenched with water, the organic layer separated, washed with water and dried over anhydrous Na_2SO_4.

After evaporation of the solvent the compound was purified by column chromatography (hexane:ethylacetate = 97.5:2.5) and 138 mg (42% yield) were obtained (m.p. 272-274°C). ^1H NMR ($CDCl_3$) δ 1.25 (bs, 20H, CH_2-$\underline{CH}$ ax), 1.72 (bs, 20H, CH_2-$\underline{CH}$-eq) 2.27 (bd, 4H, Ar-$\underline{CH}(CH_2)_2$), 3.48 (bs, 4H, Ar-CH_2-Ar eq), 4.25 (bs, 4H, Ar-CH_2-Ar ax), 6.66 (s, 8H, ArH), 10.32 (s, 4H, OH). m/z (%) 752(100), 669(45), 340(98), 271(27), 83(79), 69(27). Anal. Calcd for $C_{52}H_{64}O_4$: C, 82.93; H, 8.57. Found: C, 83.08; H, 8.50.

X-ray diffraction study:

Crystal data: $C_{36}H_{40}O_4$, Formula weight. 536.7, monoclinic; a = 12.440(2), b = 12.323, c = 19.874(3) Å, β = 100.34(2)°, U = 2997(1) $Å^3$, Z = 4, D_c = 1.19 $g.cm^{-3}$, space group (from systematic absences) P $2_1/c$ Cu-Kα radiation λ = 1.5418 Å, μ(Cu-Kα) 5.6 cm^{-1}.

Measurements: A single colorless transparent crystal of 0.2x0.3x0.4 mm dimensions was used for the X-ray measurements carried out at room temperature on a SIEMENS AED using Ni filtered Cu-Kα radiation. Lattice parameters were determined on the basis of a set of 29 $(\theta,\chi,\phi)_{hkl}$ reflections in the range $30 \leq \theta \leq 40°$. A total of 6274 +h, +k, +l reflections were collected in the range $3 < \theta < 70°$ with the θ-2θ step scanning mode and scan width from [θ-0.60] to [θ+0.60+ θ]° were $\theta = (\lambda_{\alpha 2} - \lambda_{\alpha 1}).\ ^{-1}.\mathrm{tg}\ \theta$. The intensities were determined by profile analysis following a standard procedure.[13,14] The 2876 reflections with $I_{hkl} \geq 2\sigma(I_{hkl})$ (2723 unique; internal R = 0.01) were used in the refinement of the structure.

Structure Analysis

The structure was solved and refined using the SHELX[15] package of crystallographic computer programs. The refinement was performed by several cycles of full matrix least-square methods, first with isotropic temperature factors and then with anisotropic temperature factors for all the atoms with the exception of one of the terminal CH_3 carbon atom and of the hydrogen atoms from which isotropic temperature factors were assumed. 25 Hydrogens including the phenolic ones, evidenced from the Fourier ΔFmap, were refined in the last cycle. Other 12 hydrogens were calculated with the geometrical constraint CH = 1.08 Å. The methyl hydrogens of the disordered CH_3 groups were not taken into account. A total of 470 parameters were refined. The final R value was 0.058 having used unit weights. The maximum height found in the final Fourier ΔF map was 0.3 $e.Å^{-3}$. The geometrical calculations were performed with PARST[16] and the drawings were performed

with PLUTO in the Crysruler package.[17] The scattering factors were taken from the literature.[18] All the calculations were carried out on the GOULD 6040 Power node of Centro di Studio per la Strutturistica Diffrattometrica del CNR Parma.

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REFERENCES

1.- Ungaro, R.; Pochini, A.; Andreetti, G.D.; and Domiano, P. J. Chem. Soc., Perkin Trans. 2, 1985, 197.

2.- Dhawan, B.; Chen, S.I.; and Gutsche, C.D. Makromol. Chem., 1987, 188, 921.

3.- Bocchi, V.; Foina, D.; Pochini, A.; Ungaro, R.; and Andreetti, G.D. Tetrahedron, 1982, 38, 373; Coruzzi, M.; Andreetti, G.D.; Bocchi, V.; Pochini, A. and Ungaro, R. J. Chem. Soc., Perkin Trans 2, 1982, 1133; Gutsche, C.D.; Levine, A. J. Am. Chem. Soc., 1982, 104, 2652.

4.- Gutsche, C.D. and Pagoria, P.F. J. Org. Chem., 1985, 50, 5795.

5.- No, K.; Noh, Y. Bull. Korean. Chem. Soc., 1986, 7, 442; Arimura, T.; Shinkai, S.; Matsuda, T.; Hirata, Y.; Satoh, H. and Manabe, O. Bull. Chem. Soc. Japan, 1988, 61, 3733; Shinkai, S.; Nakasaki, T.; Iwamoto, K.; Ikeda, A.; He, G.-X.; Matsuda, J. and Iwamoto, M. Bull. Chem. Soc. Japan, 1991, 64, 381.

6.- Gutsche, C.D. and Nam, K.C. J. Am. Chem. Soc., 1985, 107, 6052.

7.- Almi, M.; Arduini, A.; Casnati, A.; Pochini, A. and Ungaro, R. Tetrahedron, 1989, 45, 2177.

8.- Gutsche, C.D., Levine, J.A. and Svjeeth, P.K. J. Am. Chem. Soc., 1985, 50, 5802.

9.- Andreetti, G.D.; Pochini, A. and Ungaro, R. J. Chem. Soc. Perkin Trans. 2, 1983, 1773.

10.- Andreetti, G.D.; Ungaro, R. and Pochini, A. J. Chem. Soc. Chem. Commun., 1979, 100.

11.- Allinger, N.L. and Tribble, M.T. Tetrahedron Lett., 1971, 3259; Abraham, R.J.; Bergen, H.A. and Chadwich, D.J. Tetrahedron Lett., 1981, 2807.

12.- Gutsche, C.D. and Bauer, L.J. J. Am. Chem. Soc., 1985, 107, 6052.

13.- Belletti, D.; Ugozzoli, F.; Cantoni, A.; Pasquinelli, G. Centro di Studio per la Strutturistica Diffrattometrica del C.N.R., Parma, Italy, Internal Reports 1/79, 2/79, 3/79 (1979).

14.- Lehmann, M.S. and Larsen, F. Acta Cryst., 1974, A30, 580.

15.- Sheldrick, SHELX76 and SHELX86 Programs for Crystal Structure Determination, University of Cambridge 1976 and 1986.

16.- Nardelli, M. Comput. & Chem., 1983, 7, 95.

17.- Rizzoli, C.; Sangermano, V.; Calestani, G.; Andreetti, G.D. J. Appl. Cryst., 1987, 20, 436.

18.- International Tables for X-ray Crystallography; Kynoch Press, Birmingham, England, 1974, Vol. IV, pp. 72-98.