Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3171–3174

TETRAHEDRON: *ASYMMETRY*

Chiral calixarenes derived from resorcinol. Part 3: Functionalization of octaester derivatives with chiral amines and amino alcohols

Waldemar Iwanek *

Institute of Chemistry, Pedagogical University, Checinska 5, 25-020 Kielce, Poland

Received 27 June 1998; accepted 1 September 1998

Abstract

A new type of chiral calixresorcarene is described. The formation of both enantiomers of **3** and **4** is controlled by the chiral amines and amino alcohols used for the reaction. Formation of the dimers of these compounds in the gas phase and in solution was observed using the LSIMS and ESI-MS methods. Formation of amide dimers of the derivative **3** in chloroform was confirmed by fluorescence spectroscopy. © 1998 Elsevier Science Ltd. All rights reserved.

In the field of supramolecular host–guest chemistry, calixresorcarene macrocycles **1** are of increasing interest, being the basic skeleton for the synthesis of host compounds for ions or neutral molecules.[1] In this respect, chiral calixarenes are of pivotal importance for investigations of enantiosectivity and discrimination. Our studies are directed towards the synthesis and use of chiral calixresorcarenes as ligands in asymmetric synthesis, chiral discrimination, and preparation of novel supramolecular assemblies.

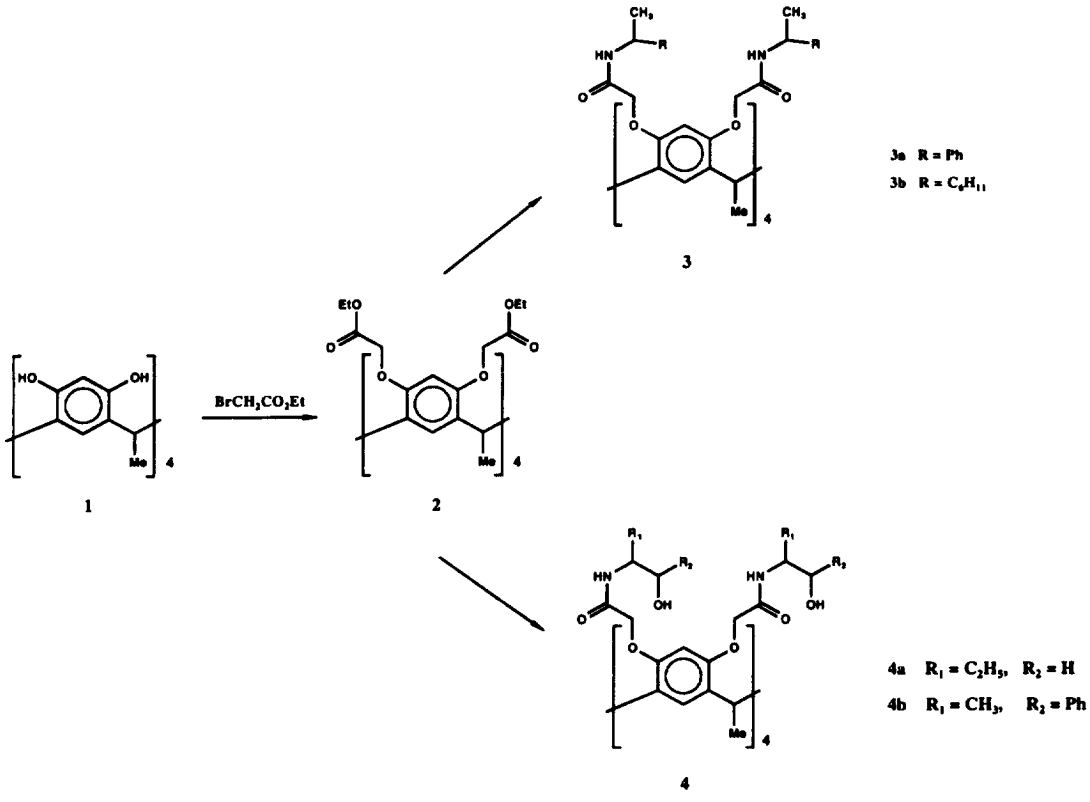
The calixresorcarene chirality can be generated by substituting the resorcinol ring at the 2 position (e.g., the oxazine[2] and oxazolidine[3] derivatives), as well as by substituting the lower rim of calixresorcarenes (e.g., the amide[4] and glycoside[5] derivatives). The synthesis of 'inherently' chiral calixresorcarene derivatives is also possible, wherein the nonplanarity of the molecule along with asymmetric substitution of the macrocycle is employed.[6]

This paper reports the synthesis of chiral amide derivatives **3** and **4** of octaester calixresorcarene **2** (Scheme 1). As chiral auxiliaries, commercially available, inexpensive chiral amines and amino alcohols were used.

The calixresorcarene **1**, prepared from resorcinol and acetaldehyde, was used as a framework molecule in this study. The reaction of **1** with ethyl bromoacetate (molar ratio of 1:20) was carried out in dry acetone in the presence of K_2CO_3 base. The reaction mixture was gently refluxed under argon for 24

* E-mail: iwanek@top.pu.kielce.pl

PII: S0957-4166(98)00351-6



Scheme 1.

h. The octaester **2** was crystallized from ethanol and isolated in 85% yield. Heating of **2** with chiral amines or amino alcohols at reflux under argon for 4 h gave the derivatives **3** or **4**, respectively. The chiral octamides **3** and **4** were purified by crystallization from ethanol and isolated in 55–80% yield (see Table 1). Both enantiomers of the amines and amino alcohols were used and the corresponding enantiomeric compounds **3** and **4** were formed in all cases. Satisfactory microanalytical and spectral data were obtained for all new products. Exact molecular masses determined by HR-MS are as follows: **3a**: found, 1834.8933; calcd, 1834.2240; **3b**: found, 1883.2689; calcd, 1882.6032; **4a**: found, 1577.8494; calcd, 1577.8672; **4b**: found, 2074.9778; calcd, 2074.4336.

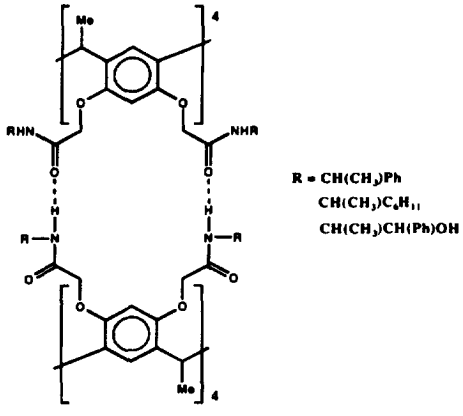
Table 1
Reaction yields and optical rotations in chloroform for the amide derivatives **3** and **4**.

Substrate	Product	Yield [%]	$[\alpha]_{546}$	c [g/100 ml]
R(+)-1-Phenylethylamine	(+) **3a**	70	+5.6	1.05
S(−)-1- Phenylethylamine	(−) **3a**	65	−5.5	1.00
S(+)-1-Cyclohexylethylamine	(+) **3b**	75	+14.4	1.10
R(−)-1-Cyclohexylethylamine	(−) **3b**	72	−14.2	1.10
S(+)-2-Amino-1-butanol	(+) **4a**	50	+16.4*	1.04
R(−)-2-Amino-1-butanol	(−) **4a**	60	-16.2*	1.02
(+)-Norephedrine	(+) **4b**	80	+24.4	1.03
(−)-Norephedrine	(−) **4b**	75	−24.6	1.05

* Because of poor solubility of **4a**, the optical rotation of this amide was determined for the alkyl substituent R=C_6H_{11} of calixresorcarene **1**.

The ^{1}H-NMR spectra of **3** and **4** taken in $CHCl_3$ at ambient temperature were identical for each pair of enantiomers. The key features of the ^{1}H-NMR spectra are the chemical shifts and line widths of the signals of $-OCH_2-$ and –CONH– groups. The signals of $-OCH_2-$ and –CONH– are broad and poorly resolved, which indicates a dynamic effect typical for high molecular mass compounds with strong dipolar interactions of the nuclei and steric hindrance of the rotation. Additionally, the ^{1}H-NMR spectra in DMSO were taken for the amide **3b**. At room temperature, the diffuse signals of the amide groups and $-OCH_2-$ groups are observed. At 80°C, these signals are slightly sharpened due to the increased molecular dynamics.

The amide groups, due to hydrogen bonding, are often employed for organization of macrocyclic compounds into larger molecular ensembles called the supramolecular capsules.[7] Examples of formation of such supramolecular capsules are known also for calixresorcarenes.[8] The LSIMS mass spectra of the discussed chiral amides indicate dimerization of these compounds in the gas phase. The molecular ions of **3a**, **3b**, and **4b** were found to have masses of 3670.4, 3765.5, and 4152.2, respectively. These masses correspond exactly to dimers of structure shown in Scheme 2, which possibly form in the gas phase.



Scheme 2.

In the solid phase, the IR spectra of all chiral amides show that the amide groups adopt the *trans* conformation. For this conformation, the non-bonding amide group bands (e.g., stretching vibration of NH at 3424 cm^{-1} for **3b**), as well as the bonding amide group bands (e.g., stretching vibration of NH at 3304 cm^{-1} for **3b**) are found. This is typical for the associated amides in the solid state.

The formation of dimers of the amide derivatives **3** in chloroform was confirmed by fluorescence spectroscopy. The fluorescence spectra of these amides in chloroform show substantial changes with time (Fig. 1). The red shift occurs and the band structure alters depending on the observation time.

No time-related changes of fluorescence spectra are observed for solvents such as tetrahydrofuran and acetonitrile. This testifies to the hydrogen-bonding interaction of the amide groups of **3** with the solvents containing the electron-donor atoms. Such interaction disables formation of dimers of these compounds. Chloroform, being the less electron-donating solvent, allows the hydrogen-bonding interaction of the solute molecules. No kinetic changes in the electron spectra (UV–vis spectroscopy) are observed for the studied amides in the solvents used. The concentration-dependent changes in the first long-wave absorption band in the electron spectrum of amides **3a** and **3b** in chloroform are very small and irregular. This precludes determination of the dimerization constants in solution using this technique. However, the presence of dimers of the mentioned amides in the chloroform/methanol solution was confirmed by the ESI-MS method. Molecular ions having masses of 3366.6 and 3431.0 were observed for **3a** and **3b**,

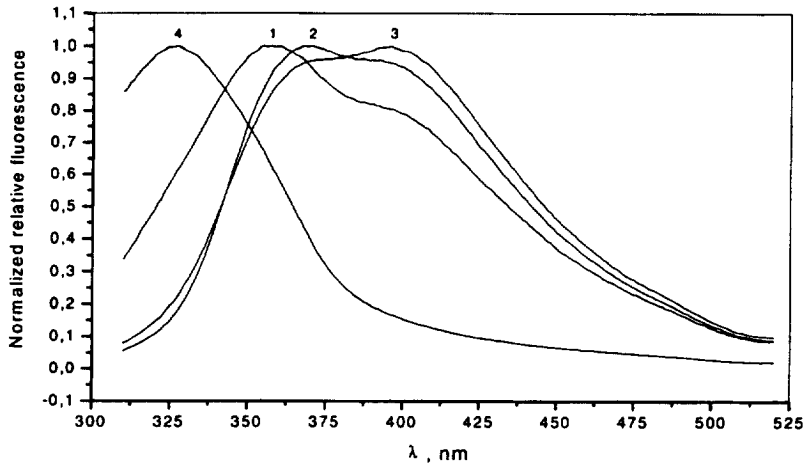


Fig. 1. Changes in the fluorescence spectrum of amide **3a** in chloroform depending on the observation time: (1) immediately after preparation of the solution; (2) after 30 min; (3) after 60 min. The curve (4) shows the fluorescence spectrum of **3a** in tetrahydrofuran

respectively. They correspond to the masses of dimers existing in the solution less the masses of two fragments, i.e., $2\times CONHCH(CH_3)Ph$ for **3a** and $2\times CH_2CONHCH(CH_3)C_6H_{11}$ for **3b**, respectively.

Thorough investigation of spectroscopic and kinetic effects of self-organization of amide derivatives of calixresorcarenes will be the object of further studies.

In summary, chiral amide derivatives of calixresorcarenes were prepared. Their dimerization in the gas phase and in solution as well as association in the solid phase were observed.

Acknowledgements

This work was supported by the Polish State Committee for Scientific Research (Project No. 3T09A00613). The author thanks the Volkswagen Foundation for delivery of the SFM-25 Fluorimeter (Kontron) within the research grant from this Foundation.

References

1. (a) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambrige, 1989; (b) *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Vicens, J.; Böhmer, V., Eds; Kluwer: Dordrecht, 1991; (d) Böhmer, V. *Angew. Chem.* **1995**, *107*, 785; (e) Timmerman, P.; Verboom, W.; Reinhoudt, D. *Tetrahedron* **1996**, *52*, 2663.
2. (a) Iwanek, W.; Mattay, J. *Liebigs Ann. Chem.* **1995**, 1463; (b) Arnecke, R.; Böhmer, V.; Paulus, E. F.; Vogt, W. *J. Am. Chem. Soc.* **1995**, *117*, 3286; (c) Airola, K.; Böhmer, V.; Paulus, E.; Schmidt, Ch.; Thondorf, I.; Vogt, W. *Tetrahedron* **1997**, *53*, 10709.
3. Iwanek, W.; Wolff, C.; Mattay, J. *Tetrahedron Lett.* **1995**, 8969.
4. (a) Botta, B.; Delle Monache, G.; Salvatore, P.; Gasparrini, F.; Villani, C.; Botta, M.; Corelli, F.; Tafi, A.; Gacs-Baitz, E.; Santini, A.; Carvalho, C. F.; Misiti, D. *J. Org. Chem.* **1997**, *62*, 932; (b) Botta, B.; Delle Monache, G.; De Rosa, C.; Seri, C.; Benedetti, E.; Iacovion, R.; Botta, M.; Corelli, F.; Masignani, V.; Tafi, A.; Gacs-Baitz, E.; Santini, A.; Misiti, D. *J. Org. Chem.* **1997**, *62*, 1788.
5. Curtis, A. D. M. *Tetrahedron Lett.* **1997**, *38*, 4295.
6. Takanishi, H.; Tamura, T.; Ohkubo, H.; Kobayashi, K.; Morikawa, O. *Chem. Lett.* **1996**, 685.
7. Conn, M. M.; Rebek, J. *Chem. Rev.* **1997**, *97*, 1647.
8. (a) MacGillivary, R. C.; Atwood, J. L. *Nature* **1997**, *289*, 469; (b) Rose, K. N.; Barbour, L. J.; Orr, G. W.; Atwood, J. L. *Chem. Commun.* **1998**, 407; Murayama, K.; Aoki, K. *Chem. Commun.* **1998**, 607.