Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2004, 14(6), 237–239

Mendeleev Communications

Chiral HPLC separation and CD spectra of the enantiomers of a molecular 'hamburger'

Salvatore Caccamese,*[a] Nunziatina Parrinello,[a] Salvatore Failla,[b] Giuseppe A. Consiglio[b] and Paolo Finocchiaro*[b]

[a] *Dipartimento di Scienze Chimiche, Università di Catania, 95125 Catania, Italy. Fax: +39 095 58 0136; e-mail: scaccamese@dipchi.unict.it*
[b] *Dipartimento di Metodologie Chimiche e Fisiche per l'Ingegneria, Università di Catania, 95125 Catania, Italy. Fax: +39 095 731 2798; e-mail: pfinocchiaro@dmfci.unict.it*

DOI: 10.1070/MC2004v014n06ABEH001993

A good enantioseparation of racemic spirobiindane bisphosphonate macrobicyclophanes was obtained by HPLC on Chiralpak AD.

In spite of the Kolbe's scepticism culminated in his intemperate and impolite attack on the paper 'Die Lagerung der Atome in Raume' by J. H. van't Hoff, in the 130 years elapsed from this mile-stone concept in chemistry, so many examples of stereostructures appeared in the chemical literature indicating the correctness and the utility of van't Hoff's ideas, which cannot be anymore ignored in order to explain the architecture, properties and biological functions of simple, as well as more complex, chemical structures.

Therefore, in order to pay a tribute to the innovative ideas of van't Hoff and Le Bel, we would like to report the synthesis, characterization and optical resolution of a highly congested molecule evolving in the space, which in its iconographic and geometrical model takes flesh as a 'hamburger'.

Scheme 1 gives a schematic description of the synthetic strategy employed for the preparation of cyclophanes. The Williamson synthetic procedure used proved to be very satisfactory, all reagents were converted almost quantitatively and only [2 + 1] cyclization products were obtained in very high yields.

The reaction of racemic monomer phosphonate **1** with 1,2,4,5-tetrakis(bromomethyl)benzene **2** afforded bromine-free products having *m*/*z* 1287.5 (MH^+) and thus confirming the 2:1 stoichiometry of the reaction.

Theoretically, the incorporation of a common tetra-substituted benzene ring between the rigid bis(phosphonate) spirobiindane units gives rise to three different isomers, *i.e.*, *ortho*/*ortho*, *meta*/*meta* and *para*/*para* **3**. Moreover, considering that spirobiindane phosphonate monomer **1** is a geometrically constrained dissymetric molecule, which exists as a pair of enantiomers, for each of them a couple of diastereoisomers (*i.e.*, meso and racemic forms) could be obtained.

Previously,[1] we demonstrated that, among possible diastereomers, only compound **3** is formed in our synthesis, which exists as a couple of enantiomers (PP, MM, **3a**) and the meso form (PM, **3b**).

The inspection of the structure of **3a** (PP or MM, *i.e.*, the racemic form) reveals that this molecule is chiral with a dis-

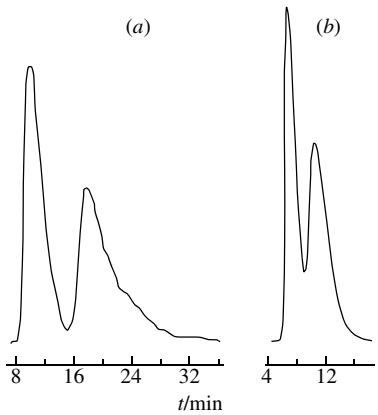
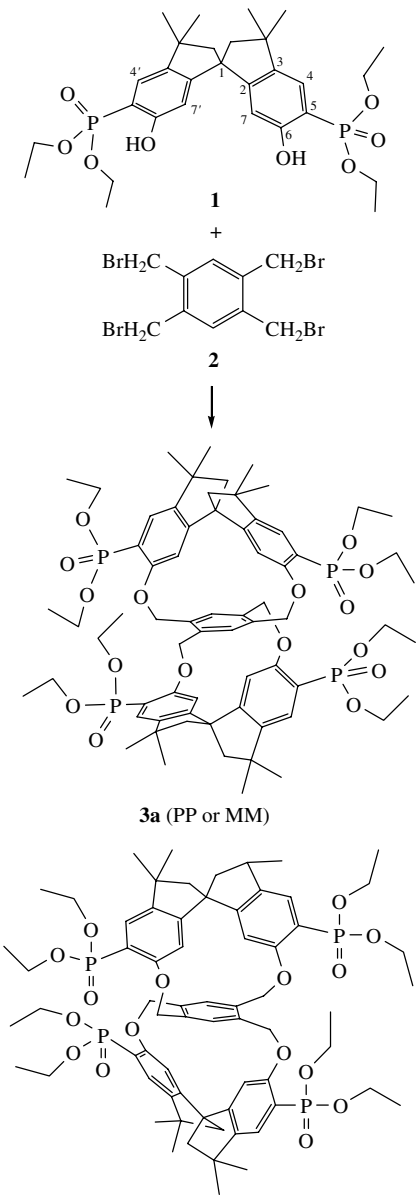


Figure 1 Chiralpak AD HPLC enantioseparation of compound **3a**.†



Scheme 1

symmetric structure (point symmetry group D_2); all atoms of the spirobiindane units, as well as those of the central tetrakismethylbenzene unit, are related by symmetry. It follows that the ^{1}H, ^{13}C and ^{31}P NMR spectra of this diastereoisomer should exhibit a set of signals for 4,4′-H, 7,7′-H, four CH_2 bridged hydrogens, *etc*.

On the contrary, the examination of the structure of **3b** (PM, *i.e*., meso form) reveals that this molecule has point symmetry group C_2; this structure is also dissymmetric and chiral[1,2] and the atoms of the spirobiindane units, as well as those of the central tetrakismethylbenzene unit, are related pairwise by symmetry. It follows that the ^{1}H, ^{13}C and ^{31}P NMR spectra of compound **3b** should exhibit, in the absence of accidental isochronies, two sets of signals for 4,4′-H, 7,7′-H, four CH_2 bridged hydrogens, *etc.*, as found previously.[1]

Considering that both diastereomers **3a** and **3b** are chiral and taking into account our experience in the enantioseparation of spirobiindane phosphonate monomer **1**,[3] we tried to resolve them by enantioselective HPLC. We used two polysaccharide-derived chiral stationary phases (CSPs) and several eluents in a normal-phase mode. A good enantioseparation of **3a** was obtained by HPLC on Chiralpak AD. The best separation factor α was found to be 2.1 with the resolution factor $R_s = 1.4$,[4] as shown in Figure 1(*a*).† A slight increase in the polarity of the mobile phase (isooctane–ethanol, to 95:5) decreases both α and R_s to 1.8 and 0.7, respectively, as shown in Figure 1(*b*). In the experiment shown in Figure 1(*a*), it was also possible to detect several impurities in the descending edge of the second peak, and these impurities were not discernible when the resolution factor R_s was too low, as shown in Figure 1(*b*). These impurities are probably more polar linear oligomers formed as by-products in the condensation reaction. The presence of impurities was confirmed by HPLC on an achiral column. Indeed, in addition to a sharp peak at 12.3 min, which was attributed to the racemic mixture, a very broad peak centred at 9.4 min appeared and partially overlapped with the main peak.‡

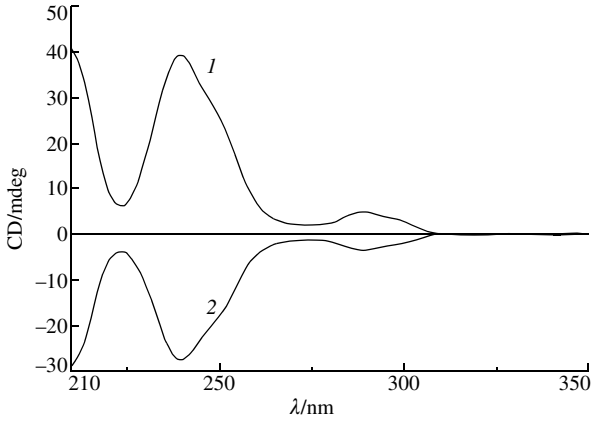


Figure 2 CD spectra (ethanol) of the enantiomers of compound **3a** obtained from the (*1*) first and (*2*) second HPLC peaks.

Based on the HPLC trace in Figure 1(*a*), we performed the isolation of the enantiomers of compound **3a**. This was accomplished by repeated 50 μl injections (0.2–0.3 mg) of daily prepared ethanolic solutions of racemic **3a** and the collection of eluates corresponding to the two chromatographic peaks. However, a 'peak shaving' was necessary to avoid the collection of impurities present as successive shoulders in the descending edge of the second peak.

The CD spectra of the eluted peaks were recorded on a Jasco 810 spectropolarimeter using a 1 mm cell after rotoevaporating the solutions from HPLC and dissolving again the residues in 1 ml of ethanol. They resulted in mirror images of each other, as shown in Figure 2, indicating the enantiomeric relationship between the two eluates.

Interestingly, the CD curves are not bisignate and are formed by residual signals. The exciton coupling present in the CD spectra of the enantiomers of compound **1** is, in fact, absent in compound **3a**. This is due to a partial 'internal compensation' between both chiral spirobiindane bis(phosphonate) moieties present in the macrocycle. As shown in Figure 3, there is a distorsion in the reciprocal space orientation of these CD-active

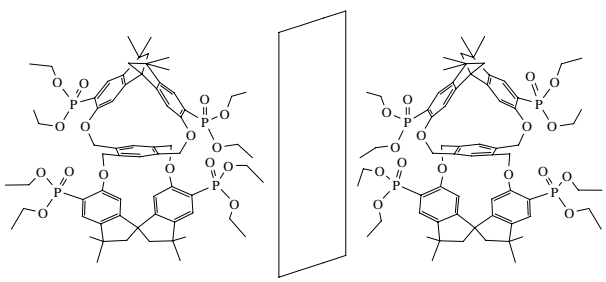


Figure 3 Enantiomers of compound **3a** (mirror plane).

† *Conditions*: column, Chiralpak AD from Daicel (25×0.46 cm i.d.) [amylose tris(3,5-dimethylphenylcarbamate)]; eluent, isooctane/ethanol (96/4); flow rate, 1 ml min^{-1}, UV detector at 240 nm.

‡ *Conditions*: column, Ultrasphere from Beckmann (15×0.2 cm i.d.) (silica gel); eluent, hexane/ethyl acetate (5/95); flow rate, 1 ml min^{-1}; UV detector at 270 nm.

moieties present in the 'upper' and 'lower' parts of the molecule. Moreover, both moieties interact with the tetra-substituted benzene ring in the middle of the molecule, and a shoulder at 255–260 nm can be related to the strong UV absorbance of this chromophore at λ_{max} = 226 and 260 nm, while compound **1** exhibits λ_{max} = 206 nm and λ_{min} = 260 nm.

Thus, the above results represent the first experimental proof of inherent chirality in a solution of compound **3a**.

We tried to resolve compound **3a** using a polysaccharide CSP containing an additional stereogenic center, Chiralpak AS-H, and a similar eluent, but only broad peaks were observed. Analogously, the enantioresolution of compound **3b** was totally unsuccessful on both the CSPs described since several irreproducible peaks appeared in the HPLC experiments indicating either the lability of the compound or a severe contamination.

References

1 G. Consiglio, S. Failla and P. Finocchiaro, *J. Phys. Org. Chem*., 2004, **17**, 760.

2 (*a*) P. Finocchiaro, D. Gust, D. Hounshell, J. P. Hummel, P. Maravigna, and K. Mislow, *J. Am. Chem. Soc*., 1976, **98**, 4945; (*b*) R. G. Kostyanovsky, G. K. Kadorkina, V. S. Kostyanovsky, V. Schurig and O. Trapp, *Angew. Chem., Int. Ed. Engl*., 2000, **39**, 2938.

3 G. Consiglio, P. Finocchiaro, S. Failla, K. I. Hardcastle, C. Ross, S. Caccamese and G. Giudice, *Eur. J. Org. Chem*., 1999, 2799.

4 S. Allenmark, *Chromatographic Enantioseparation: Methods and Applications*, 2nd edn., Ellis Horwood, Chichester, 1991, p. 82.

Received: 12th July 2004; Com. 04/2318