Notes

[Chem. Pharm. Bull. 30(9)3370—3373(1982)]

Thermal Equilibrations of 1,11-Dioxa[11]paracyclophane Derivatives in Cholesteric Liquid Crystals

Takehisa Kunieda,* Wen-Chieh Tsai, Masato Narushima, and Masaaki Hirobe*

Faculty of Pharmaceutical Sciences, University of Tokyo
Hongo, Bunkyo-ku, Tokyo, 113 Japan

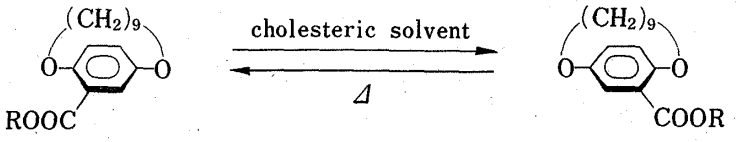
(Received February 4, 1982)

1,11-Dioxa[11]paracyclophane (2,12-dioxabicyclo[11,2,2]heptadeca-13,15,16-triene) derivatives were thermally equilibrated in cholesteric mesophases. The enantiomeric and diastereomeric equilibria were biased to the extents of 0.4 and 3.6% (e.e.), respectively, independently of the macrostructural handedness of the mesophases.

Keywords——cholesteric liquid crystal; 1,11-dioxa[11]paracyclophane-13-carboxylic acid; thermal equilibration; asymmetric induction; helical handedness

There is a great deal of current interest in the utilization of liquid crystals as anisotropic reaction media for controlling the rate and the stereochemical courses of unimolecular[1a–i] and bimolecular reactions.[2] This is partly because of their similarities to some biological media.[3]

Recent papers[1b–d,f] dealing with thermal and photochemical conversions conducted in cholesteric mesophases have led to controversy regarding the possibility of appreciable asymmetric induction, since a lack of reproducibility or extremely small extent of induction has become apparent on reevaluation of the reported reactions.[1e,g] It is still of considerable interest to demonstrate clearly the effectiveness of cholesteric liquid crystals in controlling the stereochemistry. Thus, we have explored, in anisotropic chiral media, the enantiomeric and diastereomeric thermal equilibration of 1,11-dioxa[11]paracyclophane systems (**1**)[4] with large steric requirement, which may be sensitive to a liquid crystalline environment.[5]



(*R*)-**1** (*S*)-**1**

Such paracyclophanes have appreciable barries to inversion of the methylene bridge and racemize noticeably only at temperatures above 80°C (R=CH_3: $T_{1/2}$ 7.4h at 96°C[4]; 18min at 150°C). Thus, low concentrations (5 mol%) of the paracyclophane derivatives were heated at 150°C in media consisting of cholesteric esters such as benzoate (Ch-B), cinnamate (Ch-C), 2,4-dichlorobenzoate (Ch-DCl) and *p*-methoxybenzoate (Ch-PMB), maintaining cholesteric mesophases during the reaction. The equilibrated solutes were recovered nearly quantitatively from the reaction mixture by extraction with acetone[6] and transformed into the methyl ester **1** (R=CH_3) by treatment with KOH-crown ether and diazomethane for a decisive determination of optical purity. This procedure could preclude contamination with any optically active impurity possibly derived from the cholesteryl moiety.

First we explored the diastereomeric equilibration of cholesteryl paracyclophanecarboxylate, which might be capable of structurally mimicking the mesophases. No significant asymmetric transformation was observed in the control experiments in which the solute was heated

Table I. Thermal Equilibration of 1, 11-Dioxa[11]paracyclophane-13-carboxylic Acid Derivatives (1) in Cholesteric Liquid Crystals[a]

No.	R	Medium	Temp (°C)	Time (h)	Phase	Methyl ester (1)(R=CH_3) $[\alpha]_D$[b]	(% e.e.)[c]	Conf.[d]
1	Cholesteryl	Ch-B	150	24	Anisotropic	+3.9°	(3.6)	*S*
2	Cholesteryl	Cumene/Ch-B[e]	150	24	Isotropic	+0.1	(−)	—
3	Cholesteryl	Ch-B	160	24	Anisotropic	+3.2	(3.0)	*S*
4	Cholesteryl	Ch-B	175	5	Isotropic	−0.1	(−)	—
5	Cholesteryl	Ch-C	160	24	Anisotropic	+1.1	(1.0)	*S*
6	Cholesteryl	Ch-DCl	150	5	Anisotropic	−2.3	(2.2)	*R*
7	Cholesteryl	Ch-PMB	175	24	Anisotropic	−0.8	(0.7)	*R*
8	H	Ch-B	150	24	Anisotropic	+0.3	(0.3)	*S*
9	H	Cumene/Ch-B[e]	150	24	Isotropic	−0.1	(−)	—
10	Methyl	Ch-B	150	5	Anisotropic	+0.1	(−)	—
11	Bicyclohexyl[f]	Ch-B	150	24	Anisotropic	+0.4	(0.4)	*S*
12	Bicyclohexyl[f]	Ch-B	178	24	Isotropic	+0.2	(0.2)	*S*
13	Isobutyl	Ch-B	150	24	Anisotropic	+0.4	(0.4)	*S*
14	Myristyl	Ch-B	150	24	Anisotropic	+0.3	(0.3)	*S*

a) The equilibrations were performed under the same conditions as described for the example and optical purity was determined as the methyl ester (see text). *b*) Determined in *m*-xylene (c=4—10) and with an experimental error of ±0.1°. *c*) Calculated from $[\alpha]_D$ −109.5° (*m*-xylene) for pure methyl ester.[4] *d*) Based on the CD spectrum. *e*) In a ratio of 1:1 (wt). *f*) *trans*-4-Bicyclohexyl ester was used.

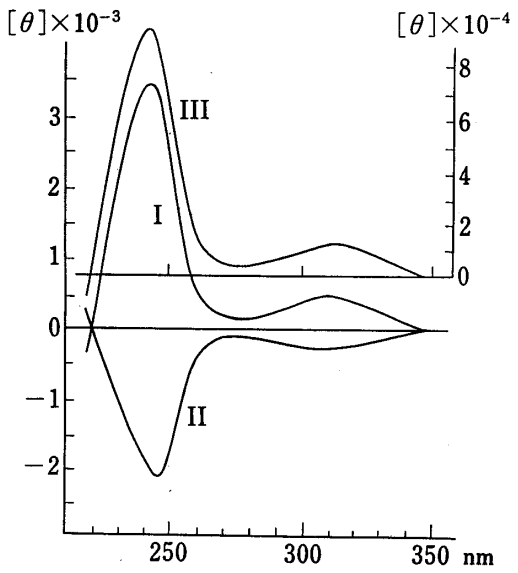


Fig. 1. The CD Spectra of Methyl 1,11-Dioxa[11]paracyclophane-13-carboxylate 1 (R=CH_3) in Methanol

I: run 1, II: run 6, III: optically pure compound resolved.

in isotropic liquid phases (Table I, run 2 and 4) and therefore this case may serve as a diagnostic system for the elucidation of solvent effect. Thermal treatment in cholesteric Ch-B and Ch-C resulted in a reproducible and appreciable enrichment in the (*S*)-methyl ester (3.6% e.e.), while the use of Ch-DCl and Ch-PMB as anisotropic media biased the equilibrium to nearly the same extent in the opposite direction. Chirality of the methyl ester was substantiated by the circular dichroism (CD) spectra, virtually parallel to that of an optically pure authentic specimen[4] (Fig. 1), for which configurational assignment had been based on a comparison with [8]paracyclophane-10-carboxylic acid.[7]

These findings not only provide an example where stereochemical control could be attained by liquid crystals, but also show an independence of the macrostructural handedness of the mesophases, since all of the cholesteryl esters used here are known to form a right-handed helix.[8] Stereochemical transformation would be governed by the local ordering of chiral mesophases, which enhances the solute–solvent interaction, as suggested previously,[1f] although mechanistic factors governing the selectivity remain to be established.

We turned then to enantiomeric equilibration of the paracyclophanes in cholesteryl benzoate. As indicated in Table I, small but reproducible asymmetric induction was observed in most of the cases examined under anisotropic conditions. The induction is of the same order of magnitude as the extent of photo-asymmetric synthesis of hexahelicene,[1g] which is one of very few examples clearly established by isolating the pure product. Control experi-

ments (run 9 and 12) conducted in isotropic liquid phases gave much less or no asymmetric induction.

The present study serves as a good example of the importance of ordered media in stereochemical control.

Experimental[9]

Substituted Benzoates of Cholesterol——These liquid crystal solvents were prepared by acylation of purified cholesterol with the corresponding acid chlorides in pyridine and showed the following transition temperatures. Ch-B:[1d,10] 147$\overset{ch}{-}$176°C; Ch-C:[1d] 161$\overset{ch}{-}$210°C; Ch-DCl:[1d] 130$\overset{ch}{-}$213°C; Ch-PMB:[11] 178$\overset{ch}{-}$260°C.

1,11-Dioxa[11]paracyclophane-13-carboxylic Acid (1) (R=H) (2,12-Dioxa[11,2,2]heptadecane-13,15,16-triene-14-carboxylic Acid)——This acid was prepared from hydroquinone in 34% yield by slight modifications of the reported procedure,[4] mp 60$\overset{ch}{-}$63°C (from aqueous EtOH) [lit.,[4] 63°C], IR(KBr) 1690 cm^{-1}, NMR ($CDCl_3$) δ: 0.6—1.2 (10H), 1.4—2.0 (4H), 4.1—4.6 (4H), 7.2(2H), 7.6 (1H). *Anal.* Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.08; H, 8.05.

The following esters were prepared in a conventional manner.

Cholesteryl Ester (1: R=cholesteryl): Colorless crystals from MeOH as a diastereomeric mixture, mp 82$\overset{ch}{-}$102°C, IR(KBr) 1700 cm^{-1} NMR ($CDCl_3$) δ: 0.7—1.2 (57H), 4.1—4.3 (4H, t, J=6.0 Hz), 4.6—5.2 (1H), 5.3—5.6 (1H), 7.1 (2H), 7.4 (1H). *Anal.* Calcd for $C_{43}H_{66}O_4$: C, 79.83; H, 10.28. Found: C, 80.12; H, 10.38. Repeated attempts to separate the diastereoisomers by careful chromatography on silica gel or by high performance liquid chromatography (HPLC) using conventional prepacked coloumns were unsuccessful. Thus, purification of the cholesteryl esters by column chromatography on silica gel (CH_2Cl_2), followed by hydrolysis gave racemic acid (1) only.

Methyl Ester (1: R=Me): An oil, bp 150°C/0.5 mmHg, IR(Nujol) 1700 cm^{-1}, NMR ($CDCl_3$) δ: 0.5—1.9 (14H), 3.9 (3H), 4.2 (4H, t, J=6.0 Hz), 7.2 (2H), 7.4 (1H). MS Calcd for $C_{17}H_{24}O_4$: m/z 292.1672 (M^+). Found: m/z 292.1658 (M^+).

Isobutyl Ester (1: R=i-Bu): A viscous oil, IR(liquid) 1700 cm^{-1}, NMR ($CDCl_3$) δ: 0.9—1.6 (21H), 4.0—4.3 (6H), 7.1 (2H), 7.4 (1H).

Myristyl Ester (1, R=$CH_3(CH_2)_{13}$–): A viscous oil, IR(liquid) 1700 cm^{-1}, NMR ($CDCl_3$) δ: 0.7—1.6 (41H), 4.1—4.5 (6H), 7.1 (2H), 7.4 (1H). MS Calcd for $C_{30}H_{50}O_4$: m/z 474.3706 (M^+). Found: m/z 474.3677 (M^+).

***trans* 4-Bicyclohexyl Ester (1, R=bicyclohexyl)**: An oil, IR (liquid) 1700 cm^{-1}, NMR ($CDCl_3$) δ: 0.9—1.6 (34H), 4.1 (4H, t, J=6.0 Hz), 4.6—5.2 (1H), 7.1 (2H), 7.4 (1H). MS Calcd for $C_{28}H_{42}O_4$: m/z 442.3080 (M^+). Found: m/z 442.3033 (M^+).

Thermal Equilibration of 1,11-Dioxa[11]paracyclophane Derivatives (1)——Low concentrations (5 mol%) of the paracyclophane derivatives in cholesteryl benzoates as liquid crystal solvents were heated at definite temperatures under argon gas for 5—24 h. After being rapidly cooled, the solutes were extracted with acetone, and removal of the solvent at ambient temperature gave the paracyclophanes nearly quantitatively. In some cases, the substrates were further purified by short column chromatography on silica gel, which caused no separation of the diastereomers as proved in control experiments. The solute thus recovered was treated with KOH-18-crown-6-ether in toluene at room temperature overnight to give the acid (1) (R=H). Esterification with diazomethane followed by purification by preparative thin-layer chromatography provided a sample for determination of optical activity. The results are summarized in Table I. The CD spectra of most of the samples were taken in MeOH (Fig. 1).

References and Notes

1) *a*) W.E. Barnett and W.H. Sohn, *J. Chem. Soc., Chem. Commun.*, **1971**, 1002; *b*) F.D. Saeva, P.E. Sharpe, and G.R. Olin, *J. Am. Chem. Soc.*, **97**, 204 (1975); *c*) L. Verbit, T.R. Halbert, and R.B. Patterson *J. Org. Chem.*, **40**, 1649 (1975); *d*) W.H. Pirkle and P.L. Rinaldi, *J. Am. Chem. Soc.*, **99**, 3510 (1977); *e*) C. Eskenazi, J.F. Nicoud, and H.B. Kagan, *J. Org. Chem.*, **44**, 995 (1979); *f*) M. Nakazaki, K. Yamamoto, and K. Fujiwara, *Chem. Lett.*, **1979**, 863; *g*) M. Hilbert and G. Solladie, *J. Org. Chem.*, **45**, 5393 (1980); *h*) M. Nakazaki, K. Yamamoto, K. Fujiwara, and M. Maeda, *J. Chem. Soc., Chem. Commun.*, **1979**, 1086; *i*) P. Seuron and G. Solladie, *J. Org. Chem.*, **45**, 715 (1980).
2) J.M. Nerbonne and R.G. Weiss, *J. Am. Chem. Soc.*, **101**, 402 (1979); Y.B. Amerik, I.I. Konstantinov, B.A. Krentsel, *J. Polym. Sci.*, **C23**, 231 (1968); C.M. Paleos and M.M. Lakes, *Mol. Cryst. Liq. Cryst.*, **11**, 385 (1970); E. Perplies, H. Ringsdorf, and J.H. Wendorff, *Makromol. Chem.*, **175**, 553 (1974) *etc.*
3) S. Iwayanagi and Y. Sugiura, *Oyo Butsuri*, **40**, 439 (1971); *idem*, *Seibutsu Butsuri*, **15**, 164 (1975).
4) A. Lüttringhaus and G. Eyring *Justus Liebigs Ann. Chem.*, **604**, 111 (1957).

5) Molecular shape plays an important role in specific interaction with liquid crystals; *cf.*) G.M. Janini, K. Johnston, and W.L. Zielinski, Jr., *Anal. Chem.*, **47**, 670 (1975); S. Wasik and S. Chesler, *J. Chromatogr.*, **122**, 451 (1976).
6) In some cases, further chromatographic separation was performed under conditions where separation of the diastereoisomers was confirmed not to occur.
7) K. Yamamoto and M. Nakazaki, *Chem. Lett.*, **1974**, 1051. The opposite configuration has been equivocally suggested (E. Langer, H. Lehner, and K. Schlögl, *Tetrahedron*, **29**, 2473 (1973).
8) L.B. Leder, *J. Chem. Phys.*, **55**, 2649 (1971); F.D. Saeva, *Mol. Cryst. Liq. Cryst.*, **18**, 375 (1972).
9) Phase transition temperatures were measured on a Yanaco micromelting point apparatus equipped with a pair of polarizers. NMR spectra were recorded on a Hitachi R-24 (60 MHz) or a JEOL FX-100 (100 MHz) spectrometer and multiplicity is given only for the signals with definite coupling constants. The mass spectra (MS) were obtained with a Hitachi RMU-7M instrument at 70 eV.
10) L. Verbit, *J. Chem. Educ.*, **49**, 36 (1972).
11) J.S. Dave and R.A. Vora, *Indian J. Chem.*, **11**, 19 (1973).