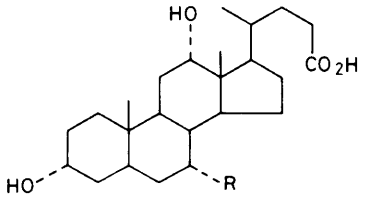
Optical Resolution of Lactones by an Inclusion Method using Cholic Acid as the Host

Mikiji Miyata, Motonari Shibakami, and Kiichi Takemoto

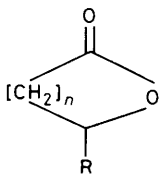
Department of Applied Fine Chemistry, Faculty of Engineering, Osaka Unversity, Suita, Osaka 565, Japan

Cholic acid serves as an effective chiral host molecule for optical resolution of lactones by an inclusion method.

Optical resolution of organic compounds with multimolecular inclusion compounds has recently received much attention on account of its high efficiency.[1] We found earlier that a steroidal acid, cholic acid [3α,7α,12α-trihydroxy-5β-cholan-24-oic acid] (**1**), and its derivatives can serve as host molecules to form inclusion compounds with a wide variety of organic substances.[2,3] Of particular interest is the ability of the chiral host (**1**) to recognize biologically important organic substances, such as lactones which are useful for perfumes, pheromones, and chiral building blocks. We report here an effective optical resolution of the lactones by the inclusion method using the host (**1**). The resolution efficiency of (**1**) for γ-valerolactone (**4**) appears to be better than that of the acetylenic diols reported by Toda and co-workers,[5] whereas the efficiency of the well-known host, deoxycholic acid (**2**),[4] for (**4**) is very low.



(**1**) R = OH
(**2**) R = H



(**3**) *n* = 1, R = Me
(**4**) *n* = 2, R = Me
(**5**) *n* = 2, R = Et
(**6**) *n* = 2, R = Pr^n
(**7**) *n* = 3, R = Me

Commercially available (**1**) was purified by recrystallization from methanol then dried *in vacuo* at 100 °C for 15 h, to afford pure crystals of (**1**) without included methanol molecules. The inclusion compounds of (**1**) with lactones were obtained by two different methods; one a recrystallization method and the other an absorption method. The latter was based on an ability of (**1**) to absorb guest molecules spontaneously. The choice of the methods depended on both the thermal stability of the inclusion compound and the solubility of (**1**) in the liquid guest compound. For example, an inclusion compound of (**1**) with γ-valerolactone (**4**) was obtained by each method, while one with β-butyrolactone (**3**) was obtained only by the recrystallization method.

The optical resolution of (**4**) is typical: The recrystallization of (**1**) from liquid (**4**) afforded a 1 : 1 inclusion compound of (**1**) and (**4**) as colourless prisms. On heating the compound *in vacuo* (3 Torr), (*S*)-(−)-(**4**), $[\alpha]_D$ −8.3° (MeOH) was obtained in 28% enantiomeric excess(e.e.). In the absorption method, a solution of (**4**) (20 mmol) in hexane (10 ml) was poured onto crystalline (**1**) (10 mmol) in a flask. On standing at room temperature for 40 h, the crystals formed a 1 : 1 complex of (**1**) and (**4**) as in the recrystallization method. Washing the crystals with ether followed by extraction with acetonitrile, afforded (*S*)-(−)-(**4**) [0.9 g; $[\alpha]_D$ −11.3° (MeOH); 38% e.e.].

Table 1 shows the result of optical rotation of lactones (**3**)—(**7**) by the inclusion method using (**1**) as the host molecule. The five-membered cyclic compounds (**4**) and (**5**) were resolved quite efficiently, the five- and four-membered ones (**3** and **6**) and the acyclic ester, sec-butyl acetate, were not (e.e ≤3.1%), indicating that the inclusion compounds of (**1**) with the lactones have cavities different from those with ethanol.[6]

Table 1. Optical resolution of lactones (**3**)—(**7**) using cholic acid (**1**) as host.

Lactone	Method[a]	$[\alpha]_D$[b]/°	% e.e.[c]	Absolute configuration	Ref.
(**3**)	R	−0.87	3.1	*S*	8
(**4**)	R	−8.3	28	*S*	5
(**4**)	A	−11.3	38	*S*	5
(**5**)	A	−18.3	34	*S*	9
(**6**)	A	+1.4	2.6	*R*	10
(**7**)	A	−8.5	17	*S*	11
$CH_3CO_2Bu^s$	R	0.0	0	–	–

[a] R = recrystallization; A = absorption method (4 °C, 40 h). [b] *c* 3.0, MeOH, 1 dm cell, 20 °C. [c] Calculated from the $[\alpha]_D$ values reported in the ref. cited, except for (**4**) which was based on ^1H n.m.r. analysis ($CDCl_3$, 400 MHz) using the chiral shift reagent, (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

In case of the absorption method, the e.e. value for (**4**) increased to >95% when the resolution procedure was repeated four times. The absorption time, temperature, and the molar ratio in the feed affected the optical resolution. *E.g.*, in a 1 : 10 molar ratio of (**1**) to (**4**), after standing for two months at 4 °C in a refrigerator, the e.e. of (**4**) was 60%.

On the other hand, we failed to resolve the lactones using a traditional host, deoxycholic acid (**2**) (<1% e.e.), results similar to those of an earlier study on insufficient optical resolution of camphor (4% e.e.) and 2-methylbutyric acid (<1% e.e.)[7] The resolution efficiency of (**1**) for the lactones is also superior to that of diacetylene diol derivatives.[5]

In conclusion, the present study shows that cholic acid (**1**), a naturally-occurring steroid, has an excellent ability to recognize organic molecules according to size, shape, polarity, and chirality. Thus, these steroidal molecules provide a new approach for studies of the molecular design of multi-molecular inclusion compounds.

We thank the Ministry of Education, Science, and Culture of Japan for a Grant-in-Aid for Scientific Research, and Dr. Shuji Senda for valuable assistance and advice.

Received, 31st December 1987; Com. 1858

References

1 F. Toda, 'Isolation and Optical Resolution of Materials Utilizing Inclusion Crystallization,' in 'Molecular Inclusion and Molecular Recognition–Clathrates I,' ed. E. Weber, *Top. Curr. Chem.*, vol. 140, Springer–Verlag, Berlin-Heidelberg, 1987, p. 43.
2 M. Miyata, M. Shibakami, W. Goonewardena, and K. Takemoto, *Chem. Lett.*, 1987, 605.
3 M. Miyata, W. Goonewardena, M. Shibakami, K. Takemoto, A. Masui, K. Miki, and N. Kasai, *J. Chem. Soc., Chem. Commun.*, 1987, 1140.
4 W. C. Herndon, *J. Chem. Educ.*, 1967, **44**, 724; E. Giglio, 'Inclusion Compounds of Deoxycholic Acid,' in 'Inclusion Compounds,' eds. J. L. Atwood, J. E. D. Davies, and D. D. MacNicol, Academic Press, London, 1984, vol. 2, p. 207.
5 F. Toda, K. Tanaka, T. Omata, K. Nakamura, and T. Ōshima, *J. Am. Chem. Soc.*, 1983, **105**, 5151.
6 P. L. Johnson and J. P. Schaefer, *Acta Crystallogr., Sect. B*, 1972, **28**, 3083.
7 H. Sobotka and A. Goldberg, *Biochem. J.*, 1932, **26**, 905.
8 T. Sato, K. Naruse, and T. Fujisawa, *Tetrahedron Lett.*, 1982, **23**, 3587.
9 U. Ravid, R. M. Silverstein, and L. R. Smith, *Tetrahedron*, 1978, **34**, 1449.
10 C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, S. Servi, and C. Zirotti, *Tetrahedron Lett.*, 1983, **24**, 3753.
11 R. Kuhn and K. Kum, *Chem. Ber.*, 1962, **95**, 2009.