New Terpenoid Hosts for Chiral Recognition: Crystal Structure and Molecular Modelling Study of an Inclusion Complex with (*S*)-(+)-Phenyloxirane

P. P. Korkas,[a] E. Weber,*[a] M. Czugler*[b] and G. Náray-Szabó[c]

[a] *Technische Universität Bergakademie Freiberg, Institut für Organische Chemie, D-09596 Freiberg/Sachsen, Germany*

[b] *Central Research Institute for Chemistry, Hungarian Academy of Sciences, H-1525 Budapest, POB 17, Hungary*

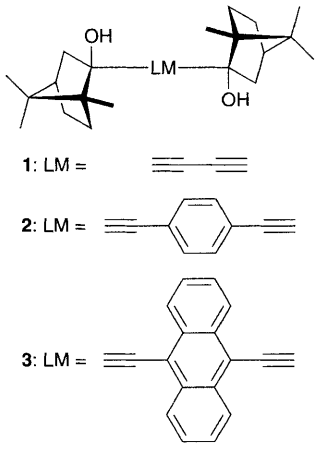
[c] *R. Eötvös University, Department of Theoretical Chemistry, H-1518 Budapest, POB 32, Hungary*

A new type of optically active inclusion host derived from natural camphor is described, enabling useful enantiomer separation of chiral compounds *via* cocrystallization; the structural rationale of an inclusion complex with (*S*)-(+)-phenyloxirane based on X-ray determination and a molecular modelling study is reported.

The design of host compounds for chiral recognition of guests in solution and in the solid state is the focus of much current interest.[1] One promising approach is the formation of crystalline complexes (clathrates)[2] and it has recently been shown that clathrates featuring a 'wheel and axle' host constitution are efficient.[3] Natural chiral compounds modified in such a way as to yield bulky lattice hosts have also been used in chiroselective experiments.[4] Nevertheless, terpenes as a chiral source have not been exploited so far in clathrate chemistry, although common in chiral catalysts and reagents.[5] We report a new design of a chiral crystalline host based on this natural resource which shows efficient enantioselective complex formation with some typical guests. X-Ray diffraction and molecular modelling studies for the complex with phenyloxirane are also reported.

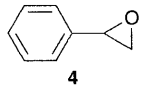
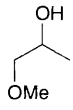
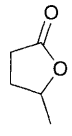
The hosts that arise from this reasoning are the optically resolved diols **1–3**. They feature a central axle-type building block with bulky terpenoid diol groups at both ends providing chirality and the possibility for H-bonding to potential guests. Depending on the central unit, molecules of different length, transverse dimension and π-stacking potential can form complexes. The optical activity derives from natural camphor. In order to make compounds **1–3**, in the first synthetic step, D-(+)-camphor was ethynylated to yield the intermediate 2α-ethynyl-2β-hydroxybornane[6] which on Eglinton coupling[7] or Pd-catalysed reaction[8] with the corresponding dibromoaryls gave the desired products [**1**,[9] 93%, mp 248 °C, $[\alpha]_D^{20}$ +16.2 (*c* 4.8 CH_2Cl_2); **2**, 82%, mp 199–200 °C, $[\alpha]_D^{20}$ +18.5 (*c* 3.8 CH_2Cl_2); **3**, 88%, mp 249–250 °C, $[\alpha]_D^{20}$ +15.5° (*c* 3.7, CH_2Cl_2)].

Crystallization of **1–3** from solutions of racemic compounds, such as ethers, exhibits selectivity of inclusion complex formation and chiral separation. Examples of compounds and enantiomeric ratios (*R*:*S*), obtained in one crystallization step, are given in Table 1. Using hosts **1** and **3**, we obtained pure enantiomers of γ-butyrolactone, phenyloxirane and 1-methoxypropan-2-ol, *i.e.* this method makes possible an easy preparation of pure enantiomers on a large scale,[4] while **2** is less efficient in enantio-separation under the experimental conditions. On the other hand, **2** forms an enantioselective inclusion compound with 3-methyltetrahydropyran, unlike **1** and **3**. Another question that arises refers to the complexes of **2** and **3** with phenyloxirane **4** since **2** includes **4** only as a racemate whereas **3** gave complete enantio-separation.



An X-ray structure† of the 1 : 1 complex between **3** and (*S*)-(+)-**4** reveals that the guest molecule is embedded in the 'lap' of the host compound such that this placement follows closely the crystallographic *a* direction (Fig. 1). The epoxy oxygen atom of the guest accepts an H-bond from the O(11) hydroxy group of the host molecule. The anchoring effect of this H-bond is possibly shown in a longer C–OH bond *vs.* the other C–OH bond in the host molecule [O(11)–C(31) = 1.441(3) *vs.* O(12)–C(32) = 1.425(3) Å, Δ = 0.016 Å]. This hydroxy group is also acting as an acceptor in an infinite chain of H-bonds from the other hydroxy function of a neighbouring host molecule, thus playing a key role in establishing the crystal lattice. Almost

Table 1 Examples of enantioselective inclusion formation[a,b]

Racemic compound (guest)	Host 1	2	3
 **4**	—	50 : 50[c,d]	0 : 100
	—	40 : 60	0 : 100
	100 : 0	—	—
	—	15 : 85	—

[a] All inclusion compounds show 1 : 1 (host : guest) stoichiometric ratio. [b] Chemical yields range between 78 and 90%. [c] Enantiomer .Utio (*R* : *S*) in each case. [d] Based on HPLC and GC determination.

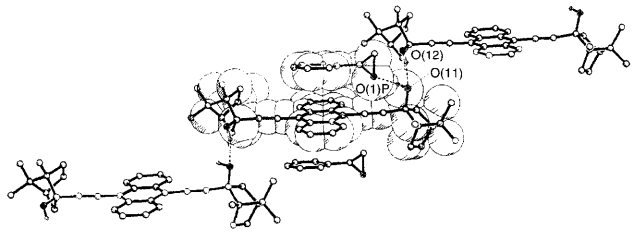


Fig. 1 X-Ray model (asymmetric unit is indicated by an augmented van der Waals envelope of non-H atoms) and packing of associate **3**·(*S*)-(+)-**4**. H-bonding specified as dotted lines; all but two H-atoms of hydroxy functions are omitted for clarity.

parallel positioning (dihedral angle 9.7°) of the aromatic ring of the guest molecule **4** overlapping the central anthracene moiety of host **3** *and the* values of the respective atomic distances from the phenyl plane (3.15–3.62 Å) all indicate the possibility of a charge transfer interaction. Contours of electron density encircling the guest indicate outlines of a 'specificity pocket' in the crystal.

Apart from repulsive steric interactions,‡ this pocket assists positioning of the guest entity through two attractive interactions: the anchoring H-bond and the facial π–π interaction on the near side alluded to above. A low resolution (1 Å) electrostatic potential map calculated using X-ray data also supports the above conclusion, showing potential deformation in the region of attractive interactions. In the light of the high uncertainty of such maps[12] we undertook further analyses of electrostatic properties using semiempirical methods.

A clearly visible positive calculated molecular electrostatic potential (MEP) region in the vicinity of the hydroxy proton H-bonded to the oxirane matches the negative MEP around the oxygen atom of **4** (Fig. 2). The molecular electrostatic field (MEF) is large both for **3** and **4** in the H-bonding region as indicated by the high density of MEP contours. The reduced MEF values near to the aromatic groups of both **3** and **4** (low density of MEP) indicates hydrophobic complementarity in this contact region. Thus the present complex gives yet another example of the *similis simili gaudet* principle.[13]

Hydrophobic complementarity can be generalized as the phenomenon of minimizing contacts between apolar solute and polar solvent regions. Since the complex was crystallized from an excess of the polar solvent **4**, it is a reasonable assumption that in the solution state solvent molecules force apolar (*i.e.* aromatic) regions of both **3** and **4** close together, thereby increasing the tendency for association. To answer this question MM$^+$ molecular mechanics calculations[14,15] were carried out. The aromatic parts of **4** and **5** (anthracene and benzene moieties) were used as models, preserving the geometry and positioning of the X-ray model with additional H atoms where needed to replenish valence states of originally substituted C atoms. While the interaction energy of the anthracene–benzene system is 4.9 kcal mol^{-1}, (1 cal = 4.184 J) this increases to 8.0 kcal mol^{-1} in the 1 : 1 adduct indicating the stabilizing effect of the host–guest H-bond. When adding a second, properly translated (corresponding to the $x - 1$ crystallographic position) benzene–anthracene adduct to this system, the interaction between these two mini-associates becomes 1.1 kcal mol^{-1}. Thus the much larger interaction of the first association step probably indicates that a bimolecular association of **3** and **4** occurs first in solution.

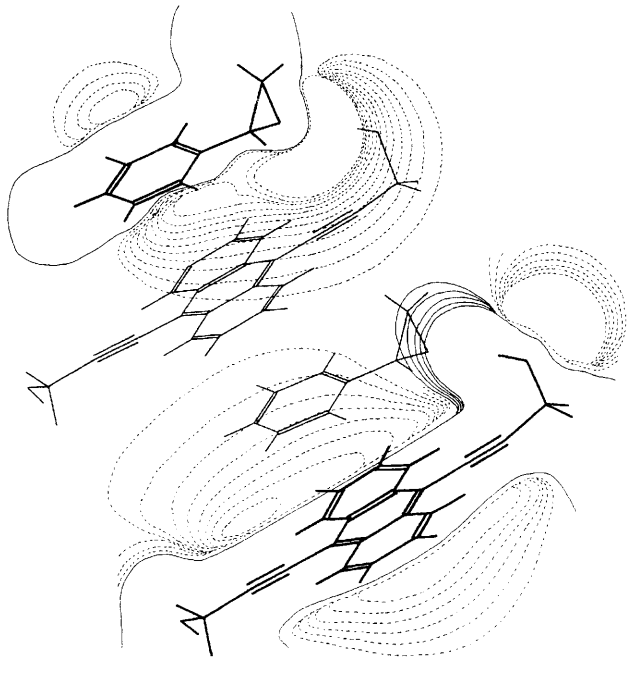


Fig. 2 Representation of electrostatic and hydrophobic matching in **3**·(*S*)-(+)-**4** exemplifying the basic packing motif following the crystallographic *a* direction (**3** is partly truncated for clarity). The molecular electrostatic potential calculated by the AM1 method (program HYPERCHEM[15]) is displayed top left for **3** (heavy lines) near **4** (light lines) and bottom right for **4** (heavy lines) near **3** (light lines). Full and dashed lines represent positive and negative potential values, respectively, decreasing by an increment of 5 kJ mol^{-1}.

In summary, chiral molecular recognition of crystalline complexes using host compounds **1–3** is evident from the present results. Since selective stoichiometric inclusion complexes of **1–3** with many other guests have been obtained, and given the many possible structural modifications that may be made to the central building block and the wide range of optically active natural terpenes that are available, there is great potential for the future design of chiral selectors.

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Footnotes

† *Crystal data* for **3**·(*S*)-(+)-**4** (1 : 1), $(C_{38}H_{42}O_2)\cdot(C_8H_8O)$, M = 650.86, triclinic, $P1$, a = 7.818(1), b = 11.238(1), c = 12.245(1) Å, α = 116.05(1), β = 100.78(1), γ = 98.11(1)°, Z = 1; total data collected = 4130, independent reflections = 4012 R_{int} = 0.0174. The initial structural model, obtained by direct method (SHELXS-86[10]), was refined against 3830 non-negative observations to convergence [final R indices $I > 2\sigma(I)$: R_1 = 0.0382, wR_2 = 0.1094, R(all data): R_1 = 0.0480, wR_2 = 0.1178] (SHELXL-93). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallograpic Data Centre. See Information for Authors, Issue No. 1.

‡ Docking experiments with the phenyloxirane molecule displaced artificially a few Å further from the crystal position indicate that the minimum energy of van der Waals interactions yields a steric alignment close to the X-ray model (computational results obtained using Biosym Technologies' INSIGHT II[11]).

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