Directed synthesis of compounds capable to spontaneous resolution

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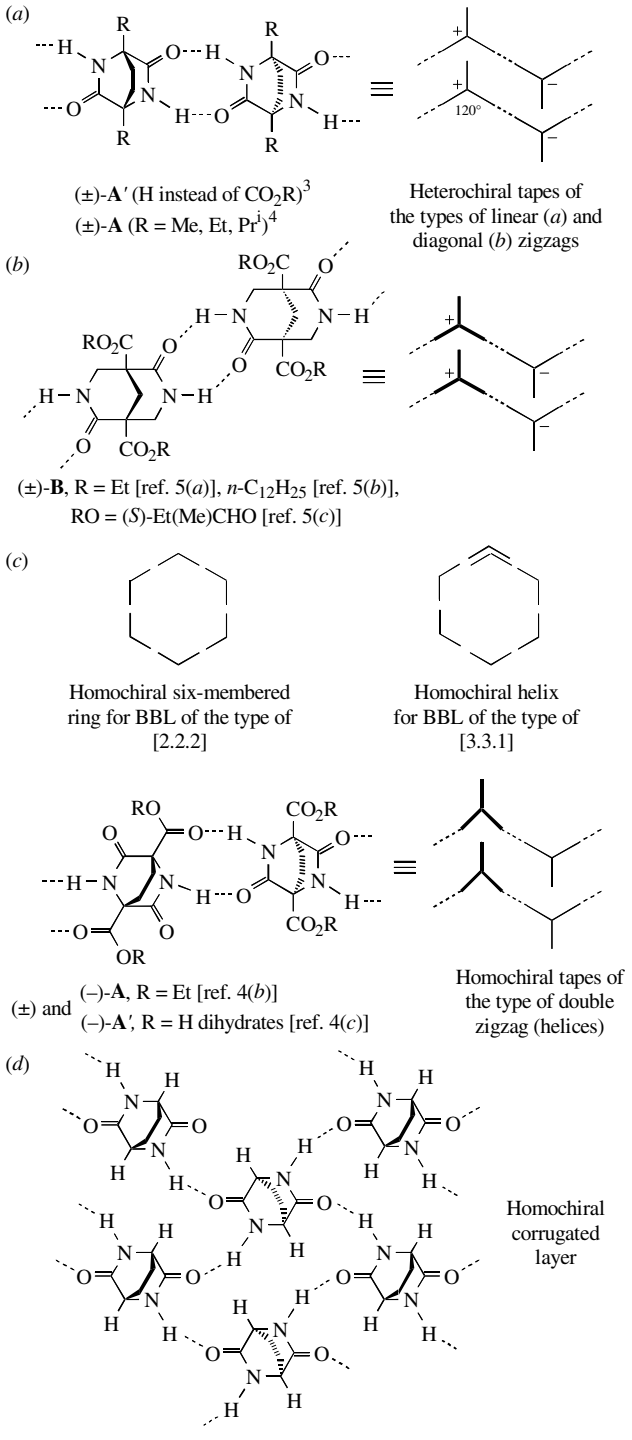
A qualitative conception for constructing conglomerates has been proposed; bis-lactam **1** has been synthesised by two methods, and it exhibited *a priori* predicted properties like formation in the optically active form under conditions of a routine crystallization.

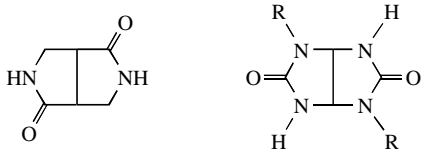
Crystallization of a racemate as a mixture of homochiral crystals (conglomerate) makes it possible to carry out a simple spontaneous resolution into enantiomers.[1] However, in most cases, the racemates yield heterochiral crystals,[1(a)] the known list of conglomerates is rather short, and for the most part they have been found by a lucky chance. Naturally, it was a matter of interest to elucidate possibilities for constructing conglomerates on the basis of prediction of the crystal structure. However, such a predictivity was entirely denied ('…nothing can be said *a priori* on the spontaneous resolution of racemic solutions by crystallization, …there are at present no really predictive concepts on this fascinating subject, which may be related to the chirality of the chemistry of life'.[2(a)] 'In crystal engineering… design and control packing arrangements… are not routinely possible from knowledge of the molecular structure alone'.[2(b)]).

Nevertheless, we have launched attempts to construct conglomerates of chiral bicyclic bis-lactams (BBL) starting from our qualitative predictive concepts as a basis. The racemates of BBL of types **A**[3,4] and **B**[5] seemed to be doomed for co-crystallization of the enantiomers [Scheme 1(*a*),(*b*)]. In crystals, they are combined in a strictly alternating sequence by H-bonds of the lactam groups into tapes of either linear (**A**)[3,4] or diagonal (**B**)[5] zigzag. These tapes are assembled into walls where the BBL skeletons are tightly packed into columns. The same pattern is observed for co-crystals of both quasi-racemate, (1*R*,4*R*)-(–)-**A** (R = Et) with (1*S*,4*S*)-(+)-**A** (R = Pr),[4(b)] and diastereomers **B** [R = (*S*)-Et(Me)CHCH$_2$O].[5(c)] The latter cannot be separated by chromatography, and enantiomers **A′** have been obtained only after the chiral chromatographical resolution of a 2,5-bis-*p*-methoxybenzyl derivative[3,6] (where the lactam-type H-bonding is absent). Comparison between the racemate[4(a)] and enantiomer[4(b)] of **A** (R = Et) points out a significant difference in the homochiral assembling of molecules in the crystal [Scheme 1(*a*),(*c*)] and a greater stability of the less soluble racemic crystal (higher density, and the melting point is higher by 37 °C).

As a first approximation to arranging a homochiral assembling of BBL and its analogues there was the following assumption. At the step of prenucleation, the self-association of the molecules occurs solely by means of H-bonding each molecule with two other ones [Scheme 1(*a*)–(*c*)]. Then, in case of BBL **A** a homochiral association through the stable lactam–lactam H-bonding is forbidden, since termination of the H-bond polymerization chain is inevitable due to the formation of a cyclic hexamer.[3,6(a)] At the same time, in case of BBL **B** and its analogues a homochiral association to form helical tapes is possible; however, some transformation to flatten these tape is necessary in order to provide a tight packing. Motive of the structure (–)-**A** (R = Et) displays a possibility for such a transformation of helix though with the weakened H-bonding O–C=O…H–N [Scheme 1(*c*)]. A perfect version of the desirable flattening may be seen in the structure of enantiomer (–)-**A′** [Scheme 1(*d*)].[3(b)] Each of its molecules is connected with four other ones by the same strong H-bonds similar to those in the structure of a racemate [Scheme 1(*a*)] and, also, it is an element of two reciprocally perpendicular flattened helices, which form corrugated layers. A tight packing of the latter occurs in such a way that a skeleton of each molecule goes into a well-shaped column. It is interesting that the racemate



Scheme 1



C[6] **D**, R = Me,[7(b)] Et[7(a),(c),8]

Scheme 2

and enantiomer structures do not differ in the parameters of H-bonds and density.[3(a)] Moreover, the melting point of the homochiral crystal (300–305 °C)[3(a)] is higher than that of the racemate (275–277 °C).[3(c)] This suggests that for ensuring the homochiral self-assembling of BBL like **B** and its analogues the substituents CO_2R, which hinder the self-assembling by Scheme 1(*d*), should be removed.

Therefore, the synthesis of earlier unknown BBL **1**,[5(a)] **C**[6] has been worked out, and their analogues like chiral glycolurils **D**[7] (Scheme 2) have been studied. Indeed, it was found that **1** is crystallised in the form of a conglomerate (space group $P2_12_12_1$, $Z = 4$), and as it was expected *a priori* its structure is very similar to that of (–)-**A′** [Scheme 1(*d*), Figure 1].[5(a)]

In this work, the synthesis of **1**[5(a)] has been optimised by two methods providing total yields of 30 and 21% (Scheme 3). Yields of compounds at the separate steps have been increased; at the next to last step (in the second method) the product, 3,7-bis-*p*-methoxybenzyl derivative of BBL **1**, has been obtained in a crystal form suitable for X-ray diffraction analysis (this product has been isolated earlier as an oil[5(a)]). For the first time, the spontaneous resolution of **1** has been accomplished by crystallization from H_2O. The separate well-formed crystals of **1** have a noticeably higher melting point than that of the racemate, and possess an optical activity† (Figure 2). A random crystal of **1** taken from the racemic mixture was used as a seed for crystallization resolution of the racemate by an internal entrainment procedure.[6(b),(c)] By analogy with (1*R*,4*R*)-(–)-**A′** [see ref. 3(*a*)] the absolute configuration of (1*R*,5*R*)-(–)-**1** can be accepted.

On the basis of the above conception, we succeeded in finding one more conglomerate in the series of chiral glycolurils **D** (R = Me)[7(b)] (Scheme 2). Spontaneous resolution of **D** (R = Me, Et)[7(a),(b)] has been carried out, and enantiomers **D** (R = Et) have been used in the synthesis of the chiral drug Albicar.[7(b),(c)] However, in these cases, though the molecular packing is similar to those shown in Scheme 1(*d*) but it is complicated by H-bonding between the layers to form three-dimensional nets.[7(b),8] Note that in case of the unsubstituted glycoluril two different patterns of packing are observed for its two forms of crystals, one being H-bonded corrugated layers according to Scheme 1(*d*), and another

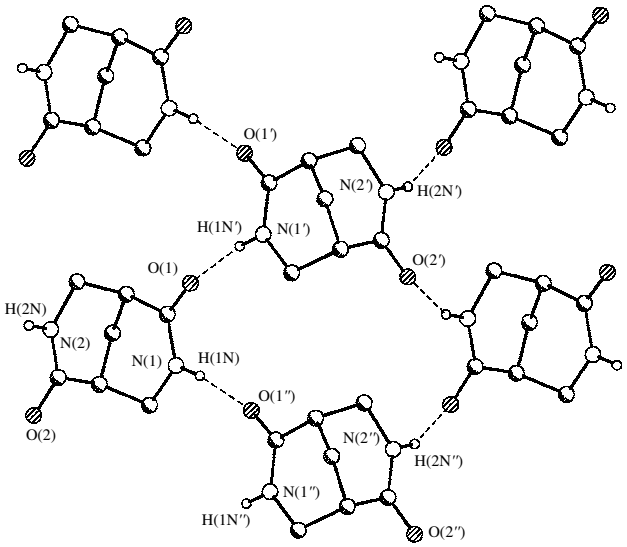
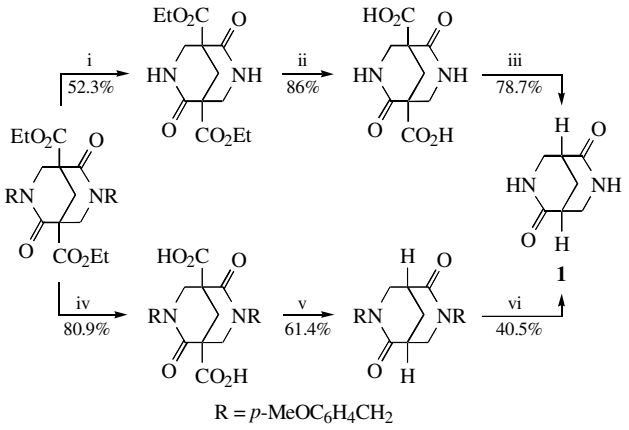


Figure 1 Homochiral corrugated layer in the crystal structure of BBL **1**[5(a)] [*cf.* Scheme 1(*d*)].



Scheme 3 *Reagents and conditions*: i, $Ce(NH_4)_2(NO_3)_6$ in MeCN–H_2O, 2 days at 20 °C, then $NaHCO_3$ and extraction of the product with $MeCO_2Et$; ii, KOH in EtOH–H_2O, 2 days at 20 °C and 1–1.5 h at 4 °C, then with CF_3CO_2H in H_2O, 2 h at 20 °C and 5 days at 4 °C, then separation of the product precipitate; iii, heating 2 h at 125–150 °C (2–3 mmHg) and sublimation, 10 h at 230–250 °C (2–3 mmHg); iv, KOH in EtOH, 2 days at 20 °C, 1–1.5 h at 4 °C, then with CF_3CO_2H in wet EtOH 1 day at 20 °C and 3 h at 4 °C, then separation of the product precipitate; v, heating 2 h at 145–150 °C (2–3 mmHg) and sublimation of the residue, 10 h at 170–180 °C (2–3 mmHg), in contrast to the earlier reported[5(a)] the product has been isolated in a crystal form, mp 31–33 °C; vi, $Ce(NH_4)_2(NO_3)_6$ in MeCN–H_2O, 2 days at 20 °C, then $NaHCO_3$, extraction of anisaldehyde with diethyl ether, heating 2 h at 145–150 °C (2–3 mmHg), and sublimation of the residue, 10 h at 170–180 °C (2–3 mmHg).

being three-dimensional nets[9] like **D**.

In conclusion, it may be said that the main feature for originating the proposed conception is a comparative analysis of both enantiomer and racemate crystal structures of key compounds in the series under study. Such an approach seems to be universal.

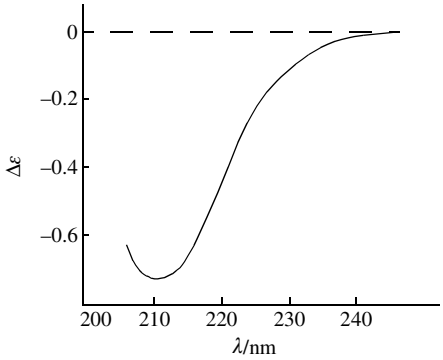


Figure 2 CD Spectrum of BBL (–)-**1**.

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† *Characteristics and spectroscopic data.* Compounds presented in Scheme 3, have been characterised by ^1H and ^{13}C NMR spectra identical to those described earlier.[5(a)]

(–)-**1**, upon crystallization from H_2O with self-evaporation at 20 °C the crystals up to 14 mg in weight have been obtained; mp 364 °C (decomp.), $[\alpha]_D^{17} = -3.0°$; $[\alpha]_{578}^{17} = -3.2°$; $[\alpha]_{546}^{17} = -4.2°$; $[\alpha]_{436}^{17} = -8.2°$; $[\alpha]_{406}^{17} = -9.5°$ (*c* 1.3, H_2O); CD spectrum (*c* 3.25×10^{-5} M in H_2O), $\Delta\varepsilon$ (λ_{max}/nm): 0.75 (212). For grinded mixtures the melting point is 355–358 °C (decomp.) in case of the crystals of opposite signs of optical rotation and to 350 °C (decomp.) in case of a non optically active mixture [*cf.* ref. 5(*a*)]. Then, the mother liquor and precipitate were combined, and crystallization from H_2O with self-evaporation at 20 °C was repeated. Solution of (–)-**1** used for the measurement of the optical rotation angle was evaporated entirely, the crystals were isolated, grinded and taken as a seed. Using an internal entrainment procedure,[6(b),(c)] the precipitate of (–)-**1** has been obtained in 26% yield, $[\alpha]_D^{17} = -2.8°$ (*c* 1.5, H_2O).

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