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Rational approach to a conglomerate-forming propranolol derivative: pointed modifications of the crystal structure

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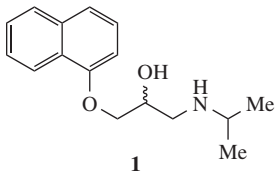
The crystal structure of racemic propranolol hydrochloride was reinvestigated and the main supramolecular solid-state motif (infinite homochiral chains) was found. Changes in the size of the central anion are accompanied by substantial differences in crystal packing leading to a homochiral crystal lattice of racemic conglomerate.

Stereochemistry plays an important role in drug action on human beings.[1] Single enantiomer drugs have powerful advantages over the racemic ones for diverse combinations of biological activities of individual enantiomers.[2] The industrial-scale production of single enantiomers may be achieved by either a direct synthesis or the resolution of racemates. Among diverse approaches to resolution, the preferential crystallization of enantiomers seems a natural limit of cost-effectiveness because it needs no chiral auxiliaries and no expensive equipment.[3,4] However, the potential of preferential crystallization is restrained by the necessity for a chiral compound subjected to resolution being a conglomerate, *i.e.*, crystallising as a mechanical mixture of single crystals formed by homochiral molecules.

The classical example of chiral drugs is 1-isopropylamino-3-(1-naphthyloxy)propan-2-ol **1**, the oldest nonselective β-adrenoblocking agent, which is known as propranolol.[5] Using this compound as an example, it has been demonstrated for the first time that individual enantiomers of β-blockers differ in physiological activity.[6] It was found that the (*S*)-isomer of propranolol serves as an eutomer β-blocker, whereas the (*R*)-distomer stimulates smooth musculature of the uterus and, hence, is responsible for side effects.[7]



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Previously, Neau *et al.*[8] described racemic propranolol hydrochloride as a conglomerate.

Our previous study of the thermochemical properties of propranolol as free base and as hydrochloride reveals that, in a solid state, they exist as racemic compounds.[9] However, in the case of hydrochloride, the region of existence of the racemic compound on the binary phase diagram is very narrow. The difference between its experimental melting temperature and the theoretically calculated value for a racemic conglomerate is less than 4 K, and the enthalpies of fusion for racemic and homochiral crystals differ by less than 2 kJ mol^{-1}.

The crystal structure of *rac*-**1**·HCl was described earlier.[10,11] Unfortunately, the quality of the available X-ray diffraction data does not allow one to judge the fine details of the solid state organization. Previously,[10] the H atoms of the hydroxy and amino groups were not located, and the secondary hydroxy group was disordered on two positions,[11] which also hinder the location of the H atom and the OH group. This disorder in the vicinity of the chiral centre of **1** makes it also impossible to reliably identify whether the character of infinite motifs in the crystal lattice is homochiral or heterochiral. The lattice has been ascribed to achiral crystallographic groups $P2_1/c$, $Z = 4$ (ref. 10) or $P2_1/n$, $Z = 4$.[11]

During the reinvestigation of the crystal structure of racemic propranolol hydrochloride,† we found that this crystal is actually non-centrosymmetric with two independent enantiomeric molecules. The molecules adopting the same configuration are linked in infinite chains by Coulomb interactions and strong hydrogen bonds with chloride anions (Figure 1).

Within the crystal structure, homochiral endless chains located around the screw axes 2_1 correspond to the similar chains of the molecules adopting an opposite configuration. The physical bonding between the enantiopure chains occurs through hydrophobic interactions of the peripheral isopropyl and naphthyl groups. In other words, the crystal structure of the hydrochloride racemic compound shows a fair degree of chiral discrimination, and enantiomers in the crystals of racemic hydrochloride are largely already resolved. Only weak dispersion forces stabilise the racemic compound, as detected by thermal analysis. Apparently, a little perturbation of the right sign would lead to a completely homochiral crystal cell.

The spherical monoanions of halogens have appreciably different crystal ionic radii varying from 2.20 Å for iodine, through 1.96 Å for bromine and 1.81 Å for chlorine to 1.33 Å for fluorine. On this basis, we assumed that modification can be performed by changing the anion. With the hydrochloride crystal data in

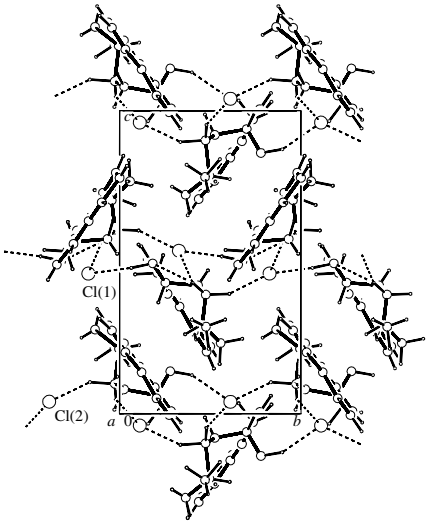

Figure 1 Homochiral enantiomeric chains in the crystal structure of **1**·HCl (and **1**·HBr). Hydrogen bonds are shown by dashed lines.

mind, one would expect that a decrease in the size of the anion would lead to a more dense organization of the molecules within the homochiral supramolecular ensembles (provided they are preserved). Consequently, more loose dispersion bonding between heterochiral molecules is expected. On the contrary, an increase of the central anion size would lead to opposite results.

We prepared‡ crystalline *rac*-**1**·HF, *rac*-**1**·HBr and *rac*-**1**·HI and studied single crystals picked from the racemic samples by X-ray diffraction.† As it was expected, the crystals of hydrobromide prove to be isostructural to that of hydrochloride and both are sufficiently different from those of terminal members of the row. The unit cell of hydroiodide belongs to triclinic space group *P*-1 (Figure 2). Centrosymmetric dimers of propranolol

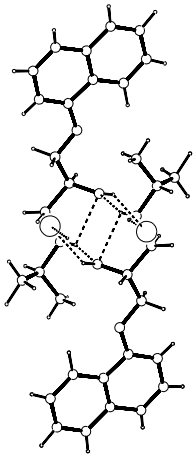

Figure 2 Hydrogen-bonded centrosymmetric dimers in the crystal structure of **1**·HI. Hydrogen bonds are shown by dashed lines.

molecules of opposite configuration bound to one another by strong intermolecular hydrogen are formed in the crystal, and these dimers are joined into endless rows by the pair of robust iodine anions.

A fragment of the crystal lattice of hydrofluoride is shown in Figure 3. Here, one can see just the same homochiral part of packing as in the case of a chlorine (or bromine) analogue with the only difference: there is no counterpart of opposite configuration within the limits of a single crystal.

Hence, as it was anticipated, propranolol hydrofluoride crystallises as a racemic conglomerate. Although a stable conglomerate is a necessary condition for the application of preferential crystallization, it can be insufficient to ensure a practical entrain-

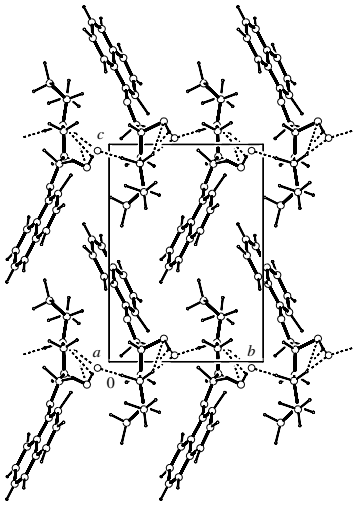

Figure 3 Parallel homochiral chains in the crystals of **1**·HF. Hydrogen bonds are shown by dashed lines.

† *Crystallographic data*. The crystals of *rac*-**1**·HF (conglomerate), $C_{16}H_{21}NO_2$·HF, M = 279.36, monoclinic, space group $P2_1$, at 298 K a = 7.104(5), b = 8.694(5) and c = 12.215(16) Å, β = 94.13(8)°, V = = 753(1) Å^3, Z = 2, d_{calc} = 1.23 g cm^{-3}, CuKα (λ = 1.54184 Å), μ = = 6.95 cm^{-1}, $\omega/2\theta$-scan, 3266 reflections measured, 1450 observed [$I \geq 2\sigma(I)$], 180 refined parameters, R = 0.061, R_w = 0.065.

The crystals of *rac*-**1**·HCl, $C_{16}H_{21}NO_2$·HCl, M = 295.81, monoclinic, space group $P2_1$, at 298 K a = 13.977(9), b = 8.274(7) and c = 14.023(8) Å, β = 98.87 (5)°, V = 1602(2) Å^3, Z = 4 (Z' = 2, two independent molecules are enantiomers), d_{calc} = 1.22 g cm^{-3}, CuKα (λ = 1.54184 Å), μ = = 21.31 cm^{-1}, $\omega/2\theta$-scan, 6834 reflections measured, 5424 observed [$I \geq 2\sigma(I)$], 360 refined parameters, R = 0.076, R_w = 0.088.

The crystals of *rac*-**1**·HBr, $C_{16}H_{21}NO_2$·HBr, M = 340.26, monoclinic, space group $P2_1$ (isostructural to *rac*-**1**·HCl), at 298 K a = 14.143(6), b = 8.341(7) and c = 14.29(1) Å, β = 100.73(5)°, V = 1675(2) Å^3, Z = 4 (Z' = 2, two independent molecules are enantiomers), d_{calc} = 1.53 g cm^{-3}, CuKα (λ = 1.54184 Å), μ = 34.48 cm^{-1}, $\omega/2\theta$-scan, 8495 reflections measured, 724 observed [$I \geq 2\sigma(I)$], 313 refined parameters, R = 0.082, R_w = 0.217.

The crystals of *rac*-**1**·HI, $C_{16}H_{21}NO_2$·HI, M = 387.26, triclinic, space group *P*-1, at 298 K a = 8.264(3), b = 8.532(2) and c = 12.290(4) Å, α = 103.39(3)°, β = 98.62(3)°, γ = 93.30(3)°, V = 829.6(5) Å^3, Z = 2, d_{calc} = 1.55 g cm^{-3}, MoKα (λ = 0.71073 Å), μ = 19.09 cm^{-1}, $\omega/2\theta$-scan, 1928 reflections measured, 1453 observed [$I \geq 2\sigma(I)$], 269 refined parameters, R = 0.029, R_w = 0.034.

All crystallographic data were measured with a Nonius CAD4 diffractometer. Structures were solved by a direct method (SIR[12]) and refined by the full-matrix least-square technique in the anisotropic-isotropic approximation (MolEN;[13] structure of *rac*-**1**·HBr was refined by the SHELXL-97 program).

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers 250226, 250225, 250227, 250228, in order of mention in this footnote. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.

‡ Racemic propranolol base **1** (13.4 g, 52 mmol) was dissolved in Pr^{i}OH (95 ml) at 45–50 °C and 3.0 g of commercial hydrofluoric acid was added to this solution. After standing overnight, the precipitated solid (*R*,*S*)-**1**·HF (12.3 g) was filtered off, washed with Pr^{i}OH and dried. The mother liquor was evaporated *in vacuo* and an additional portion (1.4 g) of (*R*,*S*)-**1**·HF was collected. Overall yield, 13.7 g (94%); mp 152–156 °C (decomp.). ^{1}H NMR (250 MHz, CD_3OH) δ: 1.37 and 1.39 (2d, 6H, Me, J 6.5 Hz), 3.19–3.51 (m, 3H, CH_2, CH), 4.17–4.27 (m, 2H, CH_2), 4.33–4.45 (m, 1H, CH), 6.92–8.29 (m, 7H, naphthyl). IR (KBr, ν/cm^{-1}): 3331, 3194 (OH, NH), 2981, 2863, 2706, 2540, 2311 (NH$^+$), 1628, 1580, 1510 (Ar). MS, m/z (I, %): 259 (28), 244 (7), 215 (14), 144 (18), 115 (18), 72 (100), 56 (14), 43 (17). M_{found} 259.157, $C_{16}H_{21}NO_2$, M_{calc} 259.1572; M_{found} 244.134, $C_{15}H_{18}NO_2$, M_{calc} 244.1338.

rac-Propranolol hydrobromide (overall yield 95%; mp 148–151 °C) and hydroiodide (overall yield 86%, mp 142–144 °C) were obtained analogously using commercial hydrobromic and hydroiodic acids, respectively.

ment effect under some circumstances.[14] Thus, we performed the resolution of racemic hydrofluoride through an entrainment procedure.§

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§ (*R*,*S*)-Propranolol hydrofluoride (4.00 g) was dissolved in 32 ml of rectified ethanol at 55–70 °C. The solution was stirred and cooled to 25 °C and seeded with finely pulverised (*R*)-**1**·HF {0.04 g, $[\alpha]_D^{20}$ +20.0 (*c* 0.7, EtOH)}. After stirring the mixture for 45 min at 25 °C, (*R*)-**1**·HF {0.60 g, $[\alpha]_D^{20}$ +8.0 (*c* 0.78, EtOH)} was collected by filtration. (*R*,*S*)-**1**·HF (0.56 g) was dissolved in the mother liquor at 55–70 °C, and the resulting solution was cooled to 25 °C. After adding to the solution (*S*)-**1**·HF {0.04 g, $[a]_D^{20}$ –19.5 (*c* 0.89, EtOH)} as seed crystals, followed by stirring the mixture for 60 min at 25 °C, (*S*)-**1**·HF {0.56 g, $[\alpha]_D^{20}$ –9.0 (*c* 0.75, EtOH)} was collected by filtration. Further resolution was carried out at 25 °C by adding (*R*,*S*)-**1**·HF to the filtrates as described above. After a second cycle, 0.42 g (*R*)-**1**·HF {$[\alpha]_D^{20}$ +9.6 (*c* 0.76, EtOH)} and 0.40 g (*S*)-**1**·HF {$[a]_D^{20}$ –9.6 (*c* 0.77, EtOH)} were obtained. After third cycle 0.45 g (*R*)-**1**·HF {$[\alpha]_D^{20}$ +8.0 (*c* 0.78, EtOH)} and 0.58 g (*S*)-**1**·HF {$[\alpha]_D^{20}$ –8.2 (*c* 0.78, EtOH)} were obtained.

The enantiomeric purity of thus obtained nonracemic **1**·HF was increased by recrystallization from rectified ethanol. Thus, the crop of (*S*)-**1**·HF {3.56 g, $[\alpha]_D^{20}$ –8.0 (*c* 0.78, EtOH)} was dissolved and stirred in EtOH (27.5 ml) at 60 °C. After cooling the solution to 25.5 °C, the mixture was stirred for 1 h at this temperature. Precipitated (*S*)-**1**·HF was filtered off and dried. Yield, 2.48 g; $[\alpha]_D^{20}$ –13.0 (*c* 0.56, EtOH). The repeated recrystallizations allowed us to obtain 0.80 g of (*S*)-**1**·HF, $[\alpha]_D^{20}$ –19.5 (*c* 0.89, EtOH). The similar recrystallizations of 0.87 g (*R*)-**1**·HF, $[\alpha]_D^{20}$ +15.9 (*c* 1.0, EtOH) give 0.37 g (*R*)-**1**·HF, $[\alpha]_D^{20}$ +19.8 (*c* 0.92, EtOH), mp 167–173 °C (decomp.).

Two samples of moderate enantiomeric purity were checked by ^{31}P NMR after derivatization by (4*R*,5*R*)-diethoxycarbonyl-2-chloro-1,3,2-dioxaphospholane following the procedure described earlier for propranolol hydrochloride.[15] It was found that a sample with $[\alpha]_D^{20}$ –15.7 (*c* 1.0, EtOH) was characterised by ee = 77%, and a sample with $[\alpha]_D^{20}$ +17.8 (*c* 1.0, EtOH), by ee = 85%. Thus, the specific rotation of enantiopure **1**·HF corresponds to $[\alpha]_D^{20}$ ±20.7±0.3 (*c* 1.0, EtOH).

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