Intermolecular Interactions Responsible for the Absence of Chiral Recognition: Aromatic C–H···O Hydrogen Bonding in the Crystal Structure of 3-Chloro-9,13-Dibutylamino-1-hydroxypropyl-6-trifluomethylphenanthrene Propan-2-ol Solvate Hydrochloride

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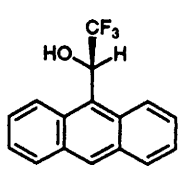
Both the 3-Cl and the more remote 6-CF_3 groups in 1-dechlorohalofantrine **3** promote strong edge-to-edge aromatic O···H(1)–C interactions, similar to those found in thiamine picrate **6**, which we suggest inhibit the resolution of **3** on chiral HPLC columns, whereas the 1-Cl substituent in halofantrine itself **2** blocks this interaction and allows resolution *via* chiral π–π face stacking.

The intermolecular forces responsible for chiral recognition can be surprisingly diverse and subtle.[1] For example, the well known chiral resolving reagent **1** unexpectedly revealed[2] the presence of unusually strong O–H···π facial hydrogen bonding in the solid state and an asymmetry between the calculated molecular electrostatic potentials of the two π-faces attributed to antiperiplanar interactions with the CF_3 group. Such π-asymmetry was also thought to contribute to chiral resolution of phaclofen on cyclodextrin HPLC columns.[3] As part of our effort to enhance the ability to predict structural requirements necessary for chiral resolution, we have compared the chromatographic behaviour of the anti-malarial compound halofantrine[4] **2** with that of the two closely related monochloro derivatives **3** and **4** using a Pirkle type chiral stationary phase. Fig. 1 shows that whereas the resolution of the enantiomers of **4** (separation factor α 1.38) is actually increased compared to that of **2** (α 1.30) the enantiomers of **3** co-elute. The retention time of **3** is the same as that of the faster eluting enantiomer (+)-**4**, which suggests the longer retention time of (−)-**4** is largely due to chiral recognition. The 1,3-didechloroisomer **5** is also resolved on the column, but less well than **4** or **2** (α 1.20) indicating that the 3-Cl group also plays a significant role in suppressing chiral recognition. We felt it imperative therefore to establish the reasons for the differing chiral behaviour of these systems.

By analogy with **1**, we initially sought an explanation for the differing behaviour of **2** and **3** in the properties of the π-faces, *via* calculation of the molecular electrostatic potentials (MEPs).[2] Since we have observed that this property might be sensitive to the orientation of the OH group, the X-ray structure† of the crystalline hydrochloride derivative of **3** was obtained; that for **2** has been previously measured.[5] These structures revealed strong hydrogen bonds to form in both compounds from the OH group to the halide counter-anion. However, PM3 calculations[6] based on the X-ray-derived OH orientation revealed no significant differences in the MEPs of **2** and **3**. In both cases the most negative region resides over the *A* rather than the *C* ring, consistent with the *A*–*C* ring complementary π–π stacking observed[5] for **2**.‡

The crystal structure of a solvated form of the hydrochloride salt of **3** shows two crystallographically independent molecules which comprise the asymmetric unit, referred to as molecules **A** and **B**, and one molecule of propan-2-ol. The two molecules are virtually identical in their molecular conformation. The C(10)–C(9)–C(15)–O(1) (numbering as on formula **3**) torsion angles (near 24°), which define the rotameric orientation of



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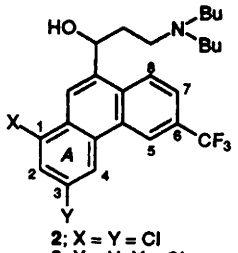


2; X = Y = Cl
3; X = H, Y = Cl
4; X = Cl, Y = H
5; X = Y = H

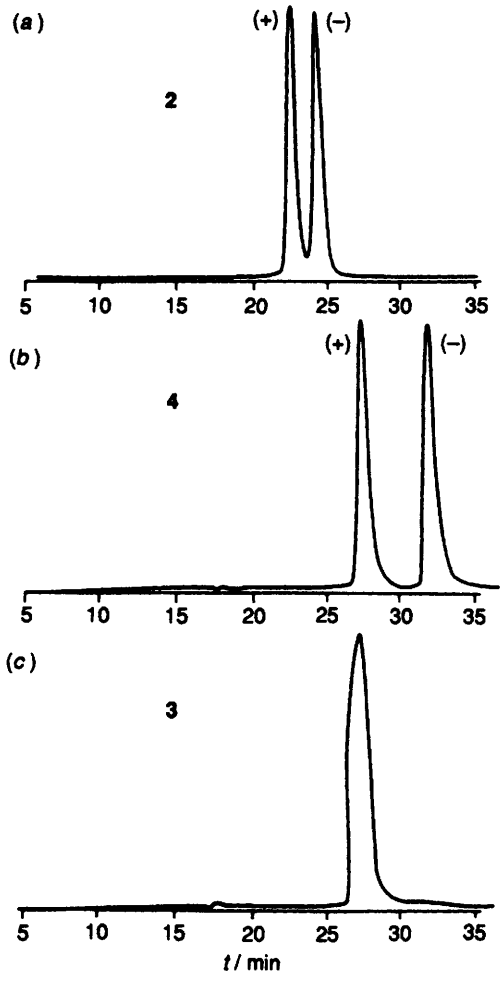
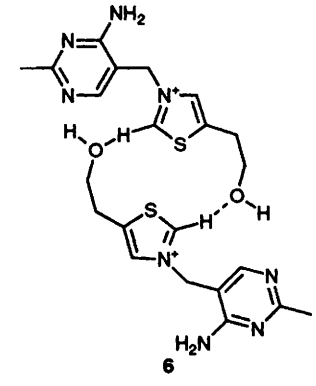


Fig. 1 Chromatographic behaviour of (*a*) **2**, (*b*) **4**, (*c*) **3**. HPLC conditions: chiral column, 250 × 4.9 mm ID; stationary phase, L-*N*-(3,5-dinitrobenzoyl) leucine covalently bound to 3-aminopropyl silica support (particle size 5 μm); mobile phase, *n*-hexane–chloroform–propan-2-ol (90 : 5 : 5 *v/v/v*) containing 1% triethylamine; flow rate 0.4 cm^3 min^{-1} at −5 °C; detection, UV at 320 nm. The value of the separation factor α can be calculated from the chromatographic data, and using the equation $\Delta\Delta g = RT \ln \alpha$, results in free energy differences of 585, 718 and 0 J mol^{-1} for **2**, **4** and **3** respectively.

the hydroxy group relative to the central ring, are remarkably small. The hydroxy hydrogen in both molecules lies in an orientation which is perpendicular to the plane of the phenanthrene ring, on the side of this ring opposite to the dibutylaminopropyl substituent at C(17). This orientation is different from those observed for the hydroxy hydrogens in the structure of halofantrine.[5] In that molecule, the hydroxy hydrogens point toward the dibutylaminopropyl substituent and are more nearly parallel to the plane of the phenanthrene ring. The packing mode in **2** is strikingly absent in the lattice of racemic **3**, where the alkyl side chains fold over the π-faces, and the rings instead adopt a complementary edge-to-edge dimeric interaction between pairs of enantiomers (Fig. 2). This interaction involves contacts between an apparently electron-deficient aromatic C(1)–H and a lone pair of the oxygen atom from a second molecule, slightly staggered to avoid contact between the two C(10)–H atoms (Fig. 2).‡ Although weak aromatic C–H hydrogen bonding has often been observed,[7] the H···O distance of 2.3 Å in **3** is relatively



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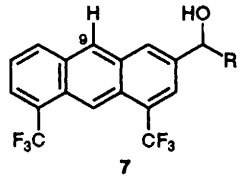

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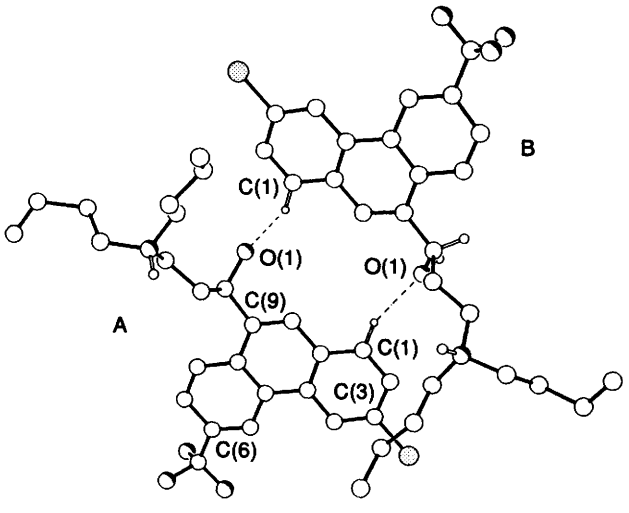

Fig. 2 Crystal structure showing the edge-to edge crystal stacking of two independent molecules of **3** (A and B) with the C–H···O interactions indicated as dashed lines. There is also an extensive network of conventional hydrogen bonding in the crystal structure of **3** with all available donors participating. Metrical details are: O1A···C12A (IV) = 3.02(1) Å, HO1A···C12A = 2.0 Å, angle at hydrogen = 180°; O1B···C12B (V) = 3.045(7) Å, HO1B···C12B = 2.0 Å, angle = 178°; N18A···C12A (II) = 3.052(9) Å, HN18A···C12A = 2.0 Å, angle = 170°; N18B···C12B = 3.06(1) Å, HN18B···C12B (III) = 2.1 Å, angle = 168°; O100···C12A (I) = 3.46(2) Å, H100···C12A = 2.3 Å, angle = 180°. Metrical details for the C–H···O interactions are: C3A···O1B (VI) = 3.29(1) Å, H2···O1B = 2.3 Å, angle = 159°; C3B···O1A (VII) = 3.27(1) Å, H33···O1A = 2.3 Å, angle = 155°. Roman numerals indicate symmetry operations as follows: (I) x,y,z $1+z$, (II) $1-x, 1-y, 1-z$; (III) $2-x, 1-y, 1-z$; (IV) $-x, 1-y, 1-z$; (V) $1-x, 1-y, -z$; (VI) $1-x, y, 1+z$; (VIII) $1+x, y, 1-z$.

short and in this case can be attributed to the acidity of 1-H induced by a combination of a W interaction with the 3-Cl substituent and a longer range seven-bond antiperiplanar (*app*) interaction along the σ-framework with the CF_3 substituent. A search of the Cambridge structural database[8] revealed that although similar hydrogen bonding is known to be induced by *m*-chloro aromatic substitution,[9] no examples of longer range CF_3-induced interactions appear to have been reported.

PM3 calculations[6] on a model compound in which the dibutylamino side chain (R) is replaced with R = H, reveal the charge on C(1)–H (0.1039 for **5**, R = H, 6-CF_3 replaced with 6-CH_3) is approximately equally increased by the 6-CF_3 and 3-Cl groups (0.1060 for **5**, R = H; 0.1067 for **3**, R = H, 6-CH_3; 0.1087 for **3**, R = H), suggesting both groups are necessary for hydrogen bonding at this position to influence chiral resolution.§ This is supported by our observation that **5** can be resolved, unlike **3**. The replacement of C(1)–H with C(1)–Cl as in **2** or **4** would also inhibit such an interaction, favouring instead the π–π stacking mode which we believe is partially responsible for chiral recognition. We also note the substantial analogy between **3** and the cyclic dimeric structure **6** of thiamine picrate,[10] where an even stronger hydrogen bond ($r_{H\cdots O}$ 2.21 Å) to the acidic 2-H ring hydrogen is formed.

An attempt was made to study the interactions responsible for the HPLC results using solution ^{1}H NMR. Initially, the free bases of **2** and **3** were studied in the presence of the methyl ester of dinitrobenzoyl leucine. Even at −40 °C, the observed ^{1}H shifts and nonequivalences were too small (<0.01–0.05 ppm) to make worthwhile comparisons, a reflection of the small differences in binding free energy between the diastereoisomeric complexes (Fig. 1). However, the use of (*S*)(+)-**1** (36 mmol dm^{-3}) as the chiral solvating agent for the free base forms of **2** and **3** (20 mmol dm^{-3} in $CDCl_3$) revealed a significant (0.24 ppm) upfield shift of the 10-H signal of **2** with an induced nonequivalence of 0.02 ppm, with similar values for **4** (0.15/0.02 ppm). In contrast the values for **3** are 0.04/0.01 ppm. The H-8 signals for all three complexes show comparable upfield shifts of ≈0.25 ppm and induced nonequivalence of ≈0.1 ppm. We interpret this as indicating significant π-stacking character in the diastereoisomeric complexes between **1** and **2**, whereas additional edge-to-edge interactions to **3** would induce downfield shifts at 10-H which largely offset upfield shifts due to π-stacking. This supports our hypothesis that the chiral HPLC recognition is associated with π–π stacking interactions in **2**, whereas stronger edge-to-edge, and apparently achiral, hydrogen bonding interactions eliminate the chiral recognition to **3**.

On the basis of our results, we predict that the shorter-range double *app* interaction in the model compound **7** should also result in C–H···O hydrogen bonding to 9-H. This prediction is supported by two types of PM3 calculation. The charge on 9-H (0.1105, **7**, R = H) *vs.* that in the unfluorinated analogue (0.1070, **7**, R = H, 4,5-CH_3) is increased compared with **3** (R = H). Secondly, the calculated enthalpy difference of +7.0 kcal mol^{-1} between **3** (ΔH −151.1 kcal mol^{-1}, R = H; 1 cal = 4.184 J) and its 1-anion (ΔH −144.1 kcal mol^{-1}) is reduced to +0.3 for **7**, R = H. The corresponding values for **5**; R = H, 6-CH_3, **5**; R = H, and **3**, R = H, 6-CH_3 are 18.9, 12.3 and 13.8 kcal mol^{-1} respectively, values which also support our contention that the electronic effects of the 3-Cl and 6-CF_3 groups in **3** are approximately equal.

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Footnotes

† *Crystal Data* for **3**: $C_{26}H_{31}ClF_3NO{\cdot}HCl{\cdot}1/2(C_3H_7OH)$, crystallized from propan-2-ol, M_r = 531.06, colourless, rectangular plate, 0.80 × 0.30 × 0.10 mm, triclinic, $P\bar{1}$, T = 223 K, a = 8.561(6), b = 18.180(6),

c = 19.286(3) Å, α = 75.41(3), β = 77.28(4), γ = 76.26(4)°, V = 2780.4(12) Å^3, Z = 4, D_c = 1.269 g cm^{-3}, μ = 2.782 cm^{-1}, $F(000)$ = 1174, Enraf-Nonius CAD4 diffractometer, Mo-Kα (λ = 0.071073 Å), lattice parameters determined from the setting angles of 25 high order reflections, variable speed ω–2θ scans for data collection in the range: $2 \leqslant 2\theta \leqslant 50°$, indices: $0 \leqslant h \leqslant 10$, $-21 \leqslant k \leqslant 21$, $-22 \leqslant l \leqslant 22$, 9937 reflections, 9217 unique (R_{int}=0.053), data corrected for Lorentz and polarization factors, 3040 data $I \geqslant 3.0\sigma(I)$, refined in blocks of 298 variables, weights = $1/\sigma^2(F_o)$ with $\sigma^2(F_o) = 1/[\sigma^2(I_o) + (0.04\,I_o)^2]$, R = 0.078, R_w = 0.093, goodness of fit = 1.897, final difference map residual density between ± 0.885 e Å^{-3}, final Δ/σ = 0.01, neutral atom scattering factors. The structure was solved by direct methods using the SHELXS program series. Atomic positions were initially refined with isotropic temperature factors and subsequently with anisotropic displacement parameters. The function minimized was $\Sigma_w(|F_o|-|F_c|)^2$. The trifluoromethyl group fluorine atoms show high isotropic thermal values which may be indicative of rotational disorder, but a chemically sensible model could not be refined for the data. The solvent molecule is disordered; it was treated isotropically at half-occupancy in a 'best-fit mode.' Positions for hydrogen atoms attached to carbons were assigned based on geometrical considerations (C–H distances of 1.0–1.1 Å) except that hydrogen atoms were omitted from the disordered solvent molecule. Positions for hydrogens attached to heteroatoms were calculated based on consideration of the putative hydrogen bonding scheme (N–H, O–H distances of 1.0–1.1 Å) and were included in the final refinement stages as fixed contributions with isotropic temperature factors assigned 1.3 (B_{eq}) of the attached atom. Programs in the SDP package were used for data reduction and refinement. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

‡ Computer readable files for Apple Macintosh and Microsoft Windows systems in Quicktime™ and MPEG video animation format illustrating the three dimensional properties of **2** and **3** and bond length and angle information are available for general access from the chemistry Gopher$^+$ server *gopher.ch.ic.ac.uk*. These files will reside in the Royal_Society_of_Chemisty/Chemical_Communications/3_03989G directory for a period of at least two years from the publication of this paper. A description of how to visualise such material, together with appropriate programs is available from the same source. The material can also be obtained by connecting to the following world-wide-web service: http://www.ch.ic.ac.uk/rzepa/RSC/CC/3_03989G.html.

§ On this basis we predict that the HPLC behaviour of **3**, 6-CH_3, should be similar to that of **5**. We thank a referee for this suggestion. Unfortunately, neither this material nor compound **7** is available to us.

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