Aryl Group π-Facial Electrostatic Asymmetry as a Contributing Factor to Chiral Resolution on β-Cyclodextrin HPLC Phases

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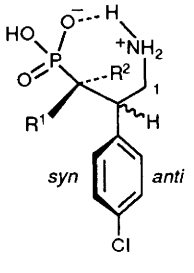
A model based on π-facial asymmetry in the calculated molecular electrostatic potentials is proposed to account for chromatographic behaviour of phaclofen **1** and its fluorinated derivatives **2–4** on a chiral cyclodextrin stationary phase.

There is much interest in understanding the interactions responsible for chiral recognition by cyclodextrin-bonded HPLC phases.[1] For racemic molecules containing an aryl ring, it is generally accepted that this moiety is reversibly complexed with the hydrophobic cavity of the cyclodextrin ring.[2] Chiral selectivity is then thought to occur according to the three-point model,[3] when the substituents on the rest of the guest molecule interact with the exposed hydrophilic centres on the glucose units *via* two further (stabilising or destabilising) interactions, although it has been speculated that an aryl ring may represent a multiple interaction point.[1,2]



1a; $R^1 = R^2 = H$
2a; $R^1 = R^2 = F$
3a; $R^1 = H$, $R^2 = F$
4a; $R^1 = F$, $R^2 = H$

In a chromatographic study of phaclofen **1** and the closely related difluoro derivative[4] **2** on an acetylated β-cyclodextrin stationary phase, we observed chiral separation for **2** but not for **1**. Furthermore, analysis of a mixture[4] of **3** and **4** revealed chiral separation only for the minor (40%) diastereoisomer (Fig. 1), assigned on the basis of NMR evidence as **4**.† We suggest here a theoretical model for the chromatographic behaviour of **1–4** in terms of asymmetry in the π-facial molecular electrostatic potentials on the aryl ring as a contributing factor to chiral resolution.

The free energy difference necessary to produce a separation factor of 1.11 in **2** (Fig. 1) is of the order of 240 J mol^{-1} in the binding of the two enantiomers to the chiral stationary phase. It has been shown that rigorously calculated gas-phase

† The ^{19}F spectrum of the mixture of **3** and **4** confirmed two isomers in the ratio of 40:60. The minor isomer (δ_F −195.1) exhibits coupling ($^2J_{P-F}$ 65.1, $^2J_{F-H}$ 46.6, $^3J_{F-H}$ 6.8 Hz) consistent with the ≈90° H–C–C–F dihedral angle calculated using PM3 for **4a**, whilst the major isomer (δ_F −214.7, $^2J_{P-F}$ 63.5, $^2J_{F-H}$ 45.8, $^3J_{F-H}$ 32.8 Hz) is consistent with the ≈154° angle calculated for **3a** (*cf.* G. Govil, *Mol. Phys.*, 1971, **21**, 953).

molecular electrostatic potentials (MEPs) can often provide a valuable insight into such small and subtle effects.[5] Here we present such PM3 molecular orbital calculations[6] for both the zwitterionic forms **1a–4a**, in which a strong P–O$^-$···H–N$^+$ hydrogen bond might be expected to impart conformational rigidity to the system, and the un-ionised neutral states **1b–4b**, in which neutral phosphate and amino groups interact *via* a weaker P–OH···N hydrogen bond. In aqueous solution at pH ≈7, the estimated pK_a values of phosphonate (≈2.5 and ≈7.0) and ammonium cation (≈10.6) groups in the appropriate environment[7] suggest that a significant proportion of these species exist as **1a–4a**, a conclusion unlikely to be modified significantly in the aqueous methanolic solvents employed in our study.

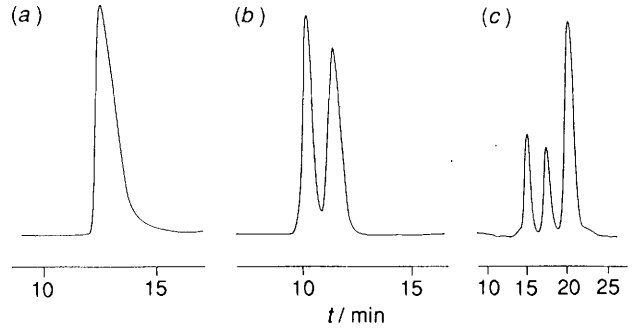


Fig. 1 Chromatographic behaviour showing (*a*) no chiral separation for **1**; (*b*) clear separation for **2**; (*c*) separation of only the minor diastereoisomer **4** and not the major isomer **3**. Conditions for (*a*) and (*b*): column, cyclobond I acetylated (250 mm × 4.6 mm); mobile phase, methanol/aqueous triethylamine–acetic acid (pH 7.2), 45 : 55. Flow rate 1 ml min^{-1}, UV detection at 220 nm, temperature ambient. Conditions for (*c*) are the same as (*a*) but the mobile phases were in the ration 40 : 60.

A clear correlation is apparent between on the one hand the large asymmetry in the calculated negative component of the MEP for the *syn*- and *anti*-π faces of **2** (Fig. 2) and its chiral separation (Fig. 1), and on the other hand the lack of asymmetry in the *syn*- and *anti*-π faces of **1** and a corresponding lack of chiral separation in this compound. These MEP calculations are performed on gas-phase models, but our previous experience with solvation models for glycine[8] suggests that the wavefunction of a solvated zwitterion would be intermediate between that of *e.g.*, **2a** and **2b**, and that therefore the facial electrostatic asymmetry in this diastereoisomer would persist. For the neutral forms of the compounds **3b** and **4b** it is possible to integrate the combined negative MEP component due to the π-face and the fluorine atom separately from that due to the phosphate group. The *anti*-π faces in the diastereoisomers **3b** (3.85 Å^3 at a potential of 0.032 Hartree) and **4b** (3.71 Å^3) are both similar in volume to the *syn*-face in **3b** (4.05 Å^3 associated with the π-face, 0.23 Å^3 with the fluorine atom), whereas the *syn*-face of **4b** (16.84 Å^3 due to the combined π-face and fluorine atom) is dramatically different. In the zwitterionic forms **3a** and **4a**, the negative MEP due to phosphate and the π-face are contiguous and cannot be separately integrated, but the same qualitative trend is apparent (Fig. 2). This result is entirely consistent with the chromatographic and NMR results.† On this basis, we predict that monofluorination on C-1 should produce similar chiral selectivity arising again from the aryl group.

The stereoelectronic origins of the asymmetry in the MEP can be probed using a localised orbital analysis of the PM3 wavefunctions,[6] which reveals the R^1 fluorine orbitals in **2b** (C–F σ, −22.65, F lone pairs, −18.31, −15.94 and −15.88 eV) to be destabilised relative to the R^2 orbitals (−22.90, −18.54, −16.19 and −16.14 eV). A larger effect is found for **2a** (R^1; C–F σ, −22.48, F lone pairs, −18.00, −15.66 and −15.60, R^2; −22.48, −18.51, −16.11 and −16.08 eV). These energy differences arise from mutual repulsion between the fluorine

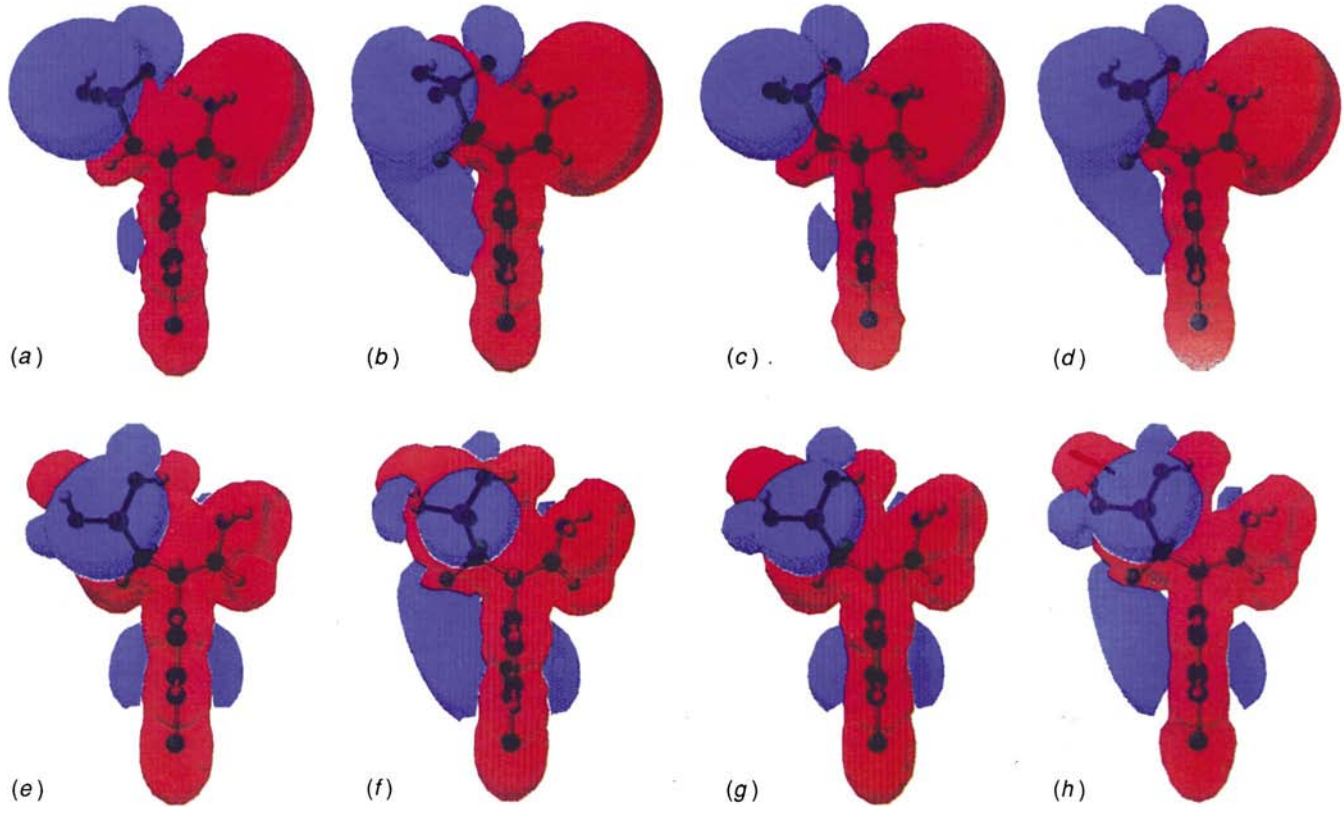


Fig. 2 Calculated PM3 molecular electrostatic potentials, contoured at 0.040 Hartree for the zwitterionic forms (*a*) **1a**, (*b*) **2a**, (*c*) **3a** and (*d*) **4a**, and at 0.025 Hartree for the neutral forms (*e*) **1b**, (*f*) **2b**, (*g*) **3b** and (*h*) **4b**. Blue areas indicate a potential attractive to a proton.

atom and the π-system, and from antiperiplanar destabilisation between the C–F bond and either the nitrogen lone pair (in **2b**) or the O^- atom (in **2a**). A striking similarity is also apparent in the asymmetry of the MEP distribution of **2** and **4** and that calculated for the highly efficient chiral resolving agent 3,3,3-trifluoro-(9-anthryl)ethanol.[9] This implies that π-facial enantioselectivity can play a significant role in the chiral recognition process, in which an aromatic ring can indeed represent a two-fold interaction point in the three-point model.[1]

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