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Partially fluorinated alkoxy groups – Conformational adaptors to changing environments

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ABSTRACT

Lipophilicities of partially fluorinated *n*-propyloxy indole derivatives and their rates of oxidative metabolic degradation are presented. Comparison of the lipophilicity data with those of compounds containing the same partially fluorinated propyl groups attached to carbon or nitrogen reveals remarkable similarities and some distinct differences. A further striking difference in lipophilicity pattern is noted between terminally fluorinated *n*-propyloxy and corresponding methoxy derivatives. The lipophilicity patterns are rationalized in a consistent way by application of a simple rule-of-thumb based on polar-bond vector superposition, taking into account conformational aspects deduced from X-ray crystal structures and quantum chemical calculations. Several of these groups can switch between polar and non-polar conformations of comparable energies and may thus be regarded as potentially effective conformational adaptors to changing chemical environments. All compounds exhibit relatively high rates of metabolic degradation with a moderate correlation between degradation rate and lipophilicity.

1. Introduction

Incorporation of fluorine into organic compounds to modulate their physicochemical and pharmacological properties has become a widely adopted strategy in lead optimization programs [1]. Fluoroaromatic and trifluoromethyl units are among the most frequently used fluorine-containing moieties [1c,2,3]. Likewise, the trifluoromethoxy group has often been used to block potential metabolic degradation of anisole-type methoxy groups [4]. However, the replacement of aryl methoxy by trifluoromethoxy generally results in a substantial increase in lipophilicity [4,5] often with undesired pharmacological consequences [4]. This lipophilicity increase can be qualitatively rationalized on the basis of a simple polar bond vector analysis [5] suggesting that the polarity of the ether unit partially compensates the local polarity exerted by the trifluoromethyl unit so that the volume increase from methyl to trifluoromethyl essentially dominates the change in lipophilicity (log *P*). Based on this simple rule-of-thumb analysis (Fig. 1) the increase in lipophilicity upon replacement of an anisole-type methoxy by a trifluoromethoxy group can thus be estimated to be $\Delta\log P_{est} \sim +0.8$. A search in the Roche compound property database for matched molecular pairs (MMPs) with the only structural difference being a trifluoromethoxy group in place of a methoxy group resulted in 36 neutral matched pairs for which the average experimental lipophilicity difference was $\Delta\log P \sim +1.0 \pm 0.3$ [5]. Very similar results have been reported by Li Xing et al. by an MMP analysis of corresponding data in the corporate database of Pfizer [4].

In recent years and fostered by significant developments in synthetic methodology [6], the difluoromethyl group has come more into focus. Unlike the axially isotropic trifluoromethyl group, the difluoromethyl counterpart is axially anisotropic and can adopt different conformations with characteristically different polarity depending on its immediate topological environment [2]. Difluoromethoxy is of particular interest as a synthetically easily accessible [7], chemically and pharmacologically rather stable unit [8]. Difluoromethoxy groups attached to aryl units are known to adopt, in the absence of steric encumbrance, either of two typical conformations [1d,5]. One is essentially orthogonal to the

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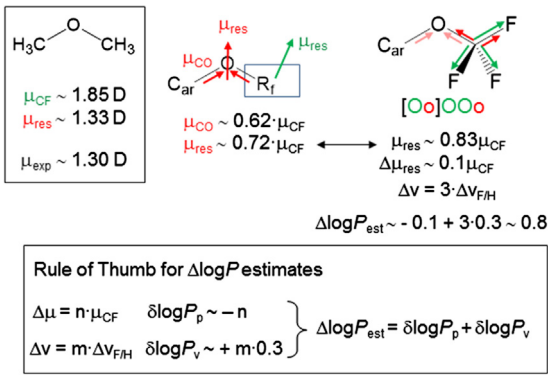

Fig. 1. A simple rule-of-thumb allows an estimate of the log *P* change upon fluorine/hydrogen exchange (F/H) at an aliphatic tetrahedral carbon of a reference compound, based on a polarity contribution, δlog P_p (in units of the C-F bond moment μ_{CF}) and a volume contribution, δlog P_v (by the number m of H/F exchanges). This is exemplified for the trifluoromethoxy group relative to the non-fluorinated parent. The C-O bond polarity is estimated at $\sim^2/_3$ μ_{CF} based on relative electronegativity differences [5]. For a tetrahedral arrangement around oxygen, the two C-O bond dipole moment vectors add up to a resultant dipole moment which, with a C-F bond polarity taken from methylfluoride (μ_{CF} ~ 1.85 D), satisfactorily reproduces the experimental gas-phase dipole moment of dimethyl ether. Going from the methoxy to the trifluoromethoxy group, assuming idealized tetrahedral geometries, the three C-F bond vectors (green) add up with the two C-O bond vectors (red), which are shifted into a common origin, resulting in four out-going vectors of different magnitudes (characterized by the large green letters 'O' and small red letters 'o'), thus in a moderate polarity of μ_{res} ~ 0.83 μ_{CF}; note that for four out-going tetrahedrally oriented vectors of equal magnitude μ_{res} = 0. Relative to the non-fluorinated CH_3-O-CH_3 reference compound this implies a minor increase of polarity by 0.1 μ_{CF}. Application of the rule-of-thumb then predicts a substantial log *P* upshift (+0.8) for the transition CH_3-OCH_3 to CH_3-OCF_3 due to an overcompensation of the small polarity contribution by a comparatively large volume change. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

aryl unit and has the two fluorine ligands in *endo* positions, i.e., *gauche* to the COC backbone thus *antiperiplanar* to the two oxygen sp^3-type lone pair orbitals. This conformation resembles that of the orthogonal aryl trifluoromethoxy group. The other conformation has one fluorine ligand in an *endo*, the other in an *exo* position, i.e., antiperiplanar to the C_{aryl}—O bond (see Fig. 2). Based on a survey of published X-ray crystal structures available in the Cambridge Structure Database (CSD) [9], this *exo-endo* arrangement for the difluoromethyl unit is encountered with in-plane, twisted, or even orthogonal difluoromethoxy groups. Density functional theory (DFT) calculations (for details see Experimental Part) predict that the two types of aryl-$OCHF_2$ conformations (conformations I and II, Fig. 2) are of similar energy in the gas-phase. While the orthogonal fluorine *endo,endo*-conformation I profits from two ($n\rightarrow\sigma^*_{CF}$) anomeric effects at the cost of anisole-type π-conjugation, the in-plane or twisted fluorine *exo,endo*-conformation has only one anomeric interaction, but regains part of the anisole-type π-conjugation. In the absence of aryl conjugation, i.e. by replacing the phenyl unit by a methyl group, the doubly anomeric conformation is predicted to be favored by ~2 kcal/mol in the gas-phase, but only ~0.7 kcal/mol in polar (water) medium. Based on a simplified vector analysis the *endo-endo* conformation of the difluoromethoxy group is estimated to be very lipophilic, similar to the trifluoromethoxy group. By contrast, the *exo-endo* conformation is predicted to be rather polar and significantly more polar than the trifluoromethoxy group (Fig. 2). These findings led to the hypothesis that a difluoromethoxy group may be able to adapt to changing environments simply by a low-energy barrier conformational switch [5]. An indirect support for this idea came from Li Xing and her group at Pfizer carrying out MMP analyses for a large set of molecular pairs differing exclusively in a difluoromethoxy in place of a trifluoromethoxy group [5]: The difluoromethoxy compounds showed a clear tendency for improved membrane permeation compared to the congeners with a trifluoromethoxy group. The same MMP analysis also indicated a substantial downshift of lipophilicity by replacing an OCF_3 by an $OCHF_2$ group. This is in line with our own findings on 15 neutral matched molecular pairs resulting in $\Delta\log P = -0.7 \pm 0.1$ for an exchange of the lipophilic OCF_3 group by the more polar $OCHF_2$ unit suggesting a significant contribution of the polar *exo-endo* conformation of the $OCHF_2$ group in polar (water) medium.

Little is known regarding the monofluoromethoxy group. This may be the result of a general notion in Medicinal Chemistry that an OCH_2F group may not be sufficiently stable either chemically or pharmacologically [4]. Our search in the Roche compound database revealed only one OCF_3/OCH_2F neutral matched molecular pair with $\Delta\log P = -1.0$. This would indicate that an OCH_2F group would be similar in lipophilicity as the parent aromatic compound or its methoxy-substituted derivative, whereas computed log *P* (clogP) would predict a slight increase in lipophilicity (Δclog $P \sim 0.0 \div 0.1$ depending on the method [10]) for the transition from OCH_3 to OCH_2F. No X-ray structural data are currently available from the literature, but DFT calculations on the model compound monofluoromethoxybenzene at the B3LYP/cc-pVDZ++ level indicate that the OCH_2F group may almost exclusively adopt the anomerically stabilized *endo* (*gauche*) conformation (Fig. 3) whereas the 'non-anomeric' *exo* conformation would be destabilized by at least 4 kcal/mol and would thus probably not contribute significantly to the overall lipophilicity. Interestingly, the simple vector analysis for the OCH_2F group indicates a very small lipophilicity change ($\Delta\log P_{est}$ ~+0.2) in going from OCH_3 to OCH_2F in the anomeric *gauche* conformation, while the 'elusive' *exo* conformation would be predicted to be significantly more polar (Fig. 3).

Of the three fluorinated aryl methoxy groups, the difluoromethoxy unit stands out as the most interesting group exhibiting a relatively balanced conformational equilibrium with a marked conformation-dependent lipophilicity. Environmental changes may thus easily induce shifts in equilibrium with concomitant modulation of lipophilicity. Neither the trifluoromethoxy nor the monofluoromethoxy group can induce such effects, the former because it is axially symmetric, the latter because it has essentially only one conformation at its disposition.

In our search for other potentially effective conformational adaptor units to environmental changes we turned to partially fluorinated *n*-propyloxy groups. The combined polarity contributions by the C—O and C—F bonds has been examined in a few cases by the simple bond vector analysis [5], identifying interesting candidates. In the current study, we report our results for a series of indole derivatives carrying partially fluorinated *n*-propyloxy groups in 5-position (Fig. 4). These studies complement our earlier work on 3-alkyl substituted indole derivatives [2,11] and *N*-alkyl-substituted piperidine carboxamide derivatives [12] with the partially fluorinated alkyl groups attached to carbon and nitrogen atoms, respectively.

2. Synthesis of partially fluorinated 5-propyloxy-indoles

The partially fluorinated 5-propyloxy-indoles **2**-**4** and the reference compound **1** are readily available through coupling of corresponding *n*-propyl nonaflates [12] to *N*-tosyl protected 5-hydroxy-indoles under mild basic conditions and subsequent indole deprotection under somewhat harsher basic conditions (Scheme 1). For the *vic*-difluoro derivative **5** somewhat milder conditions for the final deprotection of the indole unit had to be used in order to avoid undesired side reactions. The key substrate, *N*-tosyl-5-hydroxyindole **10**, was readily available in an optimized