Pergamon

Tetrahedron, Vol. 52, No. 38, pp. 12613-12622, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00749-1

How Good is Fluorine as a Hydrogen Bond Acceptor?

Judith A. K. Howard,* Vanessa J. Hoy, David O'Hagan* and Garry T. Smith

Department of Chemistry, University of Durham, Science Laboratories, South Road, Durham. DH1 3LE.

Abstract: This study is aimed at evaluating organic fluorine as a hydrogen bonding acceptor. A review of short F···H contacts from all of the organofluorine compounds deposited in the Cambridge Structural Database System (CSDS) was carried out and in parallel a theoretical estimate of the energy of such contacts with inter nuclear distance was executed. A total of 548 structures emerged which contained 1163 unique C-F bonds and only 166 of these fluorine atoms posessed short C-F···H-X contacts of ≤ 2.35Å. Contacts between fluorine and hydrogen bound to carbon (C-F···H-C) represent the major category of short contacts however these were not judged to be hydrogen bonds as they are weak with energies similar to those of van der Waals complexes. Short contacts between F and the acidic hydrogens of HO or HN are rare in the CSDS with only 12 and 28 occurring respectively. There was only one contact below 2.0Å. *Ab initio* calculations have evaluated the relative stability and optimum distance of C-F···H-O bonds between water and fluoromethane and fluoroethene. It emerges that the $C(sp^3)$-F fluorine in fluoromethane can enter into stronger hydrogen bonds than $C(sp^2)$-F of fluoroethene. The X-ray data reinforces the conclusion that $C(sp^3)$-F fluorine is a better hydrogen bond acceptor than $C(sp^2)$-F fluorine. The $C(sp^3)$-F···H-O bond is less than half the strength (2.38 kcal mol^{-1}) of a C-O···H-O and the $C(sp^2)$-F···H-O bond (1.48 kcal mol^{-1}) is about half as weak again. Overall however short contacts in the Database which are consistent with an optimal F···H bond are extremely rare.

INTRODUCTION

It has become a common practise in bio-organic chemistry to replace a hydrogen atom or hydroxyl group for fluorine to generate a fluorinated enzyme substrate analogue, which may act as a substrate or inhibitor in a given enzymatic process[1-3]. The rationale for such a strategy is that the size of the fluorine atom is intermediate between that of hydrogen and oxygen. The van der Waals radii of fluorine (1.47Å) can be compared to that of hydrogen (1.2Å) or oxygen (1.57Å) and it emerges that fluorine has a close isosteric relationship to oxygen[4]. To be a successful hydroxyl mimic in bio-organic chemistry the fluorine atom must replace the hydrogen bond acceptor ability of the hydroxyl oxygen. Clearly fluorine cannot replace the

Figure 1 The OH can act as a hydrogen bonding donor or acceptor whereas fluorine can only act as an acceptor.

Theoretical calculations variously estimate[5] the strength of a F···H bond to be between 2 to 3.2 kcal mol^{-1}. This can be compared[6] to an O···H hydrogen bond which is typically between 5 - 10 kcal mol^{-1}. Consistent with this the electrostatic influence of fluorine is approximately half that of oxygen[7]. Thus the greater electronegativity and lower polarisability of fluorine over oxygen, suppresses its electrostatic influence and renders it a poorer hydrogen bond acceptor.

X-ray structural data offers an arena in which to assess fluorine as a hydrogen bonding acceptor. In a recent survey Shimoni and Glusker,[8] building on an earlier study,[9] of organo-fluorine compounds deposited in the Cambridge Structural Database System (CSDS), revealed relatively few situations where fluorine was involved in short contacts to acidic hydrogens (HO or HN). The authors concluded that the weakness of the F···H interaction results in it being overridden by acidic hydrogens finding O and N acceptors to pair with in preference to fluorine. This study was particularly wide ranging and embraced CF, CF_2 and CF_3 containing structures including non-bonded F···H interactions up to 3Å in length. The mean H···F distances in the study emerged between 2.5-2.6Å, which is close to the sum of the van der Waals radii of hydrogen and fluorine.[4] Contacts of this length will constitute weak interactions in energy terms. If fluorine is to replace the oxygen atom directly in a highly preorganised binding situation eg. in an enzyme-substrate complex, then ideally it is required to replace oxygen in O···H and make a short F···H contact of about 2.0 - 2.3Å. The present study therefore aimed to review the shorter F···H contacts equal to or smaller than 2.35Å and was restricted to C-F containing systems. CF_2 and CF_3 systems were ignored. This restriction was introduced as the focus of interest was to evaluate the hydrogen bonding acceptor ability of the fluorine atom in monofluorinated functional groups (ie. F for O). It was judged important not to make false comparisons with CF_2 and CF_3 systems where the hydrogen bonding ability of these fluorines may be perturbed.

A theoretical study was carried out in parallel with the Database analysis to evaluate the strength of the C-F···H-O and C-F···H-C interactions with distance. Both the Database survey and the theoretical analysis make the distinction between the hydrogen bonding acceptor ability of fluorine bound to both sp^2 and sp^3 hybridised carbon. To make a quantitative assessment of the relative strengths of $C(sp^3)$-F and $C(sp^2)$-F bound fluorine atoms, the change in interaction energies with bond length between (**a**) fluoromethane and water, and (**b**) fluoroethene and water, were studied. Also this and the previous studies[8,9] have revealed that the most common F···H contacts in the Database occur between fluorine and non acidic hydrogen atoms (ie. to HC rather than to HO or HN). These C-F···H-C interactions should be weak and to assess their stabilising influence both with $C(sp^3)$-F and $C(sp^2)$-F bound fluorine atoms, the interaction energies between (**c**) fluoromethane and methane and (**d**) fluoroethene and methane, were also evaluated.

Methods

Cambridge Structural Database Search

Version 5.10 of the Cambridge Structural Database System[10] (CSDS: October 1995) containing 146,272 entries was used for the study. Searches for bonded substructures and for inter- and intra- molecular non-bonded contacts were carried out using the program QUEST3D[11]. Subsequent statistical analyses were performed using VISTA[11]. The CCDB was searched for all C-F containing structures with an R factor lower than 0.075. All CF_2 and CF_3 containing compounds were deselected. The search was restricted to shorter ($\leq$ 2.35Å) H···F contacts and was subdivided on the basis of hybridisation at carbon ie. C(sp^3)-F and C(sp^2)-F and on the *intra* or *inter* nature of the F···H contacts. Hydrogen atom positions were normalised by extending the H···X bond along the X-ray derived bond vector to a neutron derived mean X-H bond length.[12]

Theoretical calculations

The geometries of the CH_2=CHF, CH_3F and H_2O molecules were optimised at the second order Möller-Plesset level utilising analytical gradients as implemented in the GAMESS program.[13] The basis set used was Dunning's TZV[14] supplemented by 3d and 1f polarization functions with Bearpark and Handy's"V" exponents[15] and also a diffuse sp shell for C, O and F. Hydrogen atoms had a single shell of p polarisation functions and a single diffuse s shell. Diffuse functions were assigned the literature exponents[16]. This basis we denote TZV++(3d1f,1p). The molecules were then paired up to generate the appropriate dimers. The geometry chosen was that which made C-F···H-X bond colinear. Basis set expansion to higher angular momentum functions is required to saturate the dispersion term within the MP2 formalism.[17] A more economical way of approaching this situation is the use of functions at mid-bond positions.[18] Thus a dimer basis set of the TZV++(3d1f,1p) type as above supplemented with a (1p1d1f) expansion midway between the F and H atoms.

In all cases, a potential energy scan was performed by varying the F···H distance while keeping the monomer geometries frozen. Relaxation of the monomer geometries will presumably lower the dimer energy further, however due to computational cost this was not feasable and therefore we may assume that the dimer energies may be slightly underestimated. The total dimer energies were calculated at both the HF and MP2 levels on a one dimensional grid at 0.1Å spacing. Once the lowest energy point was determined, two further single point energy calculations 0.05Å either side of this were also calculated to obtain the absolute minima.

When considering the energy stabilisation on dimerisation, suitable monomer energies must be subtracted from the full dimer energy. However, straight subtraction of the energies obtained from the isolated geometry optimisations may over-estimate the binding energy due to the well known basis set superposition error (BSSE) which results from effectively performing the monomer and dimer energies with different basis sets. Thus when calculating the monomer energies, full dimer basis sets at the equlibrium position were used following Boys and Bernardi[19]. These energies were then subtracted from the dimer energies along the potential energy surface which assumed the counterpoise correction to remain constant for all monomer separations.

RESULTS

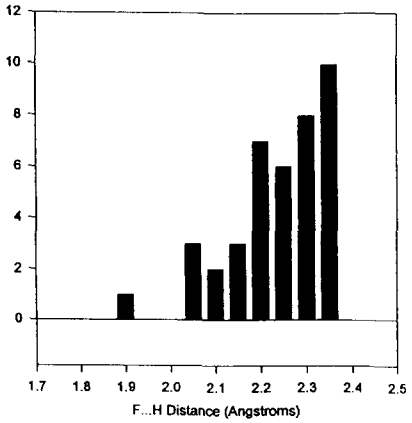
The results of the CSDS search are summarised Table 1 and in Figures 2-4.

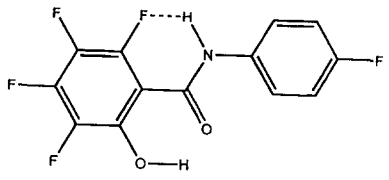
	TOTAL HITS		SHORT F···H CONTACTS			
			INTRA		INTER	
$C(sp^3)$-F	Compounds	C-F bonds	Compounds	Contacts	Compounds	Contacts
Total	177	237	28	29	20	22
O-H	71	89	5	5	1	1
N-H	69	85	8	8	3	3
C-H	177	237	15	16	18	18

			INTRA		INTER	
$C-(sp^2)$-F	Compounds	C-F bonds	Compounds	Contacts	Compounds	Contacts
Total	371	926	48	65	45	50
O-H	89	177	3	3	3	3
N-H	113	214	7	9	8	8
C-H	360	929	41	53	35	39

Table 1 Summary statistics for the Total Hits and Short Contact searches showing numbers of compounds and C-F Bonds or contacts ≤ 2.35Å in each donor acceptor sub-set.

In Table 1 the search data is divided into short contacts between $C(sp^3)$-F and $C(sp^2)$-F and subdivided to distinguish *intra* and *inter* molecular F···H contacts. In the event 548 (177 + 371) C-F containing structures emerged with a total of 1163 (237 + 926) C-F bonds. Of all of the C-F bonds only 166 participated in non-bonded C-F···H-X contacts of 2.35Å or shorter. The majority of these were C-F···H-C contacts between fluorine and non acidic carbon bound hydrogen atoms as shown in Table 1. The weakness of these C-F···H-C is discussed later and it is more relevant to consider the stronger F···H contacts to more acidic hydrogens.





1

Figure 2 Histogram summarising the frequency and bond lengths of F···H-O/N contacts identified from the CSDS. There was only one instance (compound **1**, F···H = 1.86Å, Database Ref Code, YUYTOB[20]) of a contact shorter than 2.0Å.

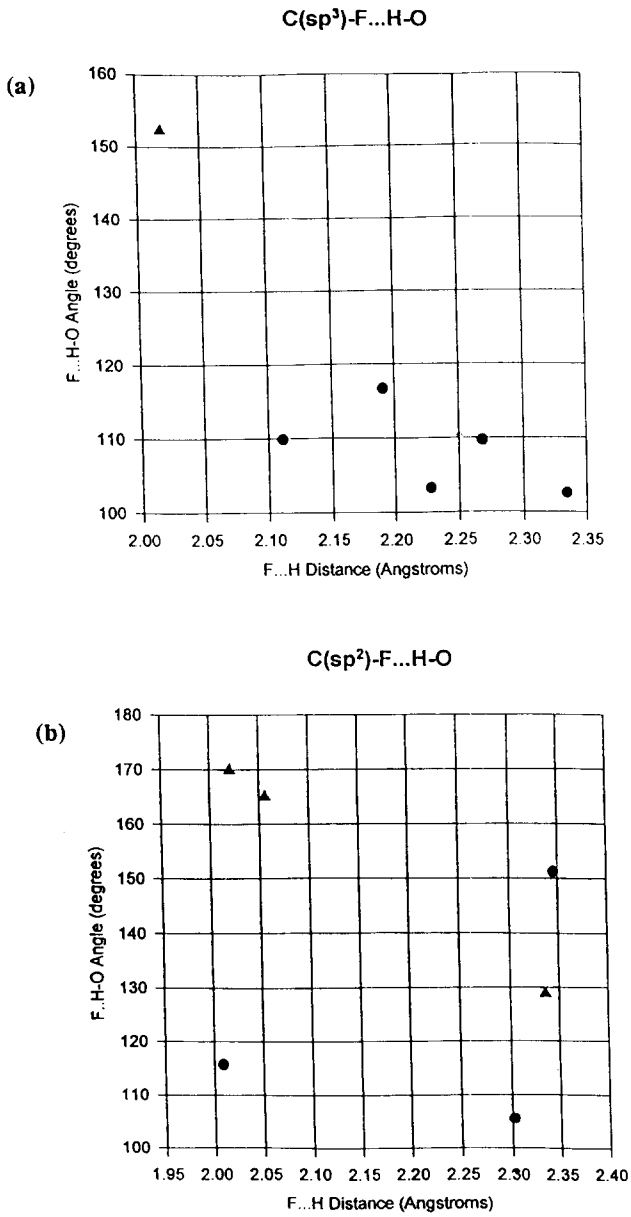


Figure 3 Scatter plots summarising the CSDS search showing the angles and lengths of *intra* (o) and *inter* (▲) molecular F···H-O contacts to (**a**) C(sp^3)-F bonded fluorine atoms and (**b**) to C(sp^2)-F fluorine bonded atoms.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.