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Organic Fluorine: Odd Man Out

Jack D. Dunitz*[a]

Organic Fluorine Hardly Ever Makes Hydrogen Bonds

Linus Pauling had a superb intuitive understanding of chemistry, backed by deep intelligence and a prodigious memory. He seldom made mistakes. The best known is perhaps his ill-fated three-stranded DNA structure, but one of the few other examples concerns hydrogen bonds involving fluorine. This is evident from a comparison between the various editions of his classic "The Nature of the Chemical Bond". In the early editions he wrote:

"only the most electronegative atoms should form hydrogen bonds, and the strength of the bond should increase with increase in the electronegativity of the two bonded atoms… It is found empirically that fluorine forms very strong hydrogen bonds, oxygen weaker ones, and nitrogen still weaker ones."[1]

Pauling went on to discuss the strong hydrogen bond in hydrofluoric acid $(HF)_n$ and the very strong one in the hydrogen fluoride ion $[HF_2]^-$ and correctly concluded that the proton in the latter should lie in a single minimum potential well or in a double minimum potential with a very small barrier. It was only in the third edition, published in 1960, some twenty years after the first, that Pauling conceded:

"It is interesting that in general fluorine atoms attached to carbon do not have significant power to act as proton acceptors in the formation of hydrogen bonds in the way that would be anticipated from the large difference in electronegativity of fluorine and carbon."[2]

Over the years, many chemists have followed Pauling's first line of thought, and more or less taken it for granted that organic fluorine acts as a powerful acceptor in the formation of hydrogen bonds. Others have looked at the available structural evidence as collected in the Cambridge Crystallographic Structural Database (CSD) and concluded that organic fluorine is at best only a weak hydrogen-bond acceptor.[3,4] A further intensive search of the CSD, including detailed inspection of individual crystal structures and backed by ab initio calculations on model systems, confirmed that organic fluorine hardly ever accepts hydrogen bonds, that is, it does so only in the absence of a better acceptor.[5] Even in such compounds like crystalline ammonium trifluoroacetate, in which there are four hydrogen donors per anion, there is no hint of N–H···F hydrogen bonding; the four N–H bonds all point towards oxygen atoms of the trifluoroacetate anions. In the ammonium monofluoro structure[6] there is just a hint of a bifurcated hydrogen bond involving carboxylate O and the *syn*-planar F atom, but the latter is 0.26 Å more distant from the H atom (Figure 1). Likewise, the evidence for hydrogen bonding to organic fluorine in protein–ligand complexes was examined and found to be unconvincing.[5]

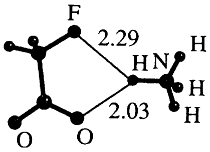

Figure 1. *A C–F···H–N interaction in the crystal structure of ammonium monofluoroacetate[6] that might be classified as part of a bifurcated hydrogen bond. Taken from J. D. Dunitz, R. Taylor,* Chem. Eur. J. ***1997****, 3, 93, copyright Wiley-VCH.*

Hydrogen bonding involving B–F bonds should be stronger than that involving C–F bonds. Yet even in crystalline ammonium tetrafluoroborate $NH_4^+BF_4^-$, surely the exemplar of such an expected interaction, no short N–H···F lengths are observed.[7] The authors commented "it is believed that hydrogen bonding contributes negligibly to the lattice energy of this crystal". A search of the CSD reveals only very few crystal structures showing short intermolecular X–H···F–B lengths; one example is 4,4,8,8-tetrafluoropyrazabole,[8] another is 2,2-difluoro-4,6-dimethyl-3-phenyl-1,3,2-difluorodiazaborine (Figure 2).[9] One can hardly deny that these should be classified as genuine hydrogen bonds, but there are few such specimens.

It seems clear that with its low polarizability and tightly contracted lone pairs, fluorine is unable to compete with stronger hydrogen-bond acceptors such as oxygen or nitrogen. The few authentic examples of O–H···F or N–H···F hydrogen bonding involve systems in which approach of the hydrogen atom to other better acceptor atoms is sterically hindered. Indeed, nowadays the occurrence of a genuine hydrogen bond involving organic fluorine seems to be regarded as sufficiently noteworthy that it deserves special mention in the title of the publication, as, for example, ref. [10].

Aliphatic Hydrocarbons and Fluorocarbons

Quite apart from its, for Pauling, unexpected reluctance to engage in hydrogen bonding, fluorine occupies a special place among the elements. It is the most electronegative. The fluorine molecule is the most reactive and the most powerful oxidizing agent known. Fluorine forms the strongest known single bonds in its links with boron, carbon, silicon, and hydrogen. With carbon the bond energy increases with degree of fluorination: for example, (D^o(C-F) = 453 kJ mol^{-1} in CH_3F, 546 in CF_4.[11] Other halogens do not behave in this way. Fluorination increases the strength of C–C single bonds but weakens the strength of C=C double bonds.[11]

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[a] *Prof. J. D. Dunitz*
Organic Chemistry Laboratory, Swiss Federal Institute of Technology
ETH-Hönggerberg, 8053 Zurich (Switzerland)
Fax: (+41) 1-632-1109
E-mail: dunitz@org.chem.ethz.ch

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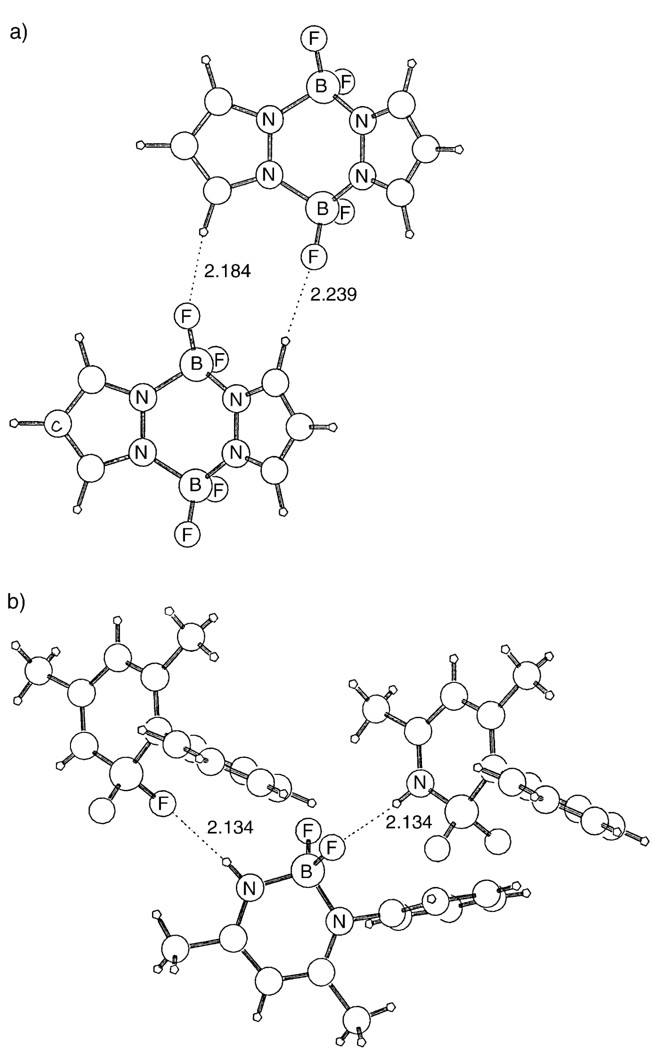

Figure 2. Hydrogen bonds in the crystal structures of 4,4,8,8-tetrafluoropyrazabole[8] and 2,2-difluoro-4,6-dimethyl-3-phenyl-1,3,2-difluorodiazaborine.[9]

Perfluorocarbons are remarkably stable and inert. They have the lowest dielectric constants of any liquids at room temperature and the lowest surface tensions—they can wet any surface! They also show striking similarities with their hydrocarbon counterparts. Although corresponding pairs, for example, hexane and perfluorohexane, differ greatly in density, they have almost the same molecular polarizabilities and boiling points (Table 1), hence closely similar cohesive energies that derive mainly from intermolecular dispersion interactions. Excellent reviews of the similarities and differences between physical properties of fluorocarbons and their hydrocarbon analogues are available.[11,12,13]

It came then as somewhat of a surprise that liquid hydrocarbons and fluorocarbons do not mix easily. As noted in the classic monograph *Regular and Related Solutions*: "before the advent of fluorocarbons, nonpolar components sufficiently unlike to yield two liquid phases were scarce… The advent of fluorocarbons provided a new set of nonpolar liquids which are only partially miscible with other common, nonpolar liquids."[14]

As examples of such mutual phobicity might be mentioned the high consolute temperatures of hexane and perfluorohexane (296 K) and of cyclohexane and perfluorocyclohexane (316 K) and the strongly nonideal behavior of butane–perfluorobutane solutions, where the partial vapor pressures of the components are much larger than expected for an ideal solution (Raoult's law), and the large positive (endothermic) heats of mixing.[14] In keeping with this behavior, gas-phase measurements indicate that perfluorocarbon–hydrocarbon interaction energies are about 10% weaker than expected on the basis of perfluorocarbon–perfluorocarbon and hydrocarbon–hydrocarbon interaction energies.[15] As far as relative hydrophobicity is concerned, perfluorocarbons are even less soluble in water than are hydrocarbons (on a mole basis).

In accord with the mutual antipathy of aliphatic hydrocarbons and fluorocarbons, chain segments of the two types of molecule tend to segregate when both are present in the same crystal structure. One of the best examples of this is found in the crystal structure of 12,12,13,13,14,14,15,15,16,16,17,17,17-tridecafluoroheptadecan-1-ol,[16] in which double layers of hydrogen-bonded hydrocarbon chain segments are separated from those of fluorocarbon segments (Figure 3). The prominent bend at the junction of the two segments allows the short intermolecular $C\cdots C$ distances between successive chains to differ; these distances are about 4 Å between hydrocarbon chain segments and about 5 Å between fluorocarbon ones. The crystal structures of the *n*-alkanes themselves have been determined recently.[17] From *n*-hexane onwards, the centrosymmetric even-membered chains pack with all chains parallel (in space group $P\bar{1}$, $Z=1$) while successive C_2-symmetric odd-membered chains are related by inversion centers ($P\bar{1}$, $Z=2$). The resulting differences in the packing of the terminal methyl groups have been invoked to explain the well-known melting-point alternation between compounds with even- and odd-membered chains.[17]

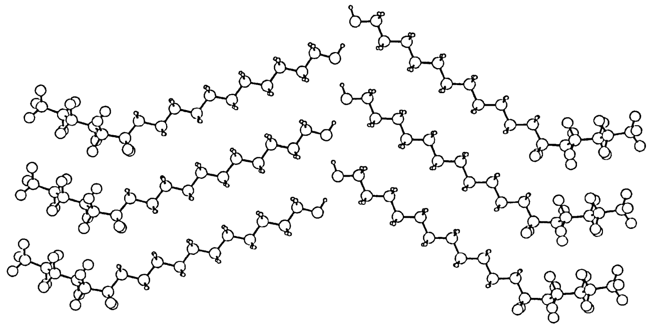

Figure 3. Segregation of hydrocarbon and fluorocarbon chain segments in the crystal structure of 12,12,13,13,14,14,15,15,16,16,17,17,17-tridecafluoroheptadecan-1-ol.[16] Taken from J. D. Dunitz et al., Helv. Chim. Acta ***2003**, 86, 4073, with permission.*

Only one perfluoroalkane crystal structure is known so far and that is perfluorohexane.[18] In contrast to the planar zigzag conformation of the *n*-alkane chain, the perfluoroalkane chain is helical with twist angles of about 13° around each C–C

Table 1. Molecular masses (M), liquid densities (ρ), refractive indices (n_D), boiling points (b.p.), and molecular polarizabilities (α) of various aliphatic and aromatic hydrocarbons and fluorocarbons. The data were collected mainly from chemical suppliers handbooks, and the polarizabilities calculated with the Clausius–Mosotti equation; $\alpha = (3M/L\rho)(n^2-1)/(n^2+2)$, where M is the molar mass, L is Avogadro's number, ρ is the density, and n is the refractive index. Where comparable α values are given in the CRC Handbook of Chemistry and Physics, the agreement is good.

compound	formula	M [g mol^{-1}]	ρ [g mL^{-1}]	n_D	b.p. [°C]	b.p. [K]	α [Å^3]
perfluoropentane	C_5F_{12}	288	1.664	1.241	29	302	10.47
perfluorohexane	C_6F_{14}	338	1.700	1.251	60	333	12.49
perfluoroheptane	C_7F_{16}	388	1.720	1.265	81	354	14.91
perfluorooctane	C_8F_{18}	438	1.730	1.282	100	373	17.73
perfluorononane	C_9F_{20}	488	1.799	1.276	126	399	18.62
pentane	C_5H_{12}	72	0.626	1.358	36	309	10.03
hexane	C_6H_{14}	86	0.659	1.375	68	341	11.87
heptane	C_7H_{16}	100	0.684	1.388	98	371	13.70
octane	C_8H_{18}	114	0.703	1.398	125	398	15.54
nonane	C_9H_{20}	128	0.718	1.405	151	424	17.35
benzene	C_6H_6	78	0.879	1.501	81	354	10.38
fluorobenzene	C_6H_5F	96	1.025	1.465	85	358	10.27
1,2-difluorobenzene	$C_6H_4F_2$	114	1.171	1.443	94	367	10.24
1,3-difluorobenzene	$C_6H_4F_2$	114	1.160	1.439	83	356	10.25
1,4-difluorobenzene	$C_6H_4F_2$	114	1.166	1.441	89	362	10.24
1,2,4-trifluorobenzene	$C_6H_3F_3$	132	1.264	1.423	88	361	10.55
1,2,3-trifluorobenzene	$C_6H_3F_3$	132	1.280	1.423	95	368	10.42
1,3,5-trifluorobenzene	$C_6H_3F_3$	132	1.277	1.415	76	349	10.27
1,2,3,4-tetrafluorobenzene	$C_6H_2F_4$	150	1.400	1.408	95	368	10.48
1,2,3,5-tetrafluorobenzene	$C_6H_2F_4$	150	1.393	1.404	83	356	10.44
1,2,4,5-tetrafluorobenzene	$C_6H_2F_4$	150	1.430	1.407	90	363	10.24
pentafluorobenzene	C_6HF_5	168	1.518	1.390	85	358	10.40
hexafluorobenzene	C_6F_6	186	1.616	1.378	82	355	10.52

bond (Figure 4). A similar helical structure (twist angle ca. 14°) was deduced many years ago for the carbon chain of poly(tetrafluoroethene) (Teflon).[19,20] As Bunn and Howells[19] pointed out, F atoms attached to a planar zigzag carbon chain in 1,3-positions would be sterically compressed, and the helical twist increases the distance between such F atoms to more tolerable values (from about 2.52 Å in the planar zigzag chain with 110° bond angle to about 2.75 Å in the helical chain with bond angle widening to about 116°). Although perfluoroalkane chains in some crystal structures are described as being nearly planar, the apparent planarization is probably the result of thermal disorder involving partial unwinding of the chains.

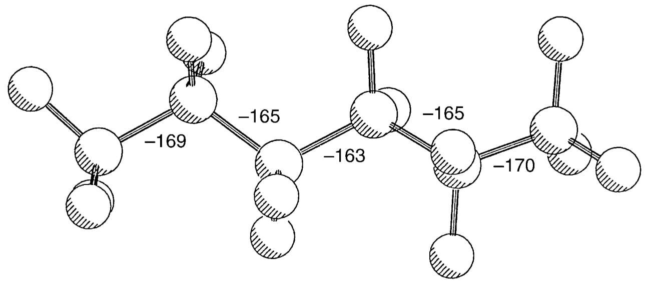

Figure 4. Perfluorohexane molecule with torsion angles about C–C bonds as observed in the crystal structure.[18] The crystal belongs to an achiral space group and contains equal numbers of enantiomeric molecules.

Aromatic Hydrocarbons and Fluorocarbons

It seems to have come as yet another surprise when, in sharp contrast to the characteristic behavior in the aliphatic series, hexafluorobenzene was found to form a 1:1 co-crystal with benzene.[21] Since then, dozens of solid compounds of hexafluorobenzene with aromatic hydrocarbons have been isolated, and their crystal structures determined. The structural information was reviewed several years ago[22] and more recently discussed in the light of density-functional theory calculations.[23,24] In contrast to the behavior of the aliphatic liquid mixtures with their positive heats of mixing, solutions of hexafluorobenzene and aromatic hydrocarbons show large negative (exothermic) heats of mixing, that is, aromatic hydrocarbon–fluorocarbon interaction energies are greater than expected from the properties of the individual components.[25,26]

As with the corresponding aliphatic hydrocarbons and perfluorocarbons, benzene and hexafluorobenzene resemble one another closely in their physical properties: melting point, boiling point, enthalpies of vaporization and of sublimation. The crystal structures are different, although both are characterized by similar herring-bone packing patterns. In the benzene structure (space group *Pbca*, $Z=4$), the molecules are situated on inversion centers and related by glide reflection in all three directions of space,[27] whereas the hexafluorobenzene structure contains two crystallographically nonequivalent sets of molecules, one situated on inversion centers, the other in general positions (space group $P2_1/a$, $Z=6$).[28] In complete contrast to both these structures, the 1:1 co-crystal is built from stacks of alternating parallel benzene and hexafluorobenzene molecules with their planes separated by about 3.5 Å (Figure 5). This co-crystal is more stable than the crystals of the individual components, at least it melts at a higher temperature (around 20 °C rather than 5 °C), and the corresponding liquid shows a negative heat of mixing (−1.98 kJ mol^{-1} at 25 °C).[24] On cooling, the co-crystal undergoes a series of phase transitions in which disorder associated with molecular rotation around the stacking axis is frozen out.[29] The same general alternating stack structure is shared by the 1:1 co-crystals of hexafluorobenzene (or octafluoronaphthalene) with many other aromatic hydrocarbons.[22–24]

It seems remarkable that all the fluorobenzenes have almost the same boiling point (349 to 367 K) as benzene itself (354 K);

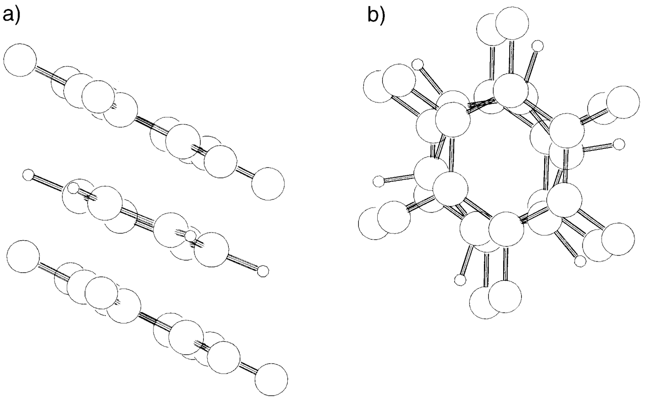

Figure 5. Alternating stacks in the 1:1 benzene/hexafluorobenzene co-crystal.[29]

they also have practically the same molecular polarizability (Table 1). The partially fluorinated compounds have melting points between 225 K and 277 K, the higher temperature being almost the same as the melting points of benzene and hexafluorobenzene. The crystal structures of most of the partially fluorinated compounds have been determined and discussed in great detail with an emphasis on the importance of C–H···F interactions.[30] From our point of view, one of the most interesting structures in this series is that of 1,3,5-trifluorobenzene, which consists of tightly packed stacks in which alternate molecules are related by inversion centers so as to place the F atoms of one molecule almost over the H atoms of its two neighbors in the stack (Figure 6). This molecule, half benzene and half hexafluorobenzene, so to say, thus forms a very similar stacking to that of the 1:1 benzene–hexafluorobenzene co-crystal, and the same has since been found to hold for the 1,2,3-isomer.[18] Similar stacks, but with larger slip displacements of adjacent molecules, also occur in the crystal structures of 1,2,4,5- and 1,2,3,4-terafluorobenzenes. It is likely that, in analogy to the 1:1 benzene-hexafluorobenzene system, cocrystals built from stacks of alternating "matched" fluorobenzenes can be prepared. This seems to be the case at least for the fluorobenzene–pentafluorobenzene system. The solid–liquid phase diagram of the binary mixture shows an elevated melting point at 1:1 composition.[31]

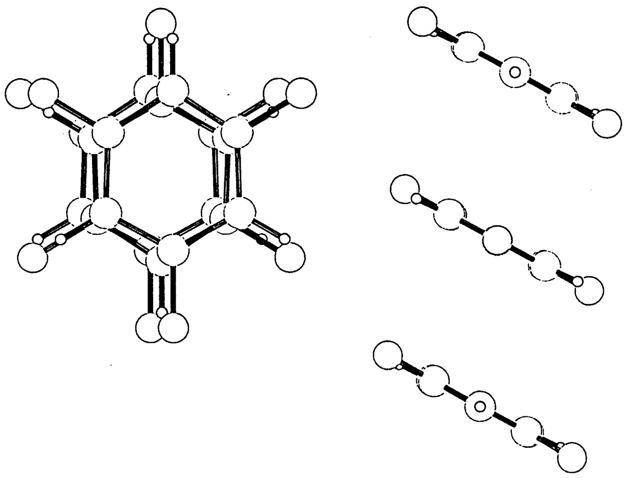

Figure 6. Molecular stacks in the crystal structure of 1,3,5-trifluorobenzene.[30] *Taken from J. D. Dunitz et al.,* Helv. Chim. Acta *2003, 86, 4073, with permission.*

How should we describe the molecular interactions leading to the patterns observed in these crystal structures? Among the various models proposed is one based on electric quadrupole–quadrupole interactions. The electric quadrupole moments of benzene and hexafluorobenzene are large and of opposite sign (-29×10^{-40} C m^2 for benzene, $+32\times10^{-40}$ C m^2 for hexafluorobenzene), and quadrupole–quadrupole interactions have been invoked to explain the herring-bone structures of crystalline benzene and hexafluorobenzene and the columnar arrangement of alternating benzene and hexafluorobenzene molecules in the 1:1 co-crystal.[32] More generally, the quadrupole–quadrupole interaction is also supposed to play a role in stabilizing mixed stacks involving hexafluorobenzene (or octafluoronaphthalene) and aromatic hydrocarbons. On the other hand, 1,3,5-trifluorobenzene has, as might be expected, quite a small electric quadrupole moment ($+3\times10^{-40}$ C m^2),[33] but it also forms very similar stacks in its crystal structure, as seen in Figure 5. In my opinion, the importance of quadrupole–quadrupole interactions in stabilizing certain types of crystal structure has been vastly overrated. Elementary electrostatics teaches us that the central multipole expansion of a charge distribution is valid only at distances that are large compared with the dimensions of the distribution. Thus, interaction energies between adjacent molecules estimated with the quadrupole–quadrupole model are quite unreliable and cannot be expected to produce meaningful results.

Energy Calculations

The recently developed SCDS (semiclassical density sums, or PIXEL) method[34,35] offers the possibility of obtaining some insight into the differences between the mixing behavior of hydrocarbons and fluorocarbons in the aliphatic and aromatic series. This method is being developed primarily for calculating lattice energies of crystals but it is also well suited for estimating energies of small supramolecular clusters. Here I summarize the results of some recent PIXEL calculations for homo- and heterodimers of hydrocarbons and fluorocarbons,[36] together with parallel results obtained with the well-known UNI force field[37], based on empirical atom–atom potentials.

The PIXEL method

The first step is to obtain the electron density for a given molecule by standard quantum-mechanical methods, for example, by a MP2/6-31G** molecular-orbital calculation.[38] This electron density is sampled on a grid containing about 10^6 pixels with step size 0.08 Å. This grid is then condensed into super-pixels each containing $n\times n\times n$ steps where n is typically 3, 4, or 5. Pixels holding less than some minimum charge of around 10^{-6}

electrons are discarded as insignificant, and the pixel contents are then renormalized to balance the sum of the nuclear charges. In this way, the molecular density ends up described by some 10 000 pixels. For a crystal calculation, the positions of all pixels and all nuclei are repeated in space by the space-group symmetry operations. Thus, the method assumes a juxtaposition of rigid, undistorted electron densities of separated molecules in a supramolecular array. The coulombic energy between any two molecules is then calculated simply as a sum over q_iq_j/r_{ij} contributions from each pair of electron-density pixels q_i and q_j in the separate molecules. At the short distances between adjacent molecules in condensed phases, the coulombic energy calculated by the PIXEL method is much more reliable than that based on electrostatic interactions among any distribution of point charges or multipoles.

The remaining terms in the interaction energy are evaluated with the help of a few assumptions and approximations. Repulsion energy is taken to be proportional to the electron-density overlap elevated to a power slightly smaller than one. For the polarization energy, the electric field is evaluated at each pixel, which is assigned the polarizability of the closest atom, and the polarization energy is obtained by the linear polarization assumption. The dispersion energy is obtained as a sum of pixel–pixel terms by a London-type formula, by using the assigned pixel polarizabilities and the overall molecular ionization potential, taken as the energy of the highest occupied molecular orbital (HOMO). In the calculation of polarization and dispersion energies, damping functions are introduced to avoid singularities. The total interaction energy is taken as the sum of the coulombic, polarization, dispersion, and repulsion terms. The method uses only four fully disposable parameters and is described in detail elsewhere.[34,35]

In discussing results obtained by the PIXEL method, it must be stressed that only the coulombic energies are parameter-free. The other terms vary significantly for relatively small changes in the numerical value of the four disposable parameters. Nevertheless, the method in its present parameterization reproduces sublimation enthalpies of many organic crystals and interaction-potential curves for some typical molecular dimers reasonably well.[34,35] Moreover, if PIXEL energies are sensitive to small changes in parameterization, quantum-chemical calculations of intermolecular interactions also give quite a spread, depending on the choice of method, basis set and basis-set superposition treatment, and other subtle factors. The underlying problem in all these approaches is that the energy of interest represents a tiny difference between huge positive and negative energy values.

The UNI force-field method

The UNI force-field is of the simple form:

$$E(R_{ij}) = A\exp(-BR_{ij}) - CR_{ij}^{-6}$$

Here R_{ij} is the distance between any two atoms *i* and *j* in different molecules. Designed specifically for the organic solid state, this force field was calibrated against observed structures and sublimation enthalpies of a collection of crystals of organic compounds.[37,39] Although these potentials were initially developed without explicit atom–atom point-charge electrostatic contributions, they may be supplemented with these by adding electrostatic potential (ESP) point charges placed at nuclear positions. Such charges are available from the electron-density distribution by fitting them to the ESP produced by this distribution. The inclusion of ESP charges allows comparison between the PIXEL method and the localized charge treatment of coulombic interactions.

Aromatic Dimers[36]

Table 2 shows the PIXEL energies for the homodimers of benzene, hexafluorobenzene, 1,3,5-trifluorobenzene, 1,2,3-trifluorobenzene, and for the benzene–hexafluorobenzene heterodimer, all in face-to-face arrangements at an inter-ring distance 3.4 Å and without lateral slip or rotation in the molecular plane. In the actual benzene–hexafluorobenzene co-crystal, adjacent molecules in the stacks are laterally displaced and mutually rotated (Figure 5), and in the crystal structures of 1,3,5- and 1,2,3-trifluorobenzene, adjacent molecules in the stacks are laterally displaced (Figure 6). According to the PIXEL calculations, the dimer energies change only little with small deviations from the face-to-face arrangement. The observed stacking displacements in the actual crystal structures could well be attributable to better interstack packing.

Table 2. PIXEL energies [kJ mol^{-1}] of aromatic dimers at fixed inter-ring distance of 3.4 Å.[a]

dimer	E_{coul}	E_{pol}	E_{disp}	E_{rep}	E_{total}
(benzene)$_2$	−0.8	−4.0	−32.3	23.5	−13.6
(HFB)$_2$	−0.8	−4.2	−36.0	19.4	−19.9
Be:HFB	−12.7	−4.7	−33.8	21.6	−29.7
(1,3,5-TFB)$_2$					
parallel	−4.1	−2.3	−34.2	21.5	−19.0
antiparallel	−8.4	−2.4	−34.2	22.5	−22.5
(1,2,3-TFB)$_2$					
parallel	−2.3	−2.5	−34.2	21.8	−17.2
antiparallel	−10.3	−2.9	−34.2	22.5	−24.9

[a] Be = benzene, TFB = trifluorobenzene, HFB = hexafluorobenzene.

From Table 2, it is seen that although the dispersion energy makes by far the largest contribution to the net stabilization of all the aromatic face-to-face dimers, it is clearly the coulombic contribution that makes the heterodimer more stable than the homodimers of benzene and hexafluorobenzene. This is perhaps not too surprising. It is interesting, however, that the coulombic energies of the benzene and hexafluorobenzene homodimers are not strongly destabilizing, as would be expected from a point-charge or quadrupole moment model, which yield for the coulombic energy approximately the same numerical value as for the heterodimer but with opposite sign.

As expected, the coulombic energy makes a large and important contribution to the stability of the antiparallel trifluorobenzene homodimers and it is also slightly stabilizing for the parallel dimers. Here again, the simple electrostatic expectation based on the parallel orientation of the 1,2,3-isomer with its fairly large electric dipole moment is not fulfilled.

Aliphatic Dimers

The description of the dimers of the aliphatic chain-like molecules is more complicated than for the disk-shaped aromatics. In the *n*-hexane dimers (Figure 7), H1 is based on translation normal to the plane of the C atoms, and H2 on translation in that plane. In the perfluorohexane dimers, P1 is based on translation, and P2 on a combination of translation, reflection, and rotation about the chain axis (recall that the perfluorohexane molecule is chiral so the molecules in the P2 pair are enantiomers). The dimers illustrated are those with the lowest calculated energy (Table 3) and they correspond closely to arrangements of successive molecules in the actual crystal structures. For the heterodimer, no crystal structure is available and indeed, judging from the behavior of the liquid mixtures, it is unlikely that a co-crystal will ever be obtained. Data for three low-energy heterodimers HP1, HP2, and HP3 are also given in Table 3.

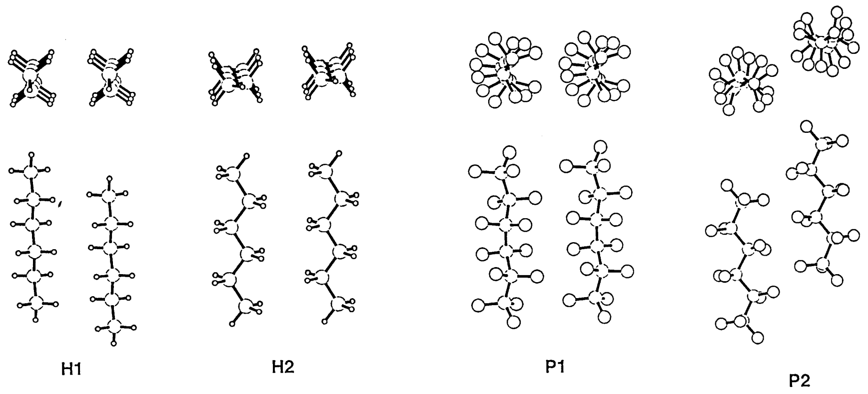

Figure 7. *Low-energy dimers of* n*-hexane and perfluorohexane calculated with the PIXEL program.*[35] *Taken from J. D. Dunitz et al.,* Helv. Chim. Acta ***2003***, 86, *4073, with permission.*

Table 3. Equilibrium distances [Å] and PIXEL energies [kJ mol^{-1}] in low-energy hexane and perfluorohexane homo- and heterodimers. The homodimers are pictured in Figure 7.

dimer	d	E_{coul}	E_{pol}	E_{disp}	E_{rep}	E_{total}
H1 (hexane)$_2$	3.8	−8.5	−3.8	−37.4	27.8	−22.0
H2 (hexane)$_2$	4.4	−5.1	−2.1	−27.1	17.3	−17.0
P1 (perfluorohexane)$_2$	5.1	−0.8	−0.1	−12.2	3.9	−9.1
P2 (perfluorohexane)$_2$	6.0	−0.3	0.0	−9.6	2.4	−7.6
HP1 heterodimer	4.9	−1.0	−0.4	−11.9	4.7	−8.5
HP2 heterodimer	5.0	−1.1	−0.4	−10.4	5.1	−7.0
HP3 heterodimer	5.0	−1.1	−0.4	−11.9	5.4	−8.0

The coulombic energy for the hexane dimers H1 and H2 amounts to −8.5 and −5.1 kJ mol^{-1}, respectively. These relatively large values may come as a surprise in view of the usual description of interactions among such aliphatic hydrocarbons as "nonpolar". With parallel planar zigzag chains separated by 3.8 Å (4.1 Å in the actual crystal structure), H1 also has the lowest total energy despite the large repulsion energy at this short distance. The perfluorohexane dimers P1 and P2 and the three heterodimers HP1, HP2, and HP3 have markedly larger interchain separations and correspondingly smaller coulombic and total stabilization energies. The coulombic energy in the heterodimers is close to zero. Since the peripheral hydrogen and fluorine atoms have opposite charges (the ESP charges are about $\pm 0.1\,e$), one might have expected a greater stabilization from this source, but one must not forget the destabilizing interactions between the charges of peripheral atoms of one molecule and the carbon atoms of the other. The UNI calculations based on ESP charges give very small coulombic energies for all the aliphatic dimers. They give a somewhat different pattern of energies, but both methods agree that the binding energy of the heterodimer is not greater than that of the homodimers but less—in sharp contrast to the results for the aromatic dimers.

What Have we Learned?

The relatively simple models described above provide some insight into the problem of hydrocarbon–fluorocarbon compatibility. In the aromatic series, the binding energy of the benzene–hexafluorobenzene dimer is found to be markedly greater than the energies of the corresponding homodimers. In the aliphatic series, the binding energy of the hexane–perfluorohexane dimer is less than the energy of the hexane homodimer, all this in accord with the contrasting behavior of aromatic and aliphatic hydrocarbon–fluorocarbon mixtures. While these results are a long way from explaining the behavior of real systems, the energy dissection afforded by PIXEL suggests some general relationships between molecular shape and intermolecular interaction energies of aliphatic and aromatic systems.

Dispersion seems to be by far the most important cohesive contribution for the molecules discussed here. It derives mainly from interactions between C atoms because of their much greater atomic polarizability. The difference between the aliphatic and aromatic systems seems to be mainly a matter of the difference in molecular shape. In the aromatic dimers, the disk shape of the molecules with H or F atoms on the outer rim allows C atoms of the separate molecules to maintain a nearly constant close distance of approximately 3.4 Å, and hence to provide a substantial and nearly constant dispersion energy throughout the series. The coulomb energy of the heterodimer then plays the decisive contribution to its greater stability over the homodimers. The same is true, to a slightly lesser extent, for the 1,2,3- and 1,3,5-trifluorobenzene dimers in suitable mutual orientation.

In the aliphatic series, the C atoms are more shielded from external influence. The closest intermolecular C···C distances are around 4 Å in the hexane homodimer but appreciably longer in the other dimers, because the F atoms with their larger packing radius get in the way of any close contact between C atoms of different molecules. Hence, dispersion energies are much smaller. In addition, there is little gain in coulombic energy in the aliphatic heterodimer, so the net result is indifference or even destabilization upon mixing.

So what is so special about organic fluorine? Why is it the odd man out? Can this be simply on account of its large electronegativity and low polarizability? In organic compounds, fluorine generally replaces hydrogen. It has approximately the same atomic polarizability as hydrogen although the fluorine atom has nine times as many electrons—and, of course, a nine-times-greater nuclear charge! And it needs more space. The low molecular polarizability of fluorocarbons relative to their molecular weights and volumes fits in with their low surface tension and low boiling points relative to their molecular weights (the very similar boiling points of hydrocarbons and corresponding fluorocarbons point to similar cohesive energies per mole but not per gram). Instead of relating to molecular weight, we may relate to molecular volume. Since polarizability α has the same dimension as volume V, the ratio $Q = \alpha/V$ is a dimensionless quantity. Among the elements commonly present in organic compounds, fluorine has the smallest value of Q.

If Q were constant over a series of molecules, it would mean that for a given external electrostatic field, the induced molecular dipole moment would be proportional to molecular volume. Since the induced dipole moment depends on the *distance* between separated charges, that is, to some extent on the linear dimension of a molecule, such a regularity could only hold for molecules of similar shape. Ignoring this complication, large molecules tend to have large polarizabilities, while small molecules have small ones. Each additional atom in a molecule adds to the molecular volume and to the molecular polarizability, keeping Q roughly constant. Only replacement of hydrogen by fluorine results in an increase in molecular volume without any concomitant change in molecular polarizability, besides changing the sign of the local charge.

Of course, this is a vastly oversimplified caricature of the underlying physics. The external electric field and the induced dipole moment are 3-vectors, and the linear polarizability is a 3×3 tensor, whereby experimental polarizability values such as those in Table 1 are isotropic averages. Nevertheless, in the absence of better data, better calculations, and better arguments, the above discussion may help to throw a hint on the question of why organic fluorine is special and so often behaves as the odd man out.

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