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An ab initio study of di- and trifluorobenzene–benzene complexes as relevant to carbonic anhydrase II–drug interactions

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Abstract Ab initio calculations at the MP2/6-31G* level have shown that variously substituted di- and trifluorobenzenes form non-covalent complexes with benzene that adopt either aromatic–aromatic or H—F binding, the choice being determined by the pattern of fluorination. The binding energies of these structures are from 3.4 to 4.5 kcal mol^{-1}. This range is large enough to account for observed variations in the binding affinity of a library of fluoroaromatic inhibitors of carbonic anhydrase. This enzyme has an aromatic amino acid at a central position in the active site. The diverse modes of binding of the dimers also suggest that aggregates of fluorobenzenes might adopt specified 3-dimensional shapes in the solid state.

Keywords Fluoroaromatic · Non-covalent complexes · Aromatic interactions · Carbonic anhydrase

Introduction

Carbonic anhydrase II (CA) is the target of several successful drugs for the treatment of high intraocular pressure associated with glaucoma. [1] These drugs interact with hydrophobic amino acid side chains, including a prominent exposed phenylalanine side chain, in the active site of the protein, affording dissociation constants from the enzyme of 10–100 nM. Recently, Doyon and Jain have described a set of CA inhibitors bearing fluoroaromatic substituents. [2] These were found to bind to CA in a manner dependent on both hydrophobicity and the pattern of substitution of the fluoroaromatic ring. Crystallographic studies of complexes of this library of inhibitors, together with quantitative structure–activity relationships of their binding to wild-type and mutant CA have implicated dipolar, [3] quadrupolar, [3] and hydrophobic [4] interactions as being relevant to binding affinity.

Computational studies have also been applied to the interactions between fluoroaromatic and aromatic groups. Two models were used to interpret the affinities of the library of fluoroaromatic inhibitors for CA: one featuring the aromatic rings stacked and the other with the rings positioned in such a way as to allow the formation of H—F bonds. As a starting point, theoretical (ab initio and density functional) methods were applied to the fluorobenzene–benzene complex. [5] Complexes featuring H—F bonds were found to be among the most stable, consistent with implications of experimental data.

However, since many of the drugs whose binding affinity for the protein was determined were polyfluorinated, [2] we thought that it might be interesting to investigate the binding of benzene to benzene rings substituted with more than one fluorine atom. Accordingly, the present work extends the theoretical calculations to difluorobenzene–benzene and trifluorobenzene–benzene complexes.

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Methods and results

The difluorobenzene–benzene complexes are shown in Fig. 1 and the trifluorobenzene–benzene complexes are shown in Fig. 2. The structures **1a,b** (comprising 1,2-difluorobenzene), **c** (comprising 1,3-difluorobenzene) and **e** (comprising 1,4-difluorobenzene) feature one or two H—F bonds. In addition, structures **1b,c** and **e** feature a T interaction, with a hydrogen of the benzene ring directed toward the center of the difluorophenyl ring. Structure **1d** (comprising 1,3-difluorobenzene) features only the T interaction, while structure **1f** (comprising 1,4-difluo-

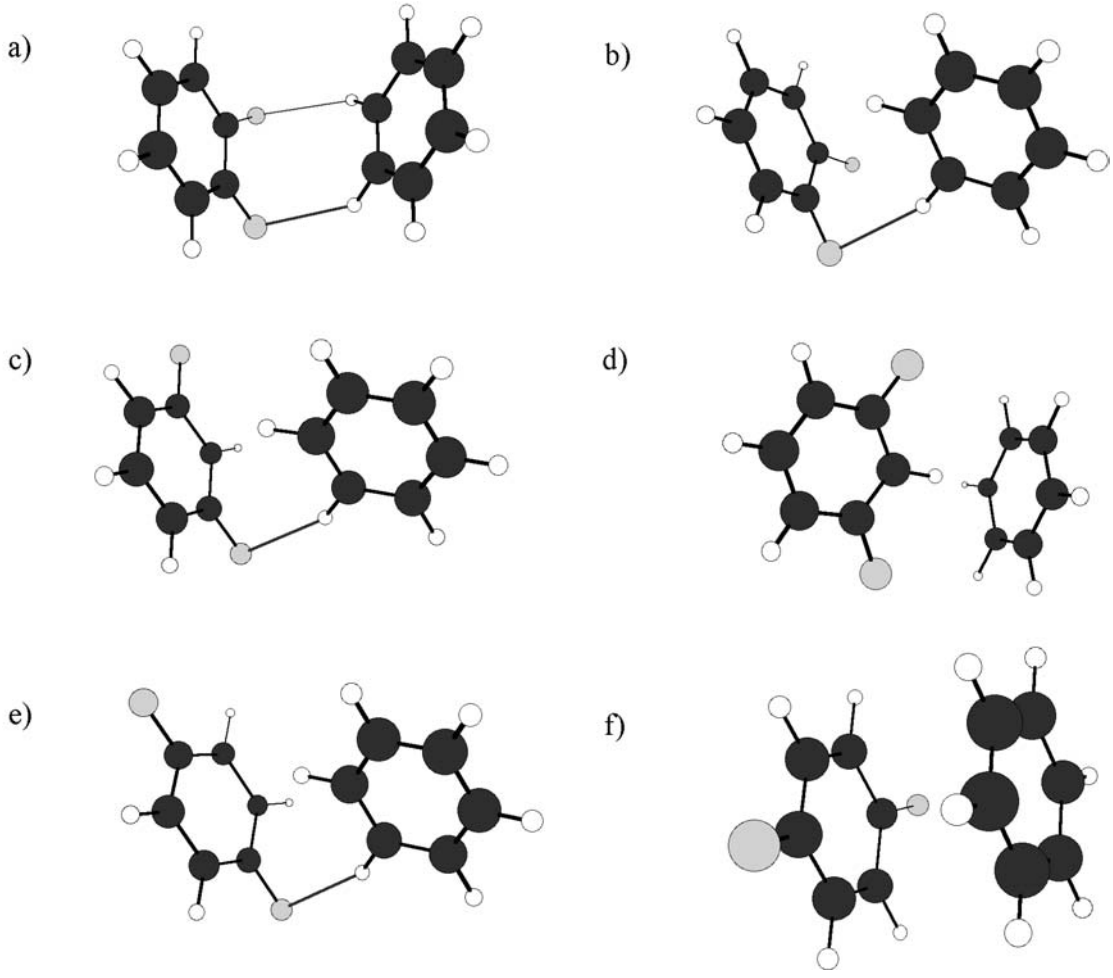

Fig. 1 Motifs observed for difluorobenzene–benzene complexes. Structures (**a**) and (**b**) involve 1,2-difluorobenzene, (**c**) and (**d**) represent 1,3-difluorobenzene, and (**e**) and (**f**) show 1,4-difluorobenzene

robenzene) features the two aromatic rings stacked. The structures **2a** (comprising 1,2,3-trifluorobenzene) and structure **2c** (comprising 1,2,4-trifluorobenzene) feature one and two H—F bonds respectively. Structures **2b,d** and **e** (comprising respectively 1,2,3- ; 1,2,4- and 1,3,5-trifluorobenzenes) feature one H—F bond (or one bifurcated H—F bond in the case of **2d**) and one hydrogen directed toward the π face of the benzene aromatic ring (T interaction). Structure **2f**, comprising a 1,3,5-trifluorobenzene, features the two aromatic rings stacked. All these structures represent minima on the energy hypersurface.

The calculations were performed at the post-Hartree–Fock level, using the MP2/6-31G* method, as implemented by the Gaussian 98W computer program. [6] The MP2 (Møller–Plesset method of second order) is applied only to the valence electrons. The 6-31G* basis set is a split valence set that uses one Slater orbital expanded in a series of six Gaussian functions for the description of the core electrons and two Slater orbitals, one expanded in a series of three Gaussians and the other approximated by one Gaussian, for the description of valence electrons. In addition, there are *d*-functions set on the non-hydrogen atoms.

Table 1 MP2/6-31G* binding energies of di- and trifluorobenzene benzene complexes

Structure	Binding energy (kcal mol^{-1})
1a	4.35
1b	4.07
1c	3.93
1d	4.51
1e	4.00
1f	3.39
2a	4.54
2b	3.86
2c	4.22
2d	3.92
2e	3.69
2f	4.03

Table 1 shows the binding energies of the complexes in kcal mol^{-1}, defined as the difference between the sum of the energy of the components and the energy of the complex. The BSSE (basis set superposition error) has been applied to complexes **2a** and **2b** using the counterpoise correction.

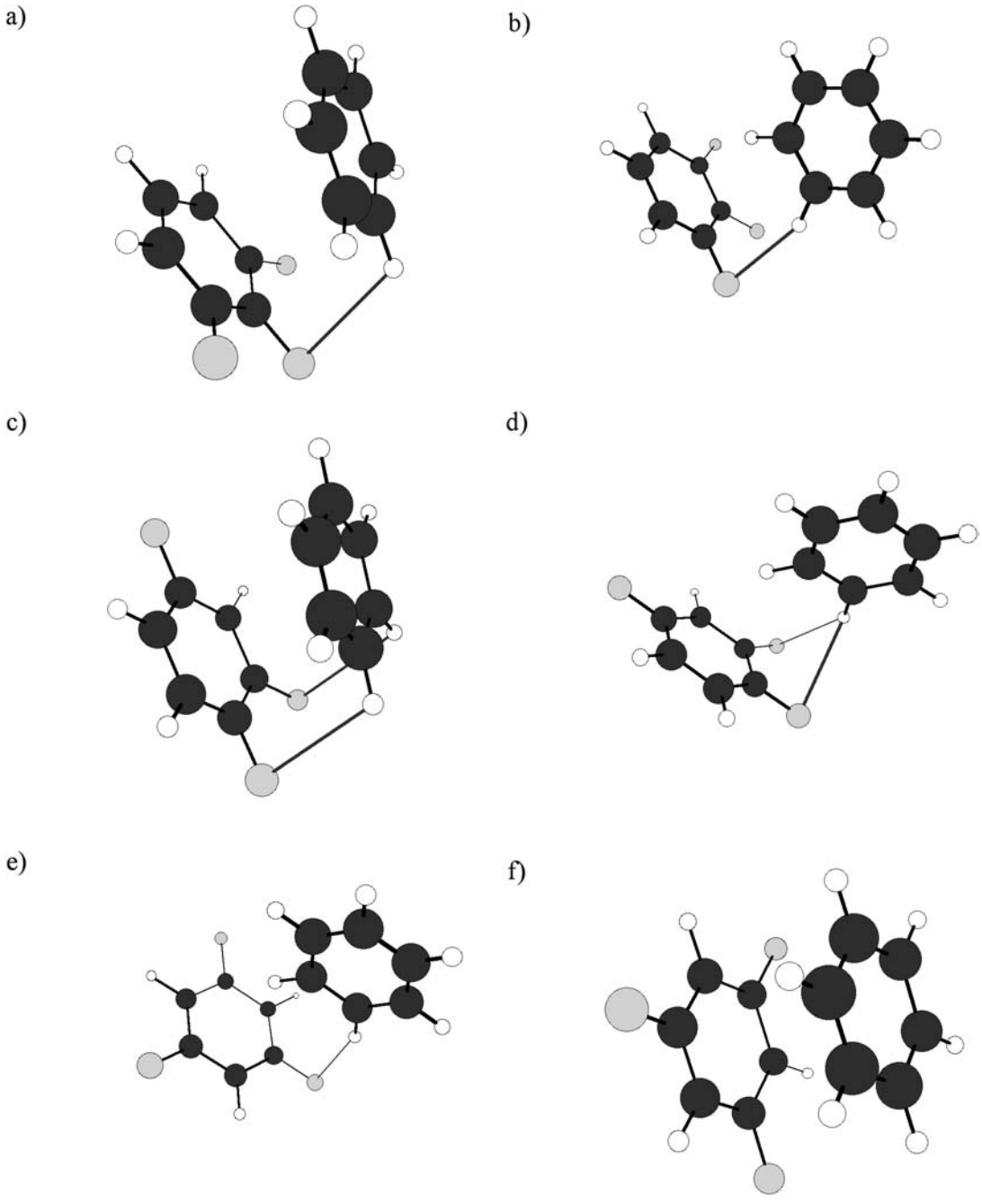

Fig. 2 Motifs observed for trifluorobenzene–benzene complexes. Structures (**a**) and (**b**) involve 1,2,3-trifluorobenzene, (**c**) and (**d**) represent 1,2,4-trifluorobenzene, and (**e**) and (**f**) show 1,3,5-trifluorobenzene

In order to examine the basis set-dependence of the binding energies in the conformations featuring an H—F bond, a simple model where one of the hydrogens of ethylene interacts via a non-covalent bond with the fluorine of HF was studied. The binding energy of this complex was calculated with the MP2(full)/6-31G*, the MP2(full)/6-311*, the MP2(full)/6-311+(3df,3pd) and the aug-cc-VQZ methods. Table 2 shows the binding energy obtained via each method.

Table 2 Binding energies of ethylene hydrogen fluoride as a function of basis set

Method	Binding energy (kcal mol^{-1})
MP2(full)/6-31G*	1.32
MP2(full)/6-311G*	1.20
MP2(full)/6-311G**	1.24
MP2(full)/6-311+G(3df,3pd)	0.86
Aug-cc-pVQZ	0.99

Discussion

As reported previously for the fluorobenzene–benzene complex, the examination of experimental data pertaining to the binding of fluoroaromatic inhibitors to CA [2, 5] shows trends that are consistent with the presence of H—F non-covalent bonds. It was found experimentally, for instance, that 1,4-difluorobenzene-containing compounds bind more tightly than 1,3-difluorobenzene-containing compounds. [2] Examining Table 1, one notices that where both H—F bonds and T interactions are involved in binding, the binding energy is higher for the 1,4-compound (**1e**) than for the 1,3- compound (**1c**). A difference this subtle (3.93 versus 4.00 kcal mol^{-1}) can result in a 12% difference in binding affinity at 298 K.

Based on results from our studies of the fluorobenzene–benzene complex, [5] it might be inferred that the main interaction occurs via F—H bonds and not via the T conformation, although in the case of 1,3-difluorobenzene–benzene, the T-conformation gives the strongest binding energy of this series (the hydrogen between the fluorines is apparently rendered quite electron-deficient due to the inductive effect of those atoms). However, in the systems studied experimentally, [2] the fluororoaromatic ring is attached to a larger moiety, which might preclude its positioning in the active site of the enzyme in such a way as to afford a T interaction. Structure **1f**, which features a parallel stacked interaction, is the least bound, even though it affords a favorable quadrupolar interaction. [7, 8]

The bond distances for the H—F interactions range from 2.4 to about 3 Å. In the case of trifluorobenzene–benzene complexes, the doubly hydrogen bonded structures **2a** and **2c** are the most stable, and these have H–F distances of 2.8–2.9 Å. Alternate structures having one H—F bond and one hydrogen in the proximity of the π face of the trifluorobenzene ring (2b,d,e) are less strongly bound than the parallel stacked structure **2f** observed for 1,3,5-trifluorobenzene. This result is consistent with the fact that the additional fluorine decreases the basicity of the aromatic nucleus and thus weakens its interaction with the hydrogen.

The results of the calculations on the binding energy of a model system, ethylene—FH, shown in Table 2, show a binding energy of 1.32 kcal mol^{-1} at MP2(full)/6-31G* calculational level. As the size of the basis sets increases, the binding energy decreases, due to the decrease of the BSSE, reaching the lowest value, 0.86 kcal mol^{-1}, for the 6-311+G(3df,3pd) basis set. The latter value becomes 0.46 kcal mol^{-1} if the BSSE correction is applied with the counterpoise correction. The same correction for the **2a** and **2c** compounds decreases the binding energy to 1.19 and 0.96 kcal mol^{-1} respectively. In both cases it is clear that the counterpoise methods overcorrects, as has been shown in the literature. [9] Comparing the results for ethylene–FH as a model to the results for the complexes of di- and trifluorobenzene with benzene, it might be inferred that the binding energies should be reduced realistically to about 65% (0.86/1.32). Obviously, this estimate represents just a rough approximation, since the model does not reproduce exactly the basis set dependence of the binding energies for the di- and trifluorobenzene–benzene complexes, and there is no reason to believe that a larger set such as 6-311+(3df,3pd) has *no* BSSE. Still, the qualitative 65% correction seems to predict a more realistic result than the counterpoise-corrected BSSE.

In conclusion, these theoretical calculations of the binding energies of di- and trifluorobenzene–benzene complexes support our interpretation of the fluorination- and pattern-dependence of the affinity of fluorobenzyl-linked benzenesulfonamides for CA. The binding energies of the variously substituted fluorobenzenes with benzene vary by up to 1 kcal mol^{-1}, which could certainly account for the variation in binding affinities (an order of magnitude) of the corresponding inhibitors to CA. We believe that even though the perturbations on binding energy as a function of orientation and substitution pattern are minimal, additive small effects like these may have the greatest potential for leading to changes in affinity of small molecules for their receptors.

Future experiments in our group will provide information regarding F–H contacts in solution from ^{19}F–^{1}H NOE (nuclear Overhauser enhancement) spectroscopy. Ultimately, we hope to be able to design non-covalent aggregates that adopt specific 3-dimesional shapes (crinkled sheets, tapes, rings, etc. [10, 11]) by propitious selection of variously substituted fluorobenzenes.

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