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The Donor Atom–π Interaction of Sulfur with Flavin. A Density Functional Investigation

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ABSTRACT: *Thiols and sulfides interact strongly with electron-deficient aromatic systems such as flavins. Using density functional methodology, we have shown that this interaction is electrostatic in nature, with very little polarization of the sulfur electron cloud.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9: 605–606, 1998

Hydrogen bonding [1], aromatic stacking [2], and cation–π [3] interactions are important in biological systems and synthetic devices [4]. In recent studies, we have used host–guest complexes to uncover a further interaction, donor atom–π binding [5]. The donor atom–π interaction is a relatively strong effect that arises from the attraction of electron-rich (donor) atoms to electron-deficient aromatics [6].

To quantify the energetics of interaction between various donor atoms and flavins, we created receptor family **1** [5]. In this family, hydrogen bonding is used to hold flavin **2** in proximity to donor atoms, allowing direct quantification of donor atom-π interactions. During the course of our investigations, we observed the strongest interaction with the sulfur-functionalized receptor **1d.** An intriguing issue is the enhanced binding of sulfur-based receptor **1d** relative to the more highly dipolar oxygen functionality of receptor **1c.** This enhancement could arise from two sources: the larger area of electrostatic overlap in the **1d–2** complex or via actual distortion of the electron cloud of **1d** in a donor–acceptor fashion. If the latter effect is operative, the largest distortion of donor electron density of the systems we studied would occur with thioether **1d.** We therefore chose the receptor **1d**-flavin **2** complex as a benchmark for donor atom–π interactions in general (see Figure 1).

To explore the nature of donor atom–π interactions of receptor **1d** with flavin, we used the B3LYP hybrid functional [7]. For purposes of computational efficiency, calculations were performed on the fragment shown in Figure 2. The thioanisole and flavin moieties were constrained at the positions shown to 5.1 Å, the distance obtained from the PM3-derived structure of the complete complex.

To determine the distortion of electron density arising from donor atom–π interaction in the receptor **1d**-flavin **2** complex, we calculated the electron density isosurface shown in Figure 2. This isosurface runs through the center of the sulfur atom and intersects the plane of the flavin ring at its closest position. From this isosurface (Figure 3), we can see

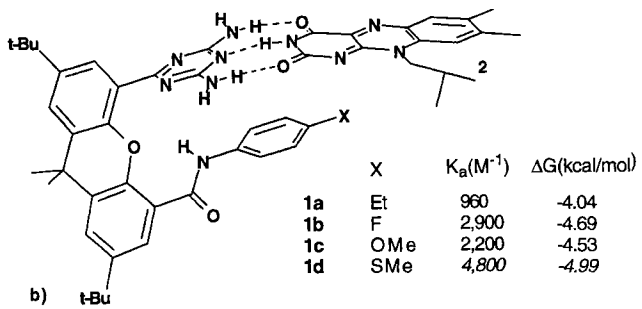

FIGURE 1 Receptor **1**-flavin **2** complex, with association constants ($CDCl_3$, 23°C).

Dedicated to Prof. Robert R. Holmes, a scientist and colleague, on the occasion of his seventieth birthday.

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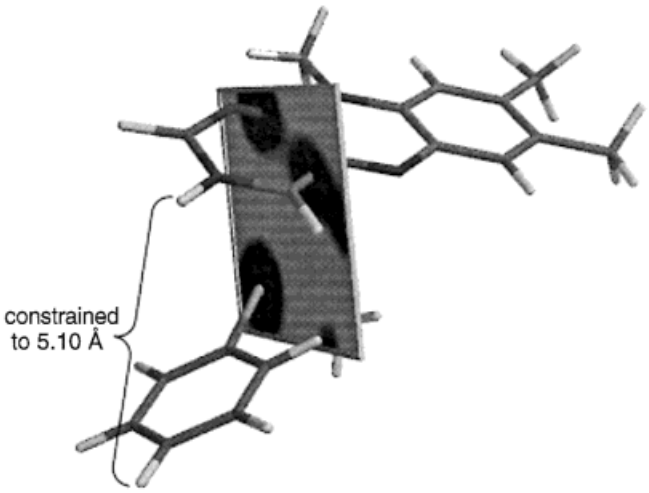

FIGURE 2 Receptor **1d**-flavin **2** fragment, showing isosurface used for electron density measurements.

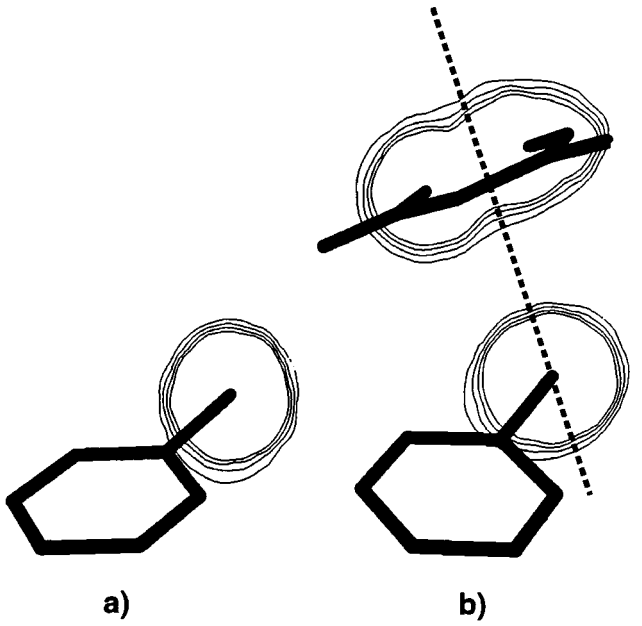

FIGURE 3 Contour electron density plots for (a) receptor **1d** and (b) the receptor **1d**-flavin **2** complex.

that there is little distortion of the sulfur electron density upon complexation. This is further demonstrated by the electron density calculated along the line shown in Figure 3. As seen in Figure 4, there is little difference between the electron densities observed in the complex and the sum of the densities for the two isolated components.

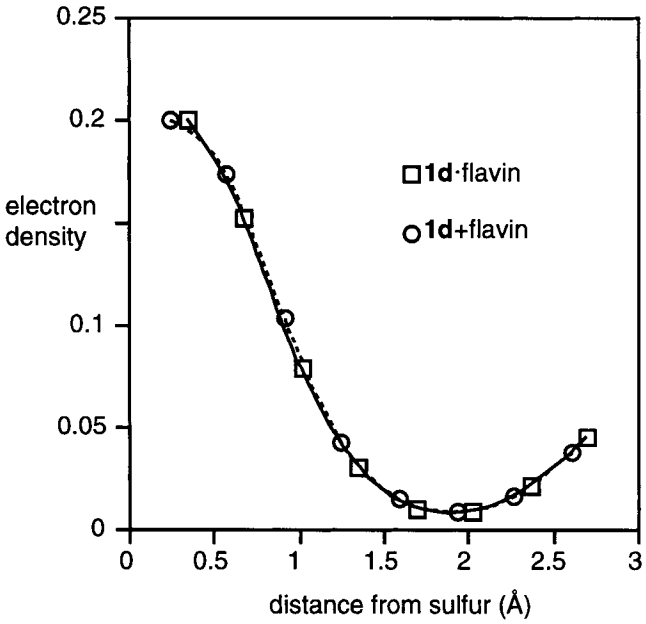

FIGURE 4 Electron density along the sulfur-flavin axis for the receptor **1d**-flavin **2** complex (**1d** · flavin) and the separated molecules (**1d** + flavin).

In summary, we have shown that there is negligible distortion of the electron cloud of sulfur upon donor–π interaction with flavin. This demonstrates that this interaction is purely electrostatic in nature: enhanced interaction for the receptor **1d**-flavin **2** arises from increased electrostatic overlap, rather than hard–soft Lewis acid-base effects. Given that thiomethyl receptor **1d** is the most polarizable of the species studied, this greatly simplifies the interpretation of donor–π interactions in proteins, a direction we are currently exploring.

REFERENCES

[1] G. A. Jeffrey, W. Saenger: *Hydrogen Bonding in Biological Structures,* Springer-Verlag, Berlin (1991).
[2] C. Hunter, J. Sanders, *J. Am. Chem. Soc., 112,* 1990, 5525.
[3] D. Dougherty, *Science, 271,* 1996, 163.
[4] For a review of host–guest chemistry, see F. Diederich, *Angew. Chem. Int. Ed. Engl., 27,* 1988, 362–386.
[5] E. Breinlinger, C. Keenan, V. Rotello, *J. Am. Chem. Soc.,* in press.
[6] For a recent study of the role of electrostatics in flavoenzyme chemistry, see Z. Zhou, R. Swenson, *Biochemistry, 35,* 1996, 12443–12454.
[7] UHF and DFT-B3LYP calculations were performed using the Gaussian 94 suite of programs on Silicon Graphics workstations, at the B3LYP 6-31G*//HF 3-21G level.