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Electrostatic Interaction of π-Acidic Amides with Hydrogen-Bond Acceptors

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Dedicated to Professor Kendall N. Houk on the occasion of his 60th birthday.

Abstract—Interactions between *N*-methylacetamide (NMA) and *N*-methylated derivatives of uracil, isocyanurate and barbituric acid have been studied using ab initio methods at the local MP2/6-31G** level of theory. The results were compared to similar interactions between the oxygen atom of NMA and the π-clouds of perfluorobenzene, quinone and trimethyltriazine. The π-acidic amides of isocyanurate and barbituric acid were found to interact with a hydrogen bond acceptor primarily through electrostatic attractions. These groups may be used as alternatives of a hydrogen bond donor to complement a hydrogen bond acceptor or an anion in molecular recognition and drug design. Examples of such interactions were identified through a search of the CSD database.

The physical basis of the hydrogen bond, according to Pauling's description, is essentially attractive electrostatic interaction between a hydrogen atom and an electron rich atom. Hydrogen bonds generally exist between H–N or H–O donors and electronegative nitrogen or oxygen atoms in biological structures.[1] The π-cloud of an aromatic ring is now generally recognized as a weak hydrogen bond acceptor.[2] It is also known that H–C groups engage in hydrogen bonds with simple organic molecules.[1,3] The electrostatic nature of hydrogen bonds suggests that nonmetal atoms other than hydrogen in a chemical functional group are capable of complementing a hydrogen bond acceptor. Consequently, an uncharged non-reactive electrophile could have the potential to interact with a hydrogen bond acceptor.

Recently, interactions between an anion and electron deficient π-acidic rings have been explored based upon molecular electrostatic potential. Several theoretical studies have examined the possibility of such interactions involving perfluorobenzene,[4] triazines[5] and nitrobenzenes.[6] NMR experiments confirmed the complexation between acetonitrile and perfluoro-benzene.[7]

An electrophile complementing a hydrogen bond acceptor versus conventional hydrogen bond donor (H–X) is conceptually analogous to an acid defined by Lewis's generalized acid versus a Brønsted-Lowry acid. A Lewis acid may be considered to be soft, whereas H–N or H–O groups are hard hydrogen bond donors. Similarly, the π-cloud of an aromatic ring would be a soft acceptor, whereas electronegative N and O atoms are hard acceptors. The principle of hardness and softness provides an alternative explanation for the prevalence of the parallel stacked geometry of the π-hydrogen bond between an amide group and phenyl ring observed in protein structures,[8] where a soft donor interacts preferably with a soft acceptor.

There are potential uses of a Lewis acidic groups for drug design and molecular recognition.[9,10] A Lewis acidic group can provide different complementary shape and topological branching opportunities, which could be explored by medicinal and combinatorial chemistry.

Because simple electron-deficient π-systems such as quinone, perfluorobenzene and nitrobenzenes are unsuitable moieties for a drug molecule,[11] we searched for Lewis acidic groups using the Cambridge Structural Database (CSD) System.[12] We then carried out computational studies to rank the energies of interactions

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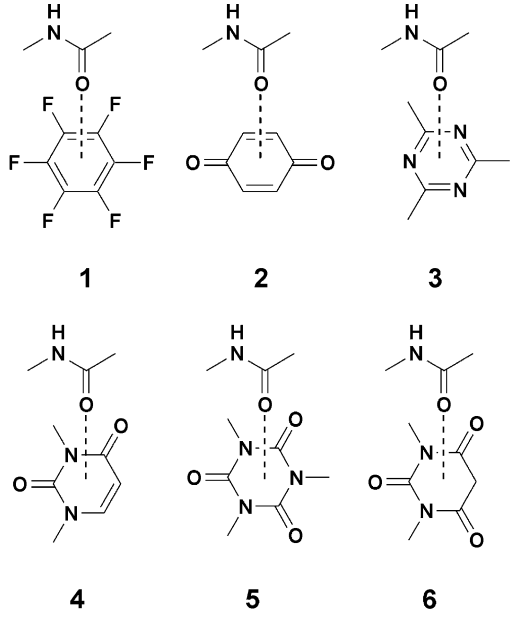
between several π-acidic rings and a hydrogen bond acceptor to find Lewis acidic groups that interact with a strength comparable to or greater than perfluorobenzene. We report here results of ab initio calculations on the interactions of the carbonyl oxygen of *N*-methylacetamide (NMA) with various aromatic and amide and π-acidic rings (**1**–**6**) as shown in Scheme 1.

Ab initio calculations were carried out using the 6-31G** basis set[13] at the level of local Møller–Plesset second-order perturbation (LMP2) theory[14] that included all atoms as implemented in the program Jaguar.[15] All structures were fully energy minimized initially at the HF/6-31G** level of theory. The nature of the HF/6-31G** stationary points was further characterized by frequency calculations at the same level of theory. The geometries were then optimized fully at the LMP2/6-31G** level of theory. Since the LMP2 method has been shown to greatly reduce basis set superposition errors (BSSE) as compared to the canonical MP2 method,[13] complexation energies were computed directly from the LMP2/6-31G** optimized structures without BSSE corrections.

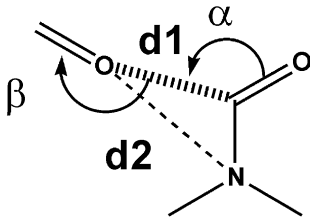
We searched the Cambridge Structural Database for intermolecular interactions between a carbonyl oxygen and C(=O)N(C)C moiety in well-resolved neutral organic molecules (*R* factor <7.5%, excluding metallorganic compounds). There are 1991 hits for the O...C=O contacts in the range of 2.5–4.0 Å; 619 hits with contact distance below the sum of the van der Walls radii; 205 hits with contact distance 0.2 Å below the sum of the van der Waals radii of O and C atoms. There are many cases where the carbonyl oxygen simultaneously maintaining contact (d2 <3.0 Å) with the amide nitrogen as listed in Table 1. In particular, the crystal packing structure of a carbonyl oxygen pointing into the center of an amide π-ring system shown in Figure 1 was found to be common. This packing arrangement was found in the crystal structures of *N*-alkyl substituted derivatives of isocyanurate,[16] barbituric acid,[17] piperazine-2,5-dione,[18] and uracil.[19] The distances between the contact oxygen and the ring atoms range from 2.9 to 3.3 Å, indicating an ideal van der Waals contact. On the other hand, the CSD contains only a handful of crystal structures involving perfluorobenzene. In one example, a carbonyl oxygen is in proximity to the center of a perfluorobenzene ring.[20]



Scheme 1.

Close contact between an electronegative atom and a carbonyl carbon is well known from extensive structural studies on the trajectory of nucleophilic additions.[21] However, close contact between an electronegative atom and the amide (urea) nitrogen has received attention

Table 1. List of refcodes with close contact (d1 <Σ vdw Radii−0.20 Å and d2 <3.00 Å) between C=O and C(=O)N(C)C moiety



Entry	Ref code	d1 (Å)	d2 (Å)	α (°)	β (°)	R factor
1	ARFOXZ	2.97	2.95	106.5	109.8	3.8
2	BAGHIA	2.97	2.99	105.7	154.4	4.5
3	COBYUN	2.86	2.94	105.2	168.5	2.5
4	COMCIQ	2.82	2.91	106.9	151.7	2.3
5	COQKAU	2.93	2.88	110.9	148.6	4.9
6	CUYJOV	2.89	2.97	91.8	154.5	3.0
7	CUYLAJ	2.94	2.99	91.1	152.2	2.6
8	DAFYIS	3.00	3.00	103.9	112.5	5.1
9	DEFLEF	2.88	2.95	93.0	147.6	5.0
10	DMBART10	2.90	2.89	104.0	151.5	4.3
11	ECAWAG	2.94	2.96	100.7	160.1	4.2
12	ECELAZ	3.00	2.95	109.3	133.8	3.8
13	FADREI	2.99	2.99	100.9	129.0	3.8
14	FOHHUF	2.75	2.89	106.6	168.3	5.6
15	FUQLAE	3.01	2.97	102.5	126.8	3.7
16	GASCOS	3.00	3.00	111.9	162.8	6.5
17	GIDRAM	2.93	3.00	104.0	167.1	6.0
18	HADFOH	2.99	2.97	106.0	157.5	5.2
19	HECBAS	2.89	2.99	104.9	136.2	4.2
20	HIPPUR	2.84	3.00	91.9	131.8	4.5
21	HTMTZC	2.98	2.99	101.2	124.7	5.3
22	ICOYII	2.96	2.88	111.0	154.7	4.0
23	KEKXIH	2.96	2.97	99.4	155.2	4.4
24	KESVIN	2.95	3.00	102.6	152.3	6.9
25	NEJJAN	2.97	3.00	89.0	134.8	4.2
26	NIFXIJ	3.01	2.90	107.0	157.2	4.8
27	NUJBOJ	2.94	2.90	96.5	160.7	4.3
28	PHCYND02	2.89	3.00	95.4	155.5	4.4
29	QEFCAF	2.97	2.98	105.6	142.4	3.9
30	SIKYAM01	2.96	2.90	112.8	152.1	4.0
31	SUQHER	2.89	2.99	88.9	132.5	5.6
32	TAMCUR	2.87	2.86	104.8	155.4	5.7
33	TEFGIU	3.00	2.88	100.6	151.9	5.4
34	VORYUW	3.00	2.98	107.6	155.9	4.9
35	VUKJIU	2.88	2.91	100.1	128.8	4.3
36	VUPGIW	2.80	2.90	104.5	142.2	7.0
37	VUPGOC	2.90	2.99	107.5	145.4	6.1
38	VUWYER	3.00	2.98	93.3	156.3	6.7
39	WELYAN	2.84	2.98	93.0	148.0	3.7
40	YOKQOE	2.90	2.88	105.8	134.1	5.3
41	YOXFIA	2.88	2.94	103.4	163.4	4.8
42	ZEXWII	2.87	3.00	91.6	147.3	2.7
43	ZOGPOA	2.90	2.90	103.3	170.9	3.9

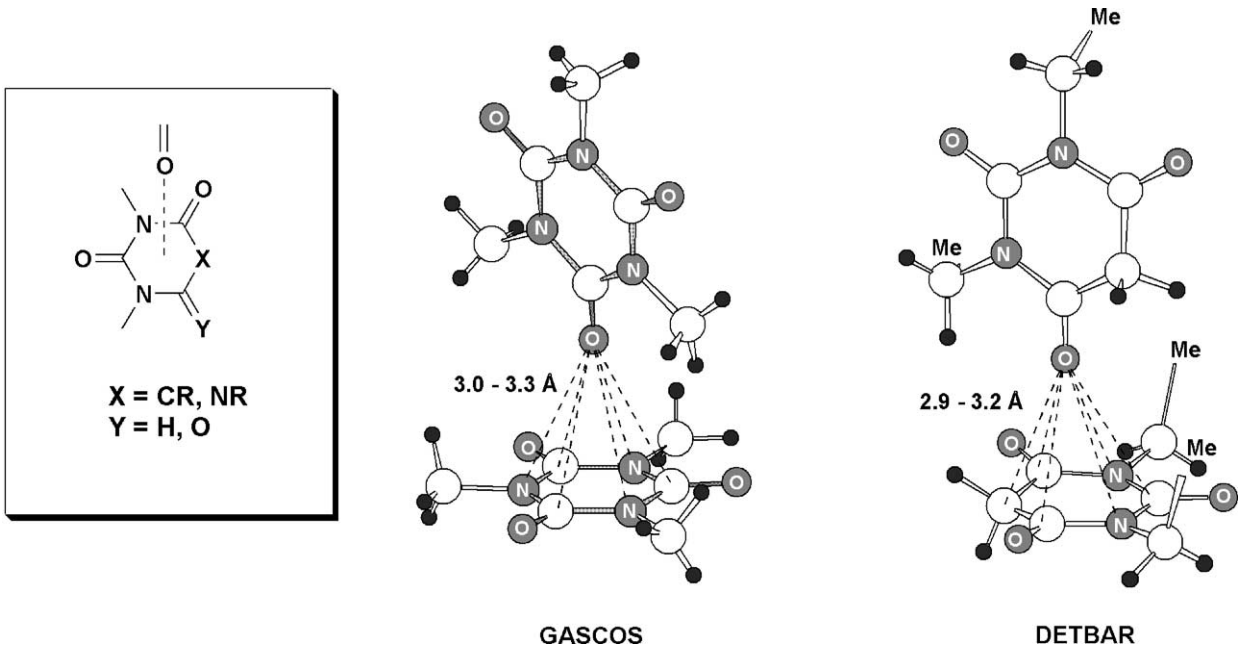


Figure 1. Crystal packing of trimethyl isocyanurate and 1,3-diethylbarbituric acid.[15b,16a]

until only recently.[10,22] The resonance structures suggest that the amide nitrogen bears a partial positive charge.[23] Thus, there are likely to be favorable intermolecular electrostatic interactions between the amide nitrogen and a partially negative carbonyl oxygen, which may contribute to the packing stabilization in the structures shown in Figure 1.

To compare stabilization energies among various amide and π-acidic rings, we carried out ab initio calculations on the interaction energies of perfluorobenzene (**1**), quinone (**2**), 2,4,6-trimethyltriazine (**3**), *N*,*N*′-dimethyl uracil (**4**), trimethyl isocyanurate (**5**), and dimethyl barbiturate (**6**) with *N*-methylacetamide (NMA) as a prototypic hydrogen bond acceptor. The optimized complex geometries at the LMP2/6-31G** level are shown in Figure 2, and the energetic results are summarized in Table 2.

Smith and co-workers reported systematic ab initio studies at the MP2 level of theory on interactions between aromatic acceptors and amide hydrogen bond donors in proteins, with estimated binding energies of up to 4 kcal/mol.[8a] Although the amide proton of NMA can participate as a hydrogen bond donor to form complexes with either the π-cloud or carbonyl oxygen atom of the rings, we only searched for complexes involving the carbonyl oxygen of NMA as a hydrogen bond acceptor. The estimated complexation energies of **1**–**6** at the LMP2/6-31G** range from −3 to −8 kcal/mol as shown in Table 2.

The molecular electrostatic potential (MEP) maps indicate that perfluorobenzene has the most positively charged centroid among all six π-acidic rings studied here. However, its interaction energy with NMA is about 2–3 kcal/mol less than those of the bartiburate and isocyanurate derivatives. In fact, the carbonyl oxygen of NMA in the optimized complex **1** is not located centrally at the most positively charged area along the normal axis of the C_6F_6 ring. This is likely due to weak interactions between the *N*-methyl group of NMA and the F atom of perfluorobenzene as manifested by the short distance of 2.55 Å between the H and F atoms.

The calculated complexation energy between quinone and NMA is estimated to be about −4 kcal/mol, which is about 1 kcal/mol less exothermic than the interaction between C_6F_6 and NMA. In the optimized complex geometry **2**, the carbonyl oxygen of NMA is located asymmetrically between the two carbonyl carbons of quinone. The *N*-methyl group of NMA forms a weak C–H...O=C hydrogen bond with the carbonyl oxygen of quinone.

Optimization of NMA-trimethyltriazine π-acidic complex led to C–H donating complex **3** (Fig. 2), in which the *N*-methyl group of NMA interacts with one of the sp2-nitrogen atoms on the triazine ring. The complexation energy is estimated to be only −3 kcal/mol by LMP2/6-31G**.

Complex **4** was found between NMA and *N*,*N*′-dimethyl uracil involving the π-acidic amide nitrogen as shown in Figure 2. The carbonyl oxygen of NMA makes a selective contact with one of the nitrogen atoms, and forms a weak C–H...O=C hydrogen bond with the *N*-methyl group at that nitrogen atom. There is an additional weak C–H...O=C hydrogen bond between the acetyl methyl group of NMA and the proximal carbonyl oxygen atom. The calculated interaction energy is about −5 kcal/mol at the LMP2/6-31G** level.

In the optimized complex **5** between NMA and trimethyl isocyanurate, the carbonyl oxygen of NMA is

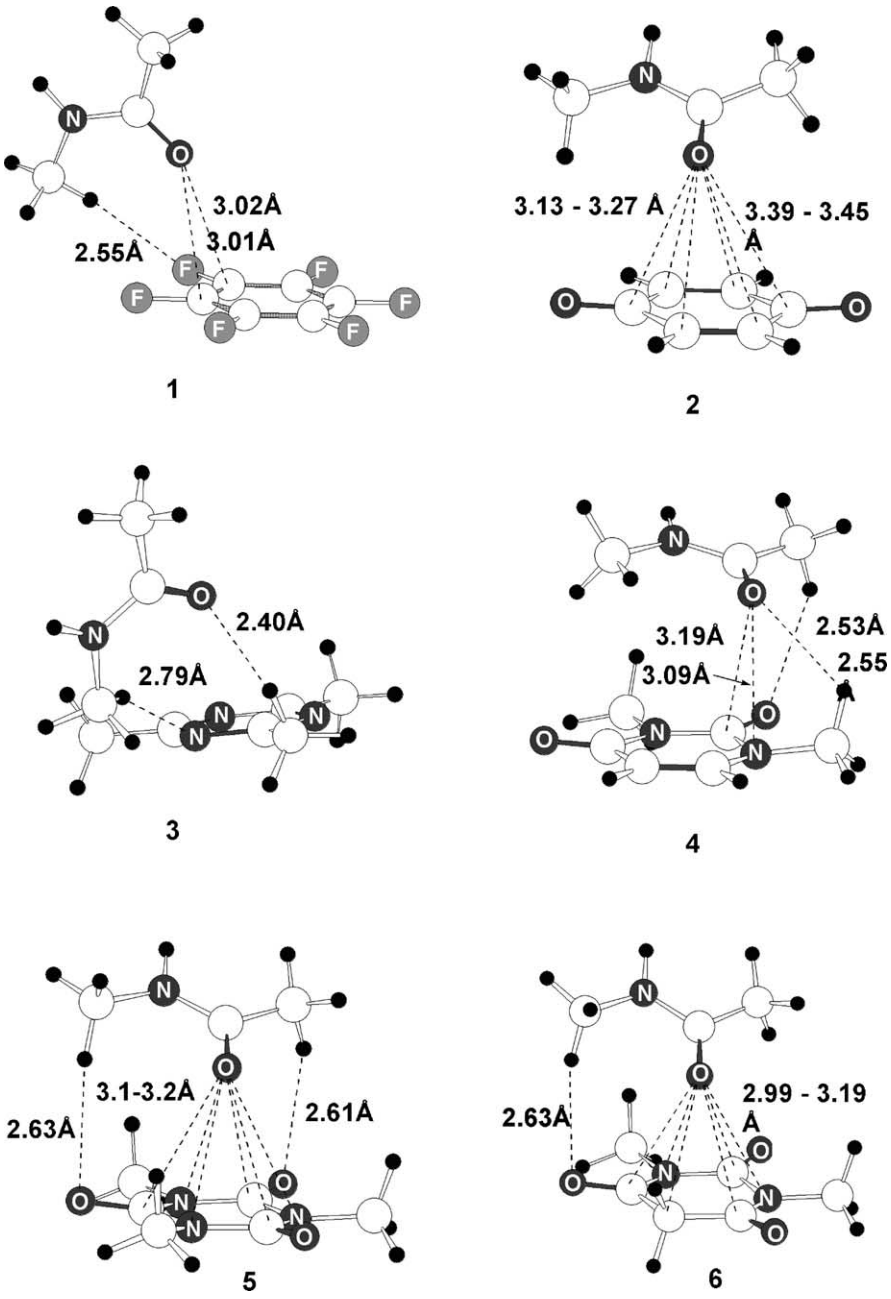


Figure 2. Optimized complex structures at the LMP2/6-31G** level.

Table 2. Calculated interaction energies (kcal/mol) with NMA at the LMP2/6-31G** level

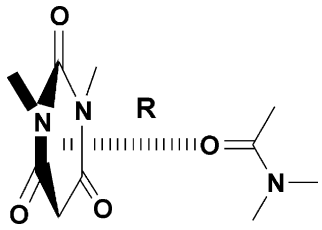
Method	1	2	3	4	5	6
ΔE	−5.5	−4.8	−3.8	−6.0	−8.7	−9.2
ΔE + ZPE[a]	−4.7	−3.9	−2.9	−4.6	−7.6	−7.8

[a]Values with zero-point energy (ZPE) corrections calculated at the HF/6-31G** level.

more or less centrally located along the normal axis of the ring. Its contact distances with the ring atoms range from 3.1 to 3.2 Å, which are in good agreement with those observed in the crystal packing structures as shown in Figure 1. There are secondary weak C–H...O=C hydrogen bond interactions between the methyl groups of NMA and the carbonyl oxygen atoms of isocyanurate.

Similarly, complex **6** between NMA and dimethyl barbiturate was energy minimized. The oxygen atom of NMA interacts with the centroid of the π-acidic amide ring, as observed in the crystal structures. There are peripheral C–H...O=C hydrogen bond interactions between the methyl groups of NMA and the carbonyl oxygen atoms of bartiturate. The calculated complex stabilization energies of both **5** and **6** at the LMP2/6-31G** level are 8 kcal/mol, which is the most exothermic of all six complexes shown in Scheme 1.

To estimate the contribution of weak C–H...O=C hydrogen bonds to the complexation energy in **6**, we



Scheme 2.

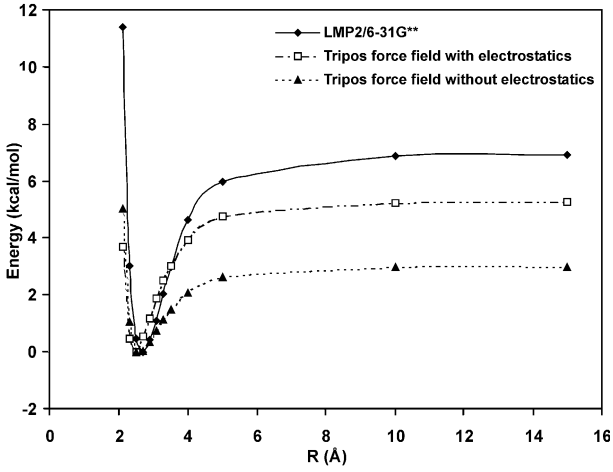


Figure 3. Single-point energy calculations on the dimethylbarbiturate–NMA complex.

carried out single-point energy calculations on the dimethyl barbiturate–NMA complex using the LMP2/6-31G** optimized geometries of isolated NMA and dimethyl barbiturate. The complex varies in distance (R) between the centroid of the barbiturate ring and oxygen atom of NMA, but maintains an orthogonal orientation between the barbiturate ring plane and the molecular plane of NMA (Scheme 2). The calculated energies are plotted in Figure 3 as a function of distance between the centroid of the ring and the oxygen atom of NMA. The stabilization energy of dimethyl barbiturate–NMA interaction was found to be 7 kcal/mol, compared to 9.2 kcal/mol for the fully optimized complex (all without zero-point energy corrections), indicating an upper-limit of ~2 kcal/mol for the C–H...O=C hydrogen bonds in **6**, which is within the range of estimates by Hay and coworkers.[3b]

The significance of electrostatic attractions to the overall stabilization energy in **6** was also demonstrated by the potential energy profiles from single point calculations using the Tripos force field[24] and Gasteiger–Huckel[25] charges as shown in Figure 3. The simple molecular force field reproduced the ab initio energy curve reasonably well. When the electrostatic terms were turned off, the stabilization energies dropped significantly, suggesting that electrostatic interactions account for more than half of the total stabilization energy in **6**.

The π-acidic amide can complement a hydrogen bond acceptor through electrostatic interaction. The present computational studies suggest barbituric acid and isocyanuric acid derivatives are potential structural motifs capable of complementing a hydrogen bond acceptor or anion through electrostatic interactions. To interact with a hydrogen bond acceptor or anion, the partially positively charged amide nitrogen and carbonyl carbon provide electrostatic attraction, balanced by the electrostatic repulsion from the electronegative carbonyl oxygen atoms.

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References and Notes

1. (a) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer: New York, 1994. (b) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.
2. (a) Gokel, G. W.; De Wall, S. L.; Meadows, E. S. *Eur. J. Org. Chem.* **2000**, 2967. (b) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond*; Oxford University Press: Oxford, 1999. (c) Gallivan, J. P.; Dougherty, D. A. *Org. Lett.* **1999**, *1*, 103. (d) Kim, E.; Paliwal, W.; Wilcox, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 11192.
3. (a) Green, R. D. *Hydrogen Bonding by C–H Groups*; Macmillan: London, 1974. (b) Vargas, R.; Garza, J.; Dixon, D. A.; Hay, B. *J. Am. Chem. Soc.* **2000**, *122*, 4750.
4. (a) Alkorta, I.; Rozas, I.; Elguero, J. *J. Am. Chem. Soc.* **2002**, *124*, 8593. (b) Quinonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deya, P. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 3389.
5. Mascal, M.; Armstrong, A.; Bartberger, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 6274.
6. Quinonero, D.; Garau, C.; Frontera, A.; Ballester, P.; Costa, A.; Deya, P. M. *Chem. Phys. Lett.* **2002**, *359*, 486.
7. Alkorta, I.; Rozas, I.; Jimeno, M. L.; Elguero, J. *Struct. Chem.* **2001**, *12*, 459.
8. (a) Duan, G.; Smith, V. H., Jr.; Weaver, D. F. *J. Phys. Chem. A* **2000**, *104*, 4521. (b) Kemmink, J.; Van Mierlo, C. P. M.; Scheek, R. M.; Creighton, T. E. *J. Mol. Biol.* **1993**, *230*, 312. (c) Boyd, J.; Skrynnikov, N. R. *J. Am. Chem. Soc.* **2002**, *124*, 1832.
9. (a) For recent examples of synthetic neutral receptor that recognizes anions, see: Hayashida, O.; Shivanyuk, A.; Rebek, J., Jr. *Angew. Chem. Int. Ed.* **2002**, *41*, 3423. (b) Kubik, S.; Goddard, R.; Kirchner, R.; Nolting, D.; Seidel, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2648.
10. For a recent example of C–F...C=O interaction, see: Olsen, J. A.; Banner, D. W.; Seiler, P.; Sander, U. O.; D'Arcy, A.; Stihle, M.; Müller, K.; Diederich, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 2507.
11. These groups are susceptible to metabolism in vivo to generate reactive or toxic species, whereas perfluorobenzene can no longer be functionalized.
12. Allen, F. H.; Kennard, O. *Chem. Des. Auto. News* **1993**, *8*, 1 and 31 (CSD Version 5.24, November 2002).
13. (a) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.
14. (a) Møller, C.; Plesset, M. S *Phys. Rev.* **1934**, *46*, 618. (b) Sæbø, S.; Pulay, P *Theor. Chim. Acta* **1986**, *69*, 357. (c) Sæbø,

S.; Pulay, P *Ann. Rev. Phys. Chem.* **1993**, *44*, 213. (d) Sæbø, S.; Tong, W.; Pulay, P *J. Chem. Phys.* **1993**, *98*, 2170.
15. *Jaguar 4.0*; Schrodinger, Inc.: Portland, OR, 2000.
16. (a) Hempel, A.; Camerman, N.; Camerman, A. *J. Med. Chem.* **1989**, *32*, 648. (b) Belaj, F.; Nachbaur, E. *Monatsh. Chem.* **1987**, *118*, 1077. (c) Thalladi, V. R.; Katz, A. K.; Carrell, H. L.; Nangia, A.; Desiraju, G. R. *Acta Crystallogr. Sect. C (Cr. Str. Comm.)* **1998**, *54*, 86. (d) Hornish, M. J.; Watt, W. *Acta Crystallogr. Sect. C (Cr. Str. Comm.)* **1994**, *50*, 263. (e) Yagupolskii, L. M.; Shelyazhenko, S. V.; Maletina, I. I.; Petrik, V. N.; Rusanov, E. B.; Chernega, A. N. *Eur. J. Org. Chem.* **2001**, 1225. (f) Depmeier, W.; von Voithenberg, H.; Jochims, J. C.; Klaska, K.-H. *Chem. Ber.* **1978**, *111*, 2010.
17. (a) Bideau, J.-P.; Huong, P. V.; Toure, S. *Acta Cryst. Sect. B* **1976**, *32*, 481. (b) Poling, M.; van der Helm, D. *Acta Crystallog., Sect. B* **1976**, *32*, 3349. (c) Bideau, J.-P.; Marly, L.; Housty, J. *C.R. Acad. Sci. Ser. C* **1969**, *269*, 549.
18. (a) Gdaniec, M. *Acta Crystallogr. Sect. C (Cr. Str. Comm.)* **1988**, *44*, 1042. (b) Sugawara, K.; Sugawara, F.; Strobel, G. A.; Fu, Y.; He, C.-H.; Clardy, J *J. Org. Chem.* **1985**, *50*, 5631. (c) Baures, P. W.; Ojala, W. H.; Costain, W. J.; Ott, M. C.; Pradhan, A.; Gleason, W. B.; Mishra, R. K.; Johnson, R. *L. J. Med. Chem.* **1997**, *40*, 3594. (d) Chai, C. L. L.; Hockless, D. C. R.; King, A. R. *Aust. J. Chem.* **1996**, *49*, 1229. (e) Glowka, M. L.; Iwanicka, I. *Acta Crystallogr. Sect. C (Cr. Str. Comm.)* **1990**, *46*, 1262.
19. (a) Marton-Meresz, M.; Kuszmann, J.; Pelczer, I.; Parkanyi, L.; Koritsanszky, T.; Kalman, A. *Tetrahedron* **1983**, *39*, 275. (b) Flippen, J. L.; Gilardi, R. D.; Karle, I. L. *Acta Crystallogr. Sect. B* **1972**, *28*, 360. (c) Flippen-Anderson, J. L.; Gilardi, R. *Acta Crystallogr. Sect. C (Cr. Str. Comm.)* **1984**, *40*, 1957. (d) Benz, G.; Born, L.; Brieden, M.; Grosser, R.; Kurz, J.; Paulsen, H.; Sinnwell, V.; Weber, B. *Liebigs Ann. Chem.* **1984**, 1408. (e) Parkanyi, L.; Kalman, A.; Czugler, M.; Kovacs, T.; Walker, R. T. *Nucleic Acids Res.* **1987**, *15*, 4111. (f) Noltemeyer, M.; Tietze, L. F.; Wolfling, J.; Schneider, G. *Acta Crystallogr. Sect. C (Cr. Str. Comm.)* **1994**, *50*, 726. (g) Courseille, C.; Hospital, M.; Decout, J.-L.; Lhomme, J. *Tetrahedron Lett.* **1990**, *31*, 5031. (h) Raic-Malic, S.; Svedruzic, D.; Gazivoda, T.; Marunovic, A.; Hergold-Brundic, A.; Nagl, A.; Balzarini, J.; De Clercq, E.; Mintas, M. *J. Med. Chem.* **2000**, *43*, 4806. (i) Schaible, H.-G.; Bats, J. W.; Engels, J. W. *Acta Crystallogr. Sect. C (Cr. Str. Comm.)* **1995**, *51*, 2410.
20. Slebodnick, C.; Fettinger, J. C.; Peterson, H. B.; Ibers, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3216.
21. (a) Dunitz, J. D. *X-ray Analysis and the Structure of Organic Molecules*; Cornellm: London, 1979. (b) Bürgi, H. B.; Dunitz, J. D. In *In Structure Correlation*, Bürgi, H. B., Dunitz, J. D., Eds.; VCH: New York, 1994; pp 163.
22. A model of face-to-face contact between amides was attributed to electrostatic attraction between amide dipoles, see: Pirkle, W.H. *Tetrahedron Lett.* **1983**, 5707.
23. (a) Jorgensen, W. L.; Swenson, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 569. (b) Duffy, E. M.; Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 7535. (c) Li, Y.; Garrell, R. L.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5895. (d) Quinonero, D.; Frontera, A.; Capo, M.; Ballester, P.; Suner, G. A.; Garau, C.; Deya, P. M. *New J. Chem.* **2001**, *25*, 259.
24. *SYBYL® 6.71*: Tripos Inc.; 1699 South Hanley Rd. St. Louis, MO 63144, USA.
25. Gasteiger, J.; Marsili, M. *Tetrahedron* **1980**, 3219.