contact angles of water on surfaces containing hydroxyl or carboxylic acid groups, in which specific polar interactions are important, deviate strongly from linearity. The apparent hydrophilicity of the polar tail groups is higher when they are in a nonpolar environment composed largely of methyl groups than when their neighbors are other polar groups. This difference may arise partly from greater electrostatic stabilization in more polar surfaces and partly from intramonolayer hydrogen bonding in surfaces that are rich in hydroxyl or carboxylic acid groups.

We believe that the polymethylene chains in these two-component monolayers are well-packed (in contrast to monolayers assembled from two thiols of different chain lengths), but we have no evidence for any translational order in the tail groups.[13] These monolayers do not phase segregate into macroscopic domains: the resulting nonpolar islands would pin the advancing drop edge and give rise to a deviation from linearity in the contact angles opposite to that observed.[14] In addition, changes in the line width and position of the O(1s) peak in XPS suggest that the local environment of dilute hydroxyl groups is different from that in a pure monolayer.[15]

In conclusion, coadsorption on gold of mixtures of thiols, with the same chain length but different tail groups, produces well-packed monolayers exposing those groups at the surface. Specific interactions between the tail groups cause nonideal behavior both in the composition and the hydrophilicity of the monolayers.

Acknowledgment. The XPS (SSX-100, Surface Science Instruments) was provided by a DARPA/URI grant and housed in the Harvard University Materials Research Laboratory. We thank J. Evall, Dr. E. B. Troughton, and Dr. R. G. Nuzzo (AT&T Bell Laboratories) for useful discussions.

(13) In addition, highly dipolar tail groups might exhibit orientational disorder if an ordered array engendered a large unfavorable electrostatic interaction.

(14) The size below which islands of different polarity no longer cause hysteresis in the contact angle is not well-established experimentally. Neumann and Good have proposed theoretically that this lower limit is ~0.1 μm (Neumann, A. W.; Good, R. J. *J. Colloid Interface Sci.* **1972**, *38*, 341-358).

(15) The O(1s) peak of the hydroxyl group in the monolayer with $\chi^{P}_{surface} = 0.05$ was 0.3 eV narrower and shifted 0.4 eV to higher binding energy compared to the pure hydroxyl-terminated monolayer. One possible explanation is that very dilute hydroxyl groups are not hydrogen-bonded. The extent to which the molecular distribution in the monolayer deviates from a statistical mixture is unclear.

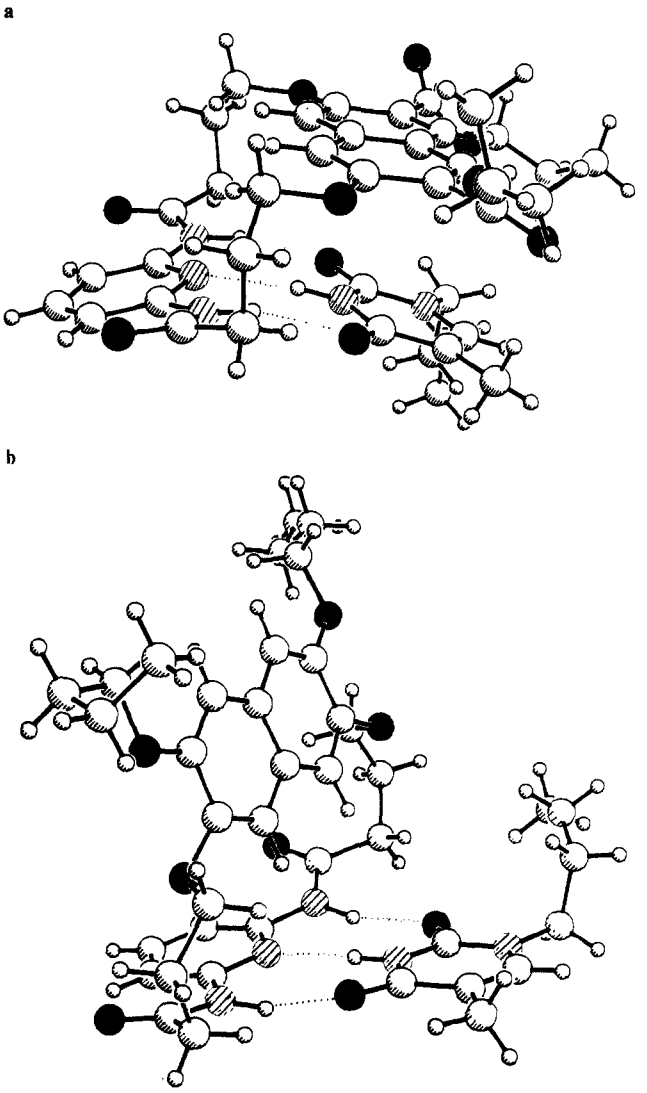

Figure 1. (a) Side view of X-ray structure of **4**:**6**. (b) Side view of X-ray structure of **5**:**6**.

Aromatic-Aromatic Interactions in Molecular Recognition: A Family of Artificial Receptors for Thymine That Shows Both Face-to-Face and Edge-to-Face Orientations

Alexander V. Muehldorf, Donna Van Engen, John C. Warner, and Andrew D. Hamilton*

Department of Chemistry, Princeton University Princeton, New Jersey 08544

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Interactions between aromatic rings play an important role in stabilizing protein structure.[1] A number of inter-ring geometries have been identified ranging from a parallel face-to-face stacking **1** to a perpendicular edge-to-face orientation **2** in which positively charged H atoms on one ring interact with negatively charged regions on a second.[1] A similar structural diversity can be seen in the protein recognition of nucleotide bases. The guanine-binding site of ribonuclease T_1 contains a tyrosine residue (Tyr 46) which stacks parallel to and at 3.4 Å from the purine plane.[3] In contrast, the human c-H-*ras* oncogene protein binds to guanine via a phenylalanine (Phe28) whose phenyl ring is positioned almost perpendicular to the nucleotide base.[4] As part of a study of general features of nucleotide base recognition[5] we sought to investigate the structural basis of these two geometries by incorporating them into artificial receptors. In this paper we report the synthesis and structural characterization of a class of thymine receptors which show either face-to-face or edge-to-face orientations, depending on the electronic properties of the stacking group.

1 **2**

The receptors are based on the two-site binding strategy (hydrogen bonding and stacking) introduced previously.[5a] Incorpo-

* Address correspondence to this author at Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260.

(1) Burley, S. K.; Petsko, G. A. *Science (Washington, D.C.)* **1985**, *229*, 23.

(2) Gould, R. O.; Gray, A. M.; Taylor, P.; Walkinshaw, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 5921. Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995.

(3) Heinemann, U.; Saenger, W. *Nature (London)* **1982**, *299*, 27.

(4) de Vas, A. M.; Tong, L.; Milburn, M. V.; Matias, P. M.; Jancarik, J.; Noguchi, S.; Nishimura, S.; Miura, K.; Ohtsuka, E.; Kim, S.-H. *Science (Washington, D.C.)* **1988**, *239*, 888.

(5) (a) Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 5035. (b) Hamilton, A. D.; Pant, N.; Muehldorf, A. *Pure Appl. Chem.* **1988**, *60*, 533.

0002-7863/88/1510-6561$01.50/0

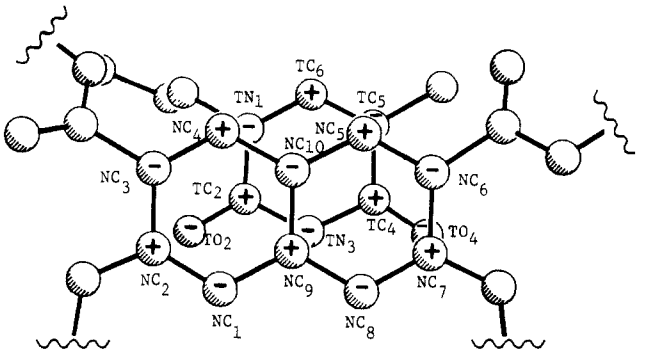
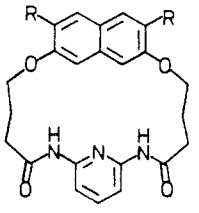
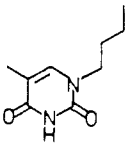


Figure 2. Top view of aromatic-aromatic interaction in **4**:**6** with electronic charge distributions (sign only) superimposed.

ration of different substituents into the naphthalene-3,6-positions in the basic receptor **3** allows us to vary the electronic charac-





6

3, R = H
4, R = $CO_2(CH_2)_2CH_3$
5, R = $O(CH_2)_3CH_3$

teristics of the stacking unit and assess its effect on the binding geometry. For example, diester macrocycle **4**[6] forms a strong complex with 1-butylthymine **6** (K_s = 570 M^{-1}, $-\Delta G°$ = 3.75 kcal mol^{-1})[7] in $CDCl_3$. Selective upfield shifts in the thymine CH and CH_3 ^1H NMR resonances (0.17 and 0.16 ppm) suggest a face-to-face geometry for the complex and this is confirmed by X-ray crystallography (Figure 1a). The naphthalene is positioned directly above and almost parallel to the pyrimidine at an interplanar distance of 3.54 Å. An insight into the origins of the special stabilization from stacking can be gained from MNDO calculations on 2,7-dimethoxynaphthalene-3,6-dicarboxylic acid (N) and thymine (T).[9,10] The resulting electronic charge distributions on the two planes are superimposed (sign only) on a downward view of **4**:**6** in Figure 2. This shows a precise alignment of *five* pairs of oppositely charged atoms (NC_2TO_2, NC_4TN_1, NC_5TC_5, NC_7TO_4, NC_9TN_3) confirming the importance of complementary electrostatic interactions in parallel stacking.[11]

Similar MNDO calculations[9] on 2,3,6,7-tetramethoxynaphthalene predict a reversal of sign at NC_3, NC_4, NC_5, and NC_6 and a diminution of charge at NC_9 and NC_{10}. Thus, in a face-to-face geometry with thymine (as in Figure 2) there would be repulsive electrostatic interactions between NC_4–TN_1 and NC_5–TC_5. To investigate this effect tetraether macrocycle **5** was prepared[6] and shown to bind 1-butylthymine **6** more weakly (K_s = 138, $-\Delta G°$ 2.92 kcal mol^{-1})[7] than either diester **4** or unsubstituted **3**.[5a,7] The absence of upfield shifts of the thymine CH and CH_3 resonances in the ^1H NMR of complex **5**:**6** argues against a parallel stacked geometry, whereas selective upfield shifts of the naphthalene-1,8-protons (0.13 ppm) suggest a solution conformation for **5**:**6** in which the 1,8-edge of the naphthalene is closer to the H-bonding plane than the 4,5-edge. Additional support for such an orientation comes from the crystal structure of complex **5**:**6** (Figure 1b) which shows the naphthalene to be almost perpendicular (77°) to the thymine–pyridine plane.[12] Furthermore, the naphthalene-1,8-protons project toward the region of negative charge formed by TO_2, TO_4, and TN_3 at distances of 2.69 and 2.24 Å from its mean plane. This edge-to-face interaction seems to be favorable as it provides a small stabilization (0.26 kcal mol^{-1}) for the complex compared to acyclic 2,6-dibutyramidopyridine.[5a,7]

Within a simple series of thymine receptors we have demonstrated that the geometry of aromatic–aromatic interactions in molecular recognition can be controlled by modifying the electronic characteristics of one component. Notably, an electrostatic complementarity between partial charges on the rings can lead to strong face-to-face stacking, while in the absence of such effects a weaker edge-to-face interaction is preferred.

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Supplementary Material Available: Crystallographic details for **4**:**6** and **5**:**6** including tables of atomic coordinates, thermal parameters, bond angles, and bond lengths (20 pages). Ordering information is given on any current masthead page.

(6) Details of the synthesis and spectroscopic properties of macrocycles **5** and **6** will be reported in full later.

(7) Determined by Foster–Fife[8] analysis of ^1H NMR titration data at 25 °C. For example, in the titration of **4** and **6** the concentration of **6** was 0–9.0 × 10^{-2} M, the maximum observed shift (at 10 equiv of **6**) of the **4**-amideNHs was 2.86 ppm, and the saturation shift was calculated[8] to be 2.92 ppm. Values for **3** and **6** are K_s = 290 M^{-1}, $-\Delta G°$ = 3.36 kcal mol^{-1} and for 2,6-dibutyramidopyridine and **6** K_s = 90 M^{-1}, $-\Delta G°$ = 2.71 kcal mol^{-1}.[5a]

(8) Foster, R.; Fife, C. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1969**, *4*, 1.

(9) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

(10) Abraham, R. J.; Smith, P. E. *Nucl. Acid Res.* **1988**, *16*, 2639.

(11) Dean, P. M. In *Molecular Foundations of Drug-Receptor Interactions*; Cambridge University Press: Cambridge, 1987; p 254. Ishida, T.; Doi, M.; Ueda, H.; Inoue, M.; Sheldrick, G. M. *J. Am. Chem. Soc.* **1988**, *110*, 2286 and references therein.

(12) For other examples of edge-to-face orientations in macrocyclic chemistry see: Anelli, P. L.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *Tetrahedron Lett.* **1988**, 1575 and references therein.

σ Delocalization Induced Stereoselectivity in the Capture of Cumyl Cations and Failure of Stabilizing Substituents To Suppress It

M.-H. Lin, C. K. Cheung, and W. J. le Noble*

Department of Chemistry, State University of New York Stony Brook, New York 11794

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One of the few questions not adequately addressed in the years of controversy about the solvolysis of 2-norbornyl derivatives[1] is whether a stabilizing α-substituent can "swamp" σ participation. The assumption that it can and would is the cornerstone of the position that such assistance is not important in determining epimeric rate ratios in solvolysis. The origin of this premise appears to be the elegant demonstration by Gassman and Fentiman[2] that α-substituents such as *p*-anisyl reduce anti/syn ratios of formation and capture of the 7-norbornenyl cation from ten million nearly to unity, thus justifying their conclusion that π participation occurs and that donating substituents can suppress it. Its extension to σ participation has only rarely been questioned,[3] and, indeed, the observation of many equilibrating pairs of tertiary 2-norbornyl ions demands that α delocalization in those cases cannot be strong enough in the fully developed ions to prevent distortion from C_{2v} symmetry. It is unfortunate that the phrase "equilibrating ions" has become virtually synonymous with "unassisted solvolysis", because such usage implies a criterion that may not be justified: the operation of swamping of σ participation has only been *assumed*.

We recently reported[4] *Z*/*E* ratios for the capture of nucleophiles by several tertiary 5-substituted adamant-2-yl cations and ada-

(1) Brown, H. C. *The Nonclassical Ion Problem*; with comments by Schleyer, P. von R. Plenum Press: New York, NY, 1977.

(2) Gassman, P. G.; Fentiman, A. F. *J. Am. Chem. Soc.* **1970**, *92*, 2549.

(3) Winstein, S. *J. Am. Chem. Soc.* **1965**, *87*, 381.

(4) (a) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598 and **1987**, *109*, 7239. (b) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874.

0002-7863/88/1510-6562$01.50/0