Analysis of a Nucleic Acid Model Receptor System

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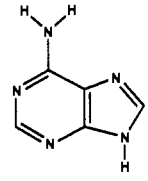
Abstract: A recent model receptor system for adenine, developed by Rebek and co-workers, is studied by semiempirical quantum chemical and molecular mechanics computational methods. The model receptor incorporates hydrogen bonding and π-stacking moieties in a convergent arrangement. The structural complementarity and contributions of the various components to the stabilization energy are analyzed. The structural characteristics are in general accord with the model deduced from experimental studies. The relative contribution of the stacking interaction to the stabilization energy is found to be considerably smaller than the hydrogen-bonding contribution.

Adenine appears in many biochemical systems, as a part of basic building blocks of DNA, or as parts of ligands such as adenosine 3′-5′-cyclic monophosphate (cAMP), adenosine 5′-diphosphate (ADP), or adenosine 5′-triphosphate (ATP). Recently, model adenine (**1**) (and adenine-containing structures) receptor systems



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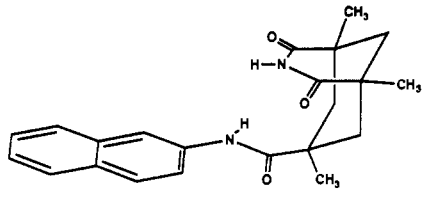
have been developed by Rebek and co-workers[1] and others.[2] The model receptors of Rebek and co-workers have hydrogen bonding and π-stacking groups arranged in a convergent manner, as illustrated in the monoimide **2** and diimide **3**. NMR studies by



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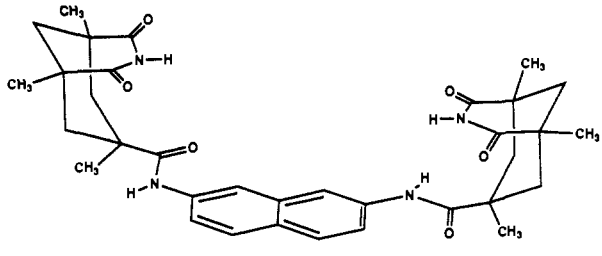

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Rebek et al.[1] suggest that both hydrogen bonding (both Watson-Crick and Hoogsteen) and π-stacking interactions occur in the monoimide **2** and related systems. For the diimides, there is less experimental evidence available; however, the findings are consistent with both the hydrogen bonding and π-stacking interactions. The diimides are particularly interesting as representing a potentially high degree of complementarity for the ligand. The diimides tend to have much greater association constants than the monoimides, suggesting that the second set of hydrogen bonds do contribute significantly to the interaction energy. We note, however, that while the association constants of the model receptor systems vary with changes in the aromatic group (suggesting a role for the π-stacking interaction), there are also examples in which there is little difference in association constants between model receptors in which the hydrogen bonding and π-stacking moieties are placed in convergent versus divergent arrangements.[1] Also, in computational studies of a related model receptor system developed by Rebek et al.,[3] Jorgensen et al. claimed that a "two-point binding" mechanism for pyrazine would not be possible because the cavity of that model receptor was not large enough to accommodate both sides of the pyrazine ring simultaneously.[4] In the present work we employ computational chemical methods to explore whether the diimide **3** can accomodate both sets of hydrogen bonds simultaneously (i.e., as designed) and to what extent π-stacking plays a role.

Figure 1 shows the structure obtained from a semiempirical PM3[5] calculation, using version 5.0 of MOPAC,[6] on the complex of the adenine/diimide. All geometric parameters were fully optimized. For computational convenience, the methyl groups have not been included in the PM3 calculations. The results of molecular mechanics calculations, both with and without these methyl groups, were essentially the same, thereby providing some justification for the approximation. Two very similar local minima were obtained. Both minima have three short and one slightly longer hydrogen bond. No other minima (e.g., different three short, two short, or four short hydrogen bonds) were found. The energetic and structural features are summarized in Table I and Figure 1. Most importantly we note that the optimized structures are in good agreement with the model proposed by Rebek et al., suggesting that both sides of the adenine ring system are accom-

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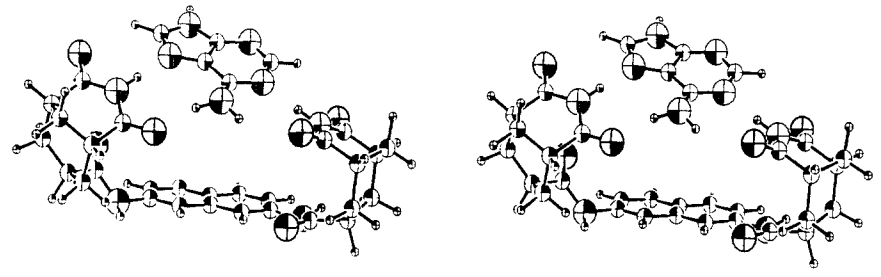

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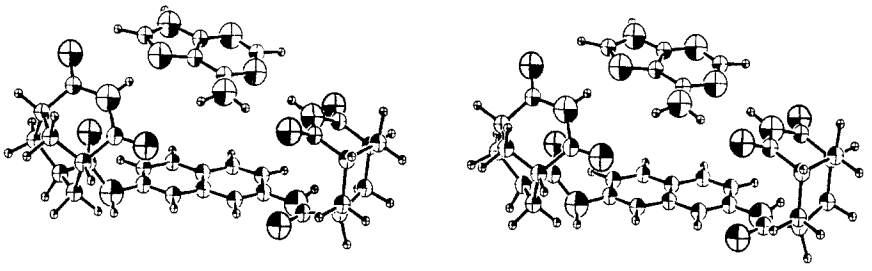
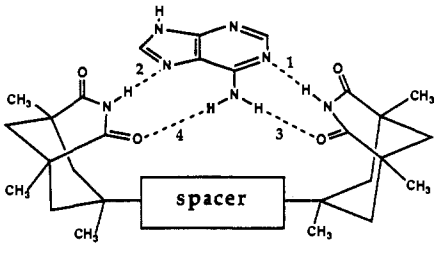


A2

Figure 1. Stereo representation of PM3 optimized structures of the adenine/model-receptor complexes: (A1) lowest energy structure obtained for the diimide developed by Rebek and co-workers, (A2) second local minimum structure obtained for the same complex.

Table I. Summary of Interaction Energies and Structures of Model Receptor–Adenine Complexes[a]



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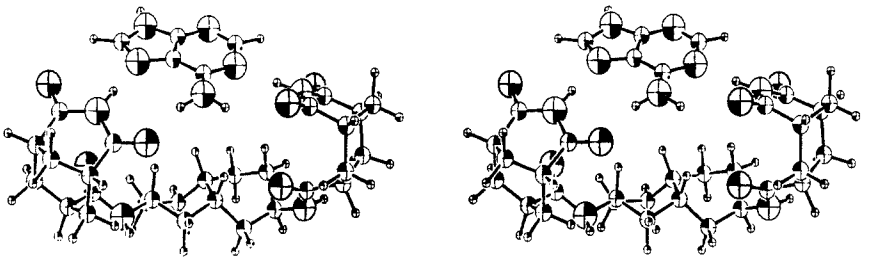
complex	interaction energy	hydrogen bond length no. 1	no. 2	no. 3	no. 4	angle between planes	closest C–C distance between planes
A1	−8.34 (−31.60)	1.81 (1.96)	1.77 (1.94)	2.58 (2.00)	1.84 (2.05)	26.2 (3.11)	4.7 (3.7)
B	−7.39 (−33.43)	1.81 (1.99)	1.78 (1.96)	2.47 (2.00)	1.84 (2.01)	12.9 (28.7)	4.8 (3.7)
difference	−0.95 (1.83)						
A2	−7.98	1.77	1.80	1.85	2.58	12.4	4.6
A1 frozen[b]	−12.05						
B frozen[b]	−11.59						
difference	−0.46						
A1 without spacer[c]	−10.96						
B without spacer[c]	−10.84						
difference	−0.12						

[a] Interaction energies are given in kcal/mol. Bond lengths are given in Å. Structures and parameters are as shown in **5** and Figures 1 and 2. Results are PM3 values and, in parentheses, Biograf values. [b] Interaction energies for these entries were obtained by using the unrelaxed structures of the adenine and model receptors for the isolated components, as described in the text. [c] Interaction energies for these entries were obtained by using the unrelaxed structures of the adenine and model receptors for the isolated components and with the spacers removed, as described in the text.

modated in this model receptor. Also, the aryl spacer group is oriented in a π-stacking arrangement, with the aromatic groups in nearly parallel orientations. It seems that the claim made by Jorgensen and co-workers that the related model receptor could not accommodate a pyrazine cannot be made in these studies. This could be a result of the fact that the pyrazine receptor model has both hydrogen bonding groups pointed at each other (appropriate for pyrazine), so that the ligand (pyrazine) would have to be centered between "anchors". As seen in Figure 1, the hydrogen-bonding arrangement in this system allows the adenine ring to be displaced from the center. Here and below, we note that the results of molecular mechanics calculation, using BioGraf[7] software and BioDesign's force field,[8] give qualitatively similar

(7) BioDesign, Inc., 199 South Los Robles Avenue, Suite 270, Pasedena, CA 91101.

(8) Mayo, S. L.; Olafson, B. D.; Goddard, W. A., III. Submitted for publication.

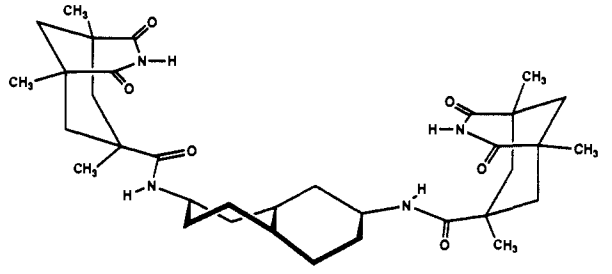


B

Figure 2. Stereo representation of the PM3 optimized structure of the adenine/alkyl analogue model–receptor complex designed herein (B).

results, although the interaction energies, for instance, tend to be larger, and there is only one local minimum with four simultaneous hydrogen bonds.

While the above results are in agreement with the previously suggested interaction model of Rebek and co-workers, it seemed interesting to further explore the extent to which the π-stacking interaction contributes to the stabilization energy. We therefore performed the same studies on a model receptor system, **4**, in which



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the aryl spacer was replaced by an alkyl spacer and which coresponds to a saturated counterpart of **3**. For the geometry optimization, the cyclohexane ring conformations were optimized around a structure that minimizes the steric interactions between the cyclohexane ring hydrogens and the adenine while maintaining optimal similarity to **3** in the region of the imides. Thus, the hydrogen-bonding framework is maintained while the π-stacking is eliminated. The results of the PM3 studies on the alkyl spacer are shown in Figure 2 and Table I. We note that not only is the structure of the adenine/alkyl-spacer complex very similar to that of the adenine/aryl-spacer complex but also the interaction energies are very similar as well, i.e., −8.34 kcal/mol versus −7.39 kcal/mol, respectively. The difference between these two interaction energies (0.95 kcal/mol) suggests that the π-stacking contribution is only a small component of the interaction energy of adenine with **3**.

To further analyze the extent to which this difference in interaction energies corresponds to the difference in the π-stacking interaction, the difference in the interaction energies was considered to contain contributions due to (1) differences in distortion energies of the components upon complexation (or equivalently, differences in relaxation energy upon dissociation), (2) differences between the aryl and alkyl interactions with the adenine (π-stacking component), and (3) differences in the hydrogen bonding energies due to structural differences with different spacers. Thus, model calculations were done as follows. (1) The dissociation energies of the aryl and alkyl systems were evaluated without allowing the isolated components (adenine, model receptor) to relax to their isolated, optimized structures, i.e., not allowing relaxation. The resulting "unrelaxed" difference in interaction energies is reduced to −0.46 kcal/mol as compared to the relaxed value of −0.95 kcal/mol. (2) At this stage, the same frozen study was done with the spacer removed from both model receptors (and hydrogen bonds added at standard bond lengths to complete valences appropriately). For the aryl system, the difference between the interaction energies with and without spacer (−12.05 versus −10.96 kcal/mol) of 1.09 kcal/mol is an estimate of the "π-stacking" interaction energy. The corresponding value for the alkyl system of 0.76 kcal/mol is an estimate of the "alkyl-stacking" (e.g., Van der Waals) interaction energy. The difference between these, 0.34 kcal/mol, represents the additional stabilization of the aryl system due to aromatic as opposed to alkyl interactions. (3) The difference between these systems due to the differences in the arrangements of the hydrogen bonding regions can be estimated from the difference in the interaction energies (0.12 kcal/mol) of the models without spacers; they are otherwise identical. The difference in the interaction energies due the differences in structure, 0.12 kcal/mol, when added to the differences due to aryl versus alkyl stacking, 0.34 kcal/mol, together account for the difference between interaction energies of the frozen models of 0.46 kcal/mol. Moreover, the π-stacking contribution (ca. 0.34 kcal/mol) seems to be a small component of the total interaction energy.[9] We note that this does not necessarily disagree with the structural model of Rebek et al., in which the aryl group is nearly parallel to the adenine in complexes with **3**, but suggests that this interaction contributes little to the overall stabilization of these complexes. The distance between the aromatic planes of 4.7 Å is relatively large for a π-stacking interaction and may account for the small contribution. These results suggest that the usual incorporation of a π-stacking functional group for model adenine receptors[1,2] may not be essential. Regarding the extent to which such models would still represent true receptors, we note that while base stacking is understood to play a role in, e.g., DNA structure, there is no evidence of such stacking interactions in the crystal structures of adenosine,[10] cAMP,[11] or, perhaps most significantly, cAMP bound to a receptor (catabolite gene activator protein) in *Escherichea coli*.[12]

Note Added in Proof. After this manuscript was submitted, we received a preprint of ref 13. In that study, diester diimides (as opposed to the diamide diimides studied herein), utilizing $-(CH_2)_n$ spacers, were found to "bind 7 [adenine] at least as well as the naphthyl diester diimide ... even without aryl stacking interactions with the guest". Preliminary molecular mechanics studies reported therein also confirm the minimum of three hydrogen bonds reported herein.

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(9) We note that these results are unlikely to be quantitatively correct because of the limits of the computational methods used. Rather we expect that the qualitative picture that emerges from the relative values of the energetic analysis provides meaningful insights.

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