Pergamon

Tetrahedron Letters, Vol. 35, No. 7, pp. 1035-1038, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0396-Z

Molecular Recognition of Adenine : Role of Geometry, Electronic Effects and Rotational Restrictions.

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Abstract: A new series of receptors for adenine, based upon Kemp's triacid has been synthesized. Their association constants with 9-ethyl-adenine in $CDCl_3$ have been measured and correlated to their geometric, electronic and rotational features.

Through the past few years, many molecules have been developed featuring affinity for adenine derivatives in various media.[1] The binding in these systems usually results from a combination of hydrogen-bonding and/or aryl stacking forces. Our own efforts rely on Kemp's triacid derivatives, in which the U-shape of the receptor allows both interactions to converge from perpendicular directions toward the adenine (figure 1). The influence of changing the size of the aromatic surface on adenine binding has been previously described.[1a] We report herein a preliminary study of the role of geometry, electronic effects and rotational restrictions.

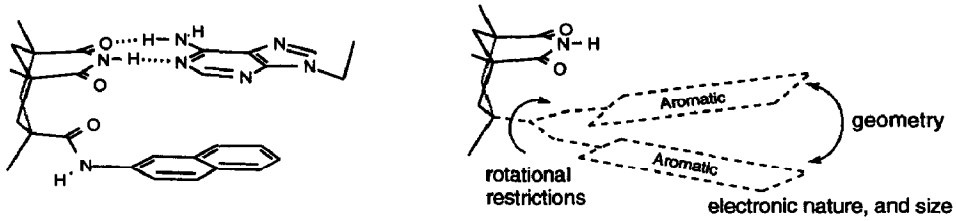
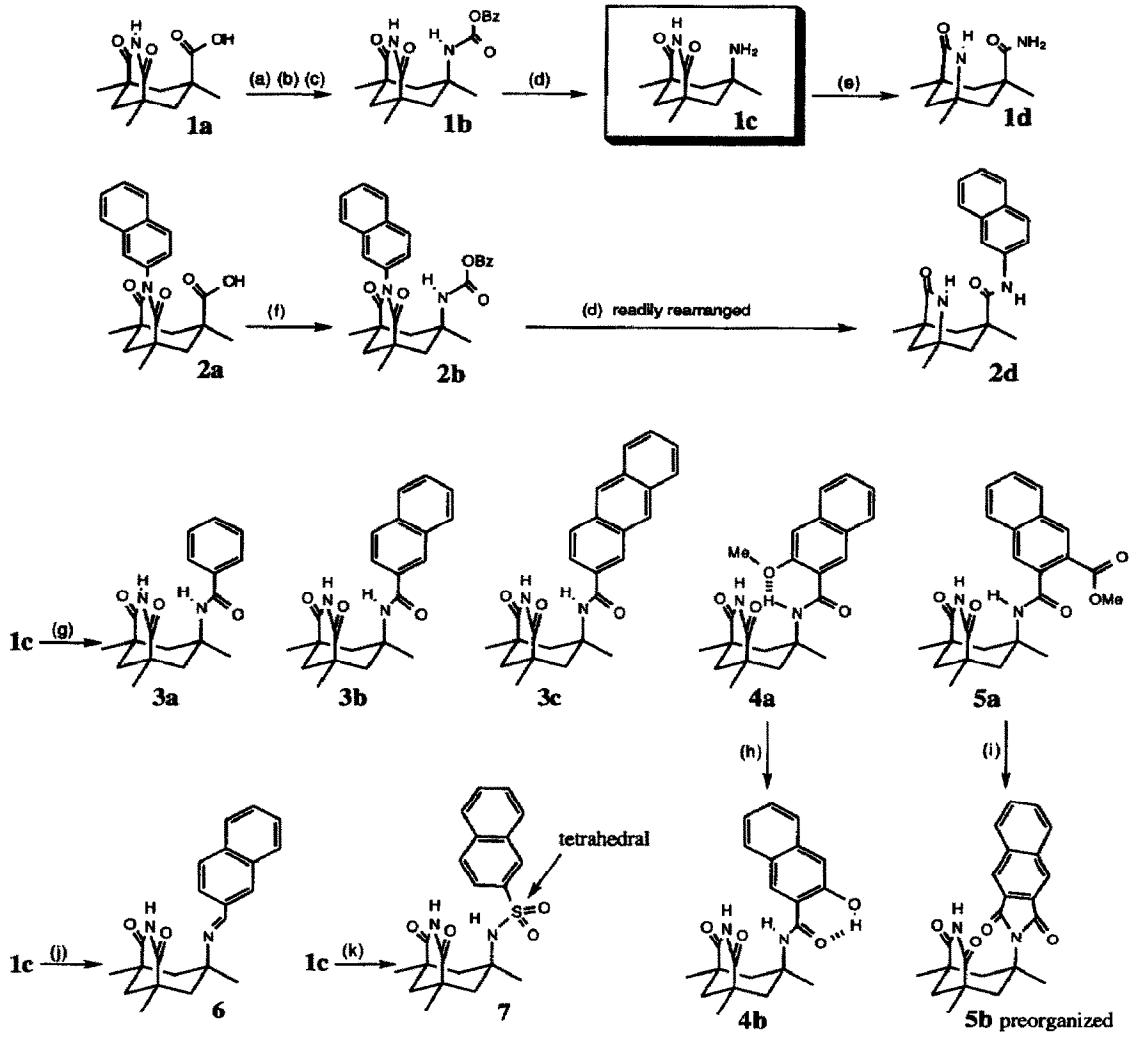


Figure 1

The synthesis of the amine **1c** (scheme 1) allowed the preparation of various receptors featuring an imide as the hydrogen-bonding surface, and aryl groups for the stacking. They differ from previous receptors through the reversal of the amide group; accordingly, the aromatic surface is electron-poorer than in the earlier systems. Association constants with 9-ethyl-adenine measured by ^1H NMR titration are reported in table 1.[2] They represent the sum of Hoogsteen, reverse-Hoogsteen, Watson-Crick and reverse-Watson-Crick contributions.



Scheme 1. (a) $SOCl_2$ CH_2Cl_2, reflux 30min; (b) NaN_3, acetone-water, 0°C 30min; (c) BzOH 5eq., toluene, reflux 12h, yield>90% ((a), (b), (c) combined); (d) Pd-C, cyclohexadiene, THF-EtOH, reflux 3h, >90%; (e) pyridine, reflux; (f) DPPA, Et_3N, BzOH, toluene, reflux 12h, 91%; (g) Aryl-COCl, Et_3N, CH_2Cl_2, RT 12h, 80-95%; (h) BBr_3, CH_2Cl_2, RT 30 min, >90%; (i) LDA 2.5eq., THF, RT 3h, 80%;(j) Aryl-CHO, Et_3N, THF, RT 12h, 90%; (k) Aryl-SO_2Cl, Et_3N, CH_2Cl_2, reflux 12h, 70%.

Table 1. Association Constants with 9-Ethyl-adenine in $CDCl_3$ at 298 K*

Host	2d	3a	3b	3c	4a	4b	5b	6	7
K_a ($L \cdot mol^{-1}$)	16	100	170	260	140	260	420	100	8.4

* Based upon imide N-H signal shift, lactam N-H for **2d**.

Geometry. A crystal structure of the parent compound of the series (amide **3b**) was obtained (figure 2). As for the previous systems, the amide linkage rigidity and trigonal geometry hold the naphthyl group roughly parallel to the imide function and therefore to the purine nucleus during binding. Replacing this carboxamide (**3b**) by a sulfonamide (**7**) results in a loss of 7.4 kJ•mol^{-1} in the binding energy. Crystal structures of similar compounds show that in addition to a relatively low energy barrier in the N-S bond rotation, the sulfonamide sulfur adopts a tetrahedral geometry.[3] Modeling with the AMBER force field[4] reveals that this geometry prevents the aromatic surface from being parallel to the imide plane, thus stacking and hydrogen-bonding cannot operate simultaneously on the purine nucleus. In certain conformations, the naphthyl group limits the access to the imide for hydrogen bonding.

The five-membered lactam **2d** can be compared with the previously described six-membered lactam **2e** (figure 2).[1b] They both adopt the required planar geometry but their hydrogen-bonding surfaces are differently oriented. Accordingly, different stacking interactions between the naphthyl group and adenine could be expected.[5] However, their binding ability is similar, showing that this element is not energetically determining; the combination of Watson-Crick and Hoogsteen pairing lead to similar overlap for **2d** and **2e**.

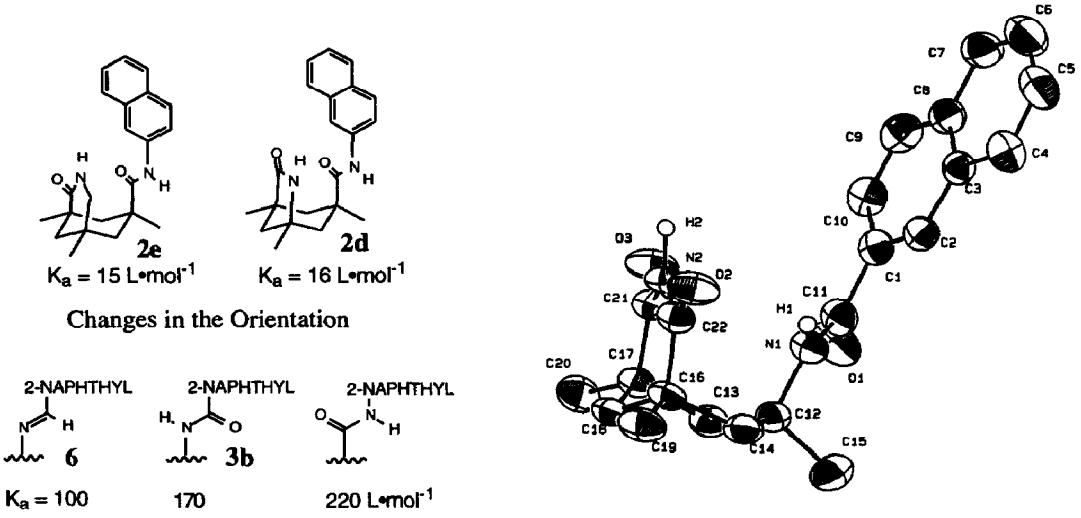


Figure 2

Electronic effects. As for the original -CO-NH-aryl series,[1a] enlarging the size of the aromatic in the -NH-CO-aryl series (cf **3a**, **3b**, **3c**) enhances the affinity for adenine. This supports face to face stacking interactions in the complex.[6] The hydrogen bonding anchors the adenine over the aryl group and overcomes the π–π repulsive forces that favor edge to face or off-set geometries.[5] As the aromatics involved here have no significant dipole moments, van der Waals interactions rather than Coulombic forces dominate the stacking.[7] Likewise, the change from electron-rich aromatics in the original series to electron-poor in the new receptors is expected to reduce the polarizability of the aryl group. It leads to a lower affinity for adenine (figure 2); the binding constant decreases with the electron withdrawing strength of the substituent.

Rotational restrictions. The rotation about the cyclohexane-amide linkage appears hindered in the crystal structure of **3b** due to the proximity of the imide; the amide-carbonyl protrudes too far from the axis of rotation to be allowed an effortless 360° turn. However, the ^{1}H NMR resonances of the cyclohexane equatorial protons (β to the amide group) are the same, which indicates that rotation is fast on the NMR time scale.

Restriction of the amide-aryl bond rotation could be achieved either by intramolecular hydrogen bonding (**4a, 4b**) or by covalent linkage (**5b**). In the methoxy-naphthyl **4a**, the NH...O hydrogen bond has no effect on adenine affinity (K_a=140 L•mol^{-1} compared to 170 L•mol^{-1} for **3b**). Orthohydroxy benzamides are known to form the stronger OH...O hydrogen bond (rather than NH...O) both in the solid state and in solution.[8] The association constant is indeed higher for naphthol **4b** (260 L•mol^{-1}) than for **3b** (170 L•mol^{-1}) but the difference is small and its interpretation is clouded as electronic effects could be involved. Finally, the strong affinity of **5b** for 9-ethyl-adenine (K_a=420 L•mol^{-1}, the highest in the naphthyl series) is probably due to its rigidity: the carbonyl-aryl linkage is locked by a covalent bond, and the rotation about the cyclohexane-amide linkage must have a high barrier. As a result, the receptor is uniquely preorganized for face to face stacking with adenine.

Conclusion. The use of small artificial receptors has the advantage of synthetic versatility. Easy access to a family of molecules throws light on the contributions of structure and electronics to the recognition process.

Acknowledgements. This work was supported by the National Institutes of Health. I. H. thanks Rhône-Poulenc for a doctoral fellowship.

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(*Received in USA* 23 *November* 1993; *accepted* 10 *December* 1993)