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A New Bile Acid-based Ditopic Adenine/Biotin Receptor with Convergent Carboxyl Groups

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A New Bile Acid-based Ditopic Adenine/Biotin Receptor with Convergent Carboxyl Groups

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Careful molecular modeling has been done to design receptor 4 which was synthesized in three simple steps from methyl deoxycholate and showed high association constants for the binding with 9-butyladenine (1) and biotin methyl ester (2) in deutero-chloroform.

Keywords: Adenine binding, deoxycholic acid, benzene dicarboxylic acids, molecular modeling

Hydrogen bonding (H-bonding) is the most extensively used noncovalent interaction in nature [1]. Needless to say, the use of this particular non-covalent interaction has attracted the maximum attention from the point of view of molecular recognition and supramolecular chemistry [2]. Pairing of bases in DNA is one of the most important manifestations of H-bonding [3]. Even the paired bases are known to take part in recognition processes as in the formation of triplexes [4] or in protein DNA interaction [5]. Such events are mediated, among other factors, by Hoogsteen H-bonding. Therefore the individual bases are formally bound in a 'bidentate' fashion. Considerable attention has therefore been directed towards building efficient synthetic-receptors for the nucleobases [6] along with the study of based pairing *in-vitro* [7]. As a part of this development a special class of synthetic receptors were developed to bind 9-*N*-alkyladenine (Ade) derivatives [8, 9]. Many of these host molecules were equipped with a pair of carboxyl groups to 'chelate' Ade [10].

Bile acids have played a major role in the explosive growth of molecular recognition and supramolecular chemistry [11]. We have also shown the utility of this class of molecules in the design of semi-rigid molecular tweezers involving π-stacking interaction [12]. In this communication we report the design, synthesis and preliminary binding properties of a bile acid-based molecular tweezer, containing a pair of carboxyl groups, for the complexation of 9-*N*-butyladenine (**1**) [13] and biotin methyl ester (**2**).

For the construction of such a chelating tweezer, it is necessary to (a) get the carboxyl functionalities separated by an appropriate spacer and (b) orient the pair of carboxyl groups appropriately for binding. In methyl deoxycholate the

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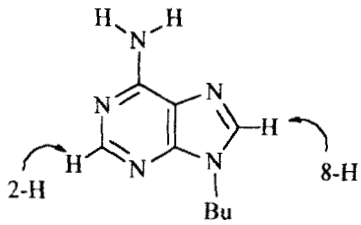

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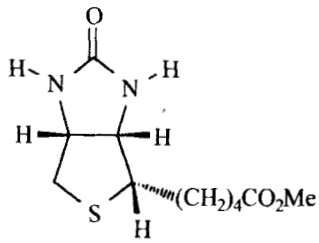

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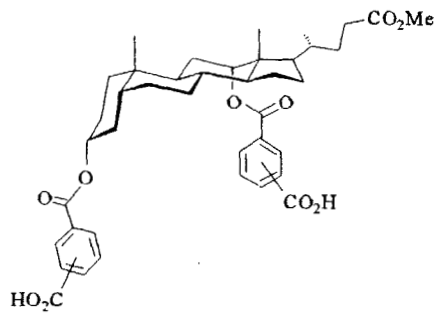

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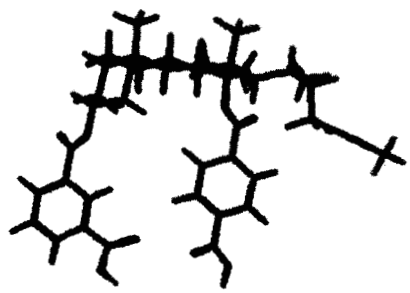
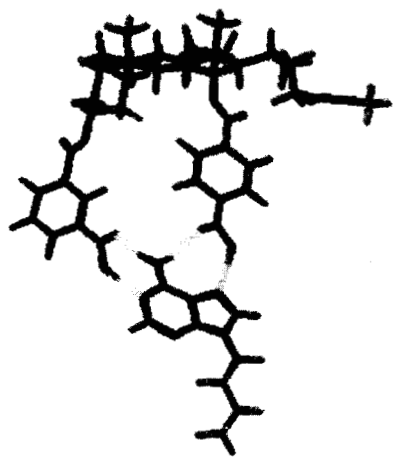


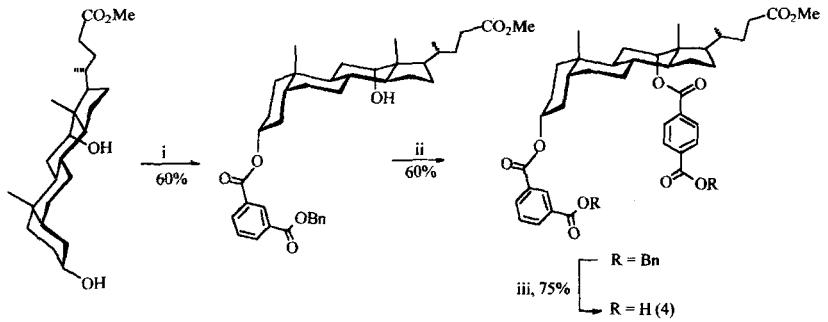
Minimized structure of **4** showing the convergent carboxyl groups. (See Color Plate I at the back of the issue).



Minimized structure of **4.1**. (See Color Plate II at the back of the issue).

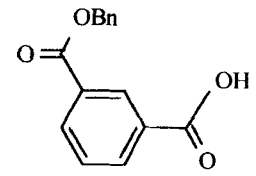
distance between the 3α-OH and the 12α-OH is ~6 Å. Our aim was to esterify the 3α-OH and the 12α-OH of methyl deoxycholate (MDC) with suitable isomers of benzenedicarboxylic acids. If successful this would result in an exceedingly simple and elegant design of the required tweezer. In an effort to design the optimum tweezer by molecular modeling, all the nine possible combinations (**3**) involving phthalic, isophthalic and terephthalic acids (and MDC) were minimized [14]. It was found that only one compound (**4**) possessed the correct orientation of the carboxyl groups required to bind adenine *via* both Watson–Crick and Hoogsteen bonding. The synthesis was carried out in three steps as shown in Scheme 1. The 3α-OH of MDC was selectively esterified with monobenzyl isophthalate using DCC and DMAP in dichloromethane. The 12α-OH of was esterfied with monobenzyl terephthalate under Oppenauer esterification condition [15]. Debenzylation using 10% Pd-C/H_2 afforded the required receptor [16].

Binding constants in deuterochloroform at 27°C were measured using ^{1}H-NMR spectroscopy. Diacid **4** was found to be sparingly



SCHEME 1 i. Monobenzyl isopthalate, DCC, DMAP, CH_2Cl_1; ii. Monobenzylterepthaloyl chloride, CaH_2, $Bn(Et)_3NCl$, PhMe; iii. H_2, Pd/C, EtOAc.

soluble in chloroform and a reverse titration with **1** was planned [17]. The concentration of the adenine derivative was kept constant at 5 mM which was titrated with 1–6 mM of acid [18]. In these studies it is conventional to follow the 6-amino signal of **1**. However, during the titration runs it was difficult to follow the amino signal amid the aromatic signals of the host. This difficulty was overcome by following the 2-H and the 8-H signals of **1** which underwent downfield shifts (*ca.* 0.2 δ) during the course of the titration [19, 7b]. The data obtained from monitoring these two signals during the titration of tweezer **4** were analyzed using a nonlinear curve fitting program (*assuming a 1:1 stoichiometry*) to provide a K_a of $3.5 \times 10^3\,M^{-1}$. The association constant for the complexation of monobenzyl isophthalate **5** with **1** was measured to be $170\,M^{-1}$. *The order of magnitude jump in the binding, as well as the downfield shifts observed for both* 2-H *and* 8-H *signifies synergistic participation of both the carboxyl groups of* **4**. Another control experiment was carried out with compound **6**, which has the 'wrong' geometric dispositions of the two carboxylic acid groups. This molecule complexed **1** with a K_a of $300\,M^{-1}$ implying independent participation of the acid functionalities of **6** for the binding. Additional support for the proposed binding mode of **4** came from the binding studies carried out with biotin methyl ester **2**. The association constants with



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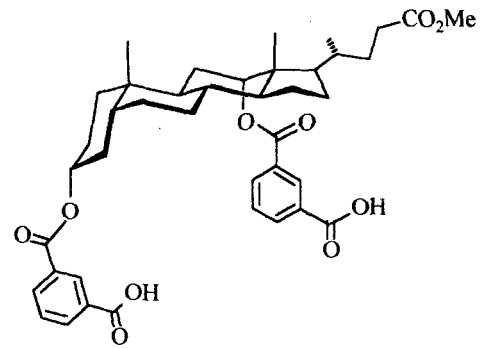

6

diacid **4** and monoacid **5** were found to be $1.5 \times 10^3\,M^{-1}$ and $220\,M^{-1}$, respectively.

This work demonstrates the power of modeling in semi-rigid systems. The synthetic ease offered in our three-step protocol allows large quantities of the receptor to be available. The binding constant observed for **1** at 27°C is high, considering the fact that no additional impetus for binding, *e.g.*, π-stacking, is provided by

receptor **4**. The high binding constant undoubtedly reflects relatively restricted rotation around the C_3—O and the C_{12}—O bonds. Davis *et al.*, have also made similar predictions in a recent paper [11]. Even though we have used a pair of carboxyl groups in the design of the tweezer, other functional groups can also be tested for their efficacy. Due to the stepwise synthesis leading to the receptor it should also be possible to synthesize tweezers with different *'biting'* functionalities at the 3 and 12 positions. We have recently developed a polymer bound tweezer by taking advantage of the bile acid sidechain for immobilizing useful derivatives on a polymer support [12a]. With receptor **4** a similar approach can lead to novel analytical applications. Work is currently being pursued in these directions and the results will be published elsewhere.

Acknowledgments

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[16] Selected Spectroscopic Data on **4**: FABMS 726 ($M^+ + Na^+ + H^+$); ^{1}H-NMR (DMSO-d_6, 400 MHz) 0.76 (d, 3H), 0.79 (s, 3H), 0.94 (s, 3H), 1.00–2.20 (m, 26H), 3.51 (s, 3H), 4.83 (s, 1H), 5.31 (s, 1H), 7.58 (t, 1H), 7.88 (d, 1H), 8.09–8.14 (5H), 8.39 (s, 1H), 13.15 (br.s, 2H); ^{13}C-NMR (DMSO-d_6, 75 MHz) 12.16, 17.24, 22.51, 23.00, 25.49, 25.77, 26.04, 30.18, 31.66, 33.41, 34.05, 35.05, 40.89, 44.91, 47.40, 49.61, 51.07, 74.29, 76.38, 129.126, 129.694, 130.36, 131.12, 132.24, 132.58, 133.63, 135.19, 164.23, 164.39, 166.34, 166.48, 173.52; IR, cm^{-1}, nujol: 1700, 3200–3700 $[\alpha]_D^{24} = +66 (c = 1.4, \text{THF})$ Found C, 70.00; H, 7.36. Reqd. $C_{41}H_{50}O_{10}C$, 70.06; H, 7.10.

[17] The solubility of **4** in $CHCl_3$ is only 1.64 mM at 27°C. However, we were able to solubilise as much as 6 mM of host **4** in the presence of the guest.

[18] The acid was initially dissolved in THF, required volumes added into the NMR tubes and evaporated to dryness in vacuo for 3 h.

[19] Lancelot, G. (1977). *J. Am. Chem. Soc.*, **88**, 7037. It is well documented in all these examples that these aromatic signals can be followed to obtain the association constant (K_a) with reliability.