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Directed H-bonding inhibition in molecular recognition: an NMR case study of the H-bonding of a dicarboxylic acid with a new mixed diamide receptor having one adjacent pyridine-*N*-oxide

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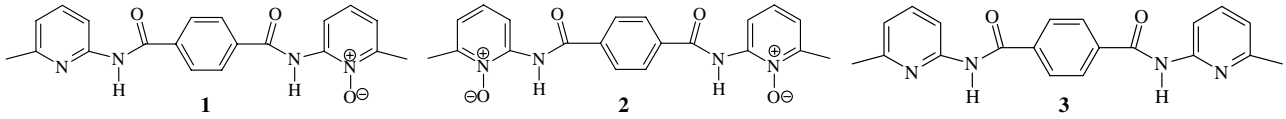
Abstract—The inhibition of hydrogen bond formation in the recognition of adipic acid by a new diamide receptor **1** having a pyridine-*N*-oxide and a simple pyridine ring adjacent to the amide moieties is observed. NMR studies show binding by the pyridine amide group in **1**, which demonstrates the discrimination in hydrogen bonding between the carboxyls and an amide adjacent to pyridine versus another adjacent to the pyridine *N*-oxide. This specific inhibition of hydrogen bonding to a carboxyl group by the two different amides in **1** is corroborated by the NMR binding studies of **1** with propionic acid.

In designing molecules to recognize other molecules specifically a prime factor is the consideration of H-bond interactions between the functional groups of hosts and guests.[1] The formation of a H-bond is a major driving force for self-association[2a] and is widely used in the design of supramolecular crystals.[1] Of all the binding forces used in the development of artificial receptors, hydrogen bonding is potentially the most directed and powerful.[2b] Molecular recognition studies of mono and dicarboxylic acids are of great importance due to their versatile appearance in many biologically active molecules, for example, in drugs such as ibuprofen,[3] aspirin, various antibiotics, amino acids, prostaglandins and also in biotin, folic acid, bile acids, bilirubin, etc.

As part of our interest in the molecular recognition of mono and dicarboxylic acids, we have designed receptors with three point hydrogen bonds[4] with different spacers.[5] For enhancement in the binding of a monocarboxylic acid by a pyridine amide, we previously reported a receptor,[4] which makes three point hydrogen bonds, compared to two point hydrogen bonds, by placing a pyridine amide and another amide with an isophthaloyl spacer so that all the hydrogen bond donor–acceptor groups of the host and guest can bind cooperatively. We now report the first case study of dicarboxylic acid (adipic acid) recognition by the receptor **1**, which contains one amide adjacent to a pyridine and the other adjacent to a pyridine-*N*-oxide. Inhibition of the formation of hydrogen bonds to carboxyl groups by the amide adjacent to the pyridine-*N*-oxide is observed in contrast to that adjacent to the normal pyridine amide. For this reason a significant decrease of the overall binding constant was noted. This conclusion was corroborated by the NMR titration of receptor **1** with propionic acid. Hamilton and co-workers[6] reported dicarboxylic acid recognition where both carboxylic groups form hydrogen bonds with the two binding sites of the receptor **3**.



1 **2** **3**

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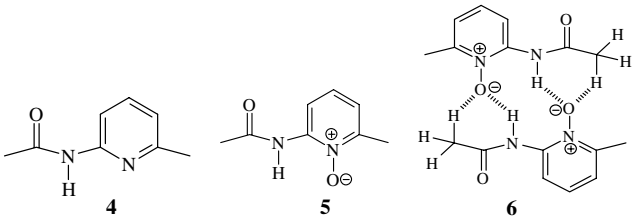
Ours is a way to discriminate two amides in molecular recognition. Thus recognition of a pyridine-2-amide by a carboxyl group can be inhibited easily by conversion into the corresponding *N*-oxide. Selective conversion to the mono *N*-oxide makes it possible to inhibit selective complexation of a dicarboxylic acid by a ditopic receptor **3**. This suggests that controlled inhibition of hydrogen bonding may lead to new supramolecular design.

Receptor **3** (prepared by the literature procedure[6]) on reaction with hydrogen peroxide in acetic acid,[7] afforded both new receptors, the mono pyridine-*N*-oxide **1** and the di-pyridine-*N*-oxide **2**.



4 **5** **6**

In the ^{1}H NMR spectrum[8] of the receptor **1** (Fig. 1A), the N–H adjacent to the pyridine-*N*-oxide is downfield (δ 11.25) relative to that adjacent to the pyridine (δ 8.60). This may be due to the positive charge on the nitrogen and also, possibly due to the intramolecular hydrogen bond between the N–H of the amide with the negatively charged oxygen of the *N*-oxide.The assignment of the *N*-oxide amide proton is based on the comparison of the NMR of compound **3** and the mono *N*-oxide **1** with that of the di-*N*-oxide **2** where both the amide protons appear at the same position (δ 11.19). Interestingly, in the complex of the receptor **1** with adipic acid, only one amide proton, which is attached to a pyridine ring, is shifted from δ 8.60 to δ 10.93 ppm ($\Delta\delta$ = 2.33 ppm) but the other N–H adjacent to the pyridine *N*-oxide does not change its position significantly on complexation suggesting its non-participation in hydrogen bonding with the carboxyl groups of the dicarboxylic acid. The methyl protons adjacent to the pyridine-*N*-oxide and those adjacent to the pyridine appear at different chemical shifts (δ 2.50 and δ 2.62) in the mono *N*-oxide **1**. In the di-*N*-oxide **2**, all the methyl protons appear as a singlet at δ 2.55 ppm.

From the mass spectra, two MH+ values are found for both the receptors **1** (MH^+ at *m*/*z* 363.3 and $2MH^+$ at *m*/*z* 725.4) and **2** (MH^+ at *m*/*z* 379.4 and $2MH^+$ at *m*/*z* 757.4), respectively, which suggests that the compounds may remain as dimers possibly through homo-intermolecular *N*-oxide and amide hydrogen bonds.

We have performed several complexation studies taking the same guest with different hosts. In a 1:1 solution of compound **5** and adipic acid in $CDCl_3$, the chemical shift in the amide proton of **5** is negligible (δ 10.17 to 10.21, $\Delta\delta$ = 0.04 ppm) and the sharp amide singlet changes to a broader peak indicating that the negative

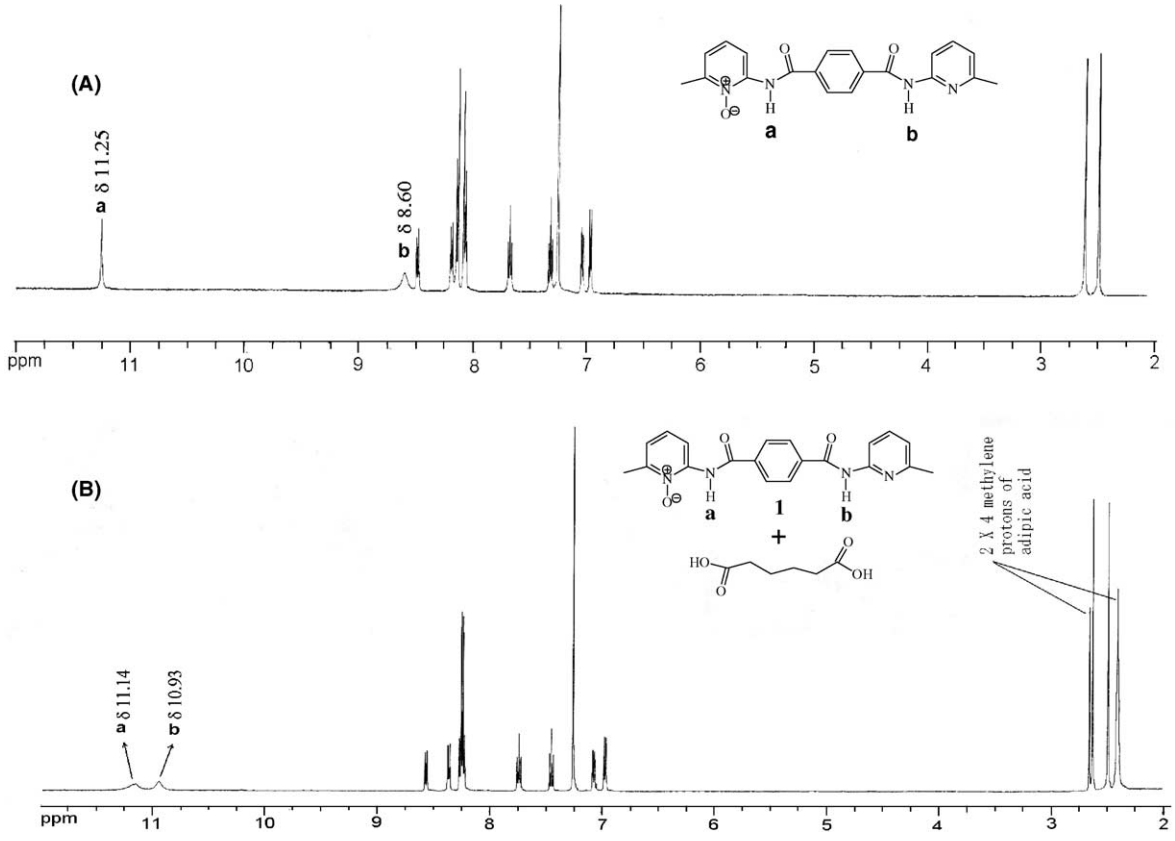


Figure 1. (A) ^{1}H NMR of receptor **1**. (B) ^{1}H NMR of the complex of receptor **1** with adipic acid.

charge on the oxygen atom makes the amide proton (adjacent to the *N*-oxide) bind to another molecule rather than to adipic acid and thus is ineffective in binding a carboxyl group. In this case also, the dilution experiments on the 1:1 complex did not affect the NMR spectrum, which suggested that the dimer form **6** probably also exists in solution. The inability of an amide adjacent to a pyridine-*N*-oxide to bind to a carboxylic group is also consistent with its strong hydrogen bonded dimer structure **6** as shown by single crystal X-ray diffraction[9] studies.

To determine the binding constant,[10] we titrated receptor **1** with adipic acid ($CDCl_3$ + 2% DMSO-d_6)[11] and propionic acid ($CDCl_3$). A plot of the titration curves is shown in Figure 2d. The effective 1:1 complexation with the adipic acid indicates that one carboxylic group of the adipic acid binds the free pyridine amide moiety of one receptor molecule and the other carboxyl group probably binds the free pyridine amide moiety of another molecule of the receptor **1** (Fig. 2a). The *N*-oxide may maintain the intramolecular hydrogen bonded structure in the dimer keeping the unbound carboxyl group in its dimer structure as the interaction between the *N*-oxide dimer and the carboxyl dimer is too poor to break self-hydrogen bonds for hetero-hydrogen bonds. It explains why such a dimer (host): dimer (guest) associate in a 1:1 fashion. This conclusion has been supported by the NMR titration of the receptor **1** with propionic acid. One equivalent of this monocarboxylic acid was saturated by one equivalent of receptor **1** forming a 1:1 complex, which was similar to the adipic acid titration. In a solution of 1:1 complex of receptor **1** and propionic acid in $CDCl_3$, the amide proton of **1** adjacent to the pyridine ring showed a significant downfield chemical shift (from δ 8.60 to 10.07, $\Delta\delta = 1.47$ ppm) with practically no shift in the amide proton adjacent to the pyridine-*N*-oxide of **1**, which suggests non-participation of the amide moiety adjacent to the pyridine-*N*-oxide. This also proves that **1** acts as a monotopic receptor in the recognition of adipic acid, which uses only one carboxylic acid moiety, in this particular case because of the non-availability of a further binding group due to the *N*-oxide in the receptor **1**. This part of the complex structure (where hetero-hydrogen bonding does not form) remains as a suitable spacer to hold the mutual hetero-binding zone in place. On gradual dilution of the complex solution of receptor **1** with adipic acid, both the amide protons (one adjacent to the pyridine and the other adjacent to the pyridine-*N*-oxide, respectively), of **1**, which do not change in the NMR supports the effective complexation of only the pyridine-2-amide of the stable pyridine-*N*-oxide dimer **1** (Fig. 2a) with a carboxyl of adipic acid.

Significantly lower K_a values (1.25×10^2 and 0.40×10^2 M^{-1} for adipic and propionic acids, respectively), which are comparable for binding monocarboxylic acid[3] with simple pyridine-2-amides, for example, **4**, were obtained for **1** and this also supports non-participation of the amide group adjacent to the pyridine-*N*-oxide in binding a carboxylic moiety of the dicarboxylic acids.

Thus, a ditopic receptor becomes monotopic by the simple conversion into its mono *N*-oxide showing a K_a similar to monocarboxylic acid binding by a simple pyridine-2-amide. Using the PCMODEL program,[12] it was also found that the pyridine-*N*-oxide oxygen of receptor **1**

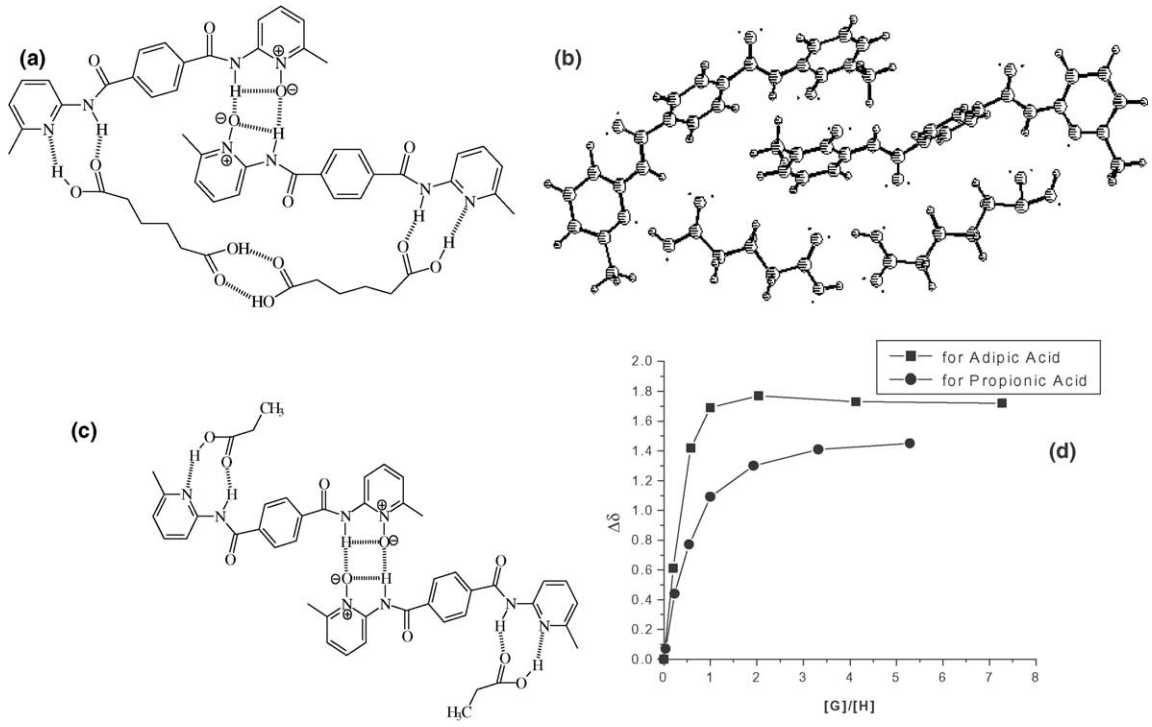


Figure 2. (a) Proposed complex structure of receptor **1** with adipic acid; (b) energy minimized structure of the complex of **1** and adipic acid; (c) proposed complex structure of receptor **1** with propionic acid; (d) titration curves of receptor **1** with adipic and propionic acids, respectively.

is intramolecularly hydrogen bonded with the amide-NH forming a five-membered ring and is also intermolecularly hydrogen bonded with the amide of the other pyridine-*N*-oxide molecule (Fig. 2b). This explains the specific binding of the amide adjacent to pyridine and not that adjacent to pyridine-*N*-oxide in the recognition of adipic acid (Fig. 2a and b) and also propionic acid (Fig. 2c).

In conclusion, we report an interesting case of hydrogen bond inhibition in molecular recognition. In the mixed amide receptor **1**, the two amides are differentiated in the NMR, which in turn leads to different hydrogen bonding behaviour in dicarboxylic acid recognition. Thus, almost total inhibition of hydrogen bonding by the amide group adjacent to the pyridine-*N*-oxide moiety is manifested in binding experiments with both dicarboxylic (adipic) and monocarboxylic (propionic) acids. Three different *N*-oxides have been synthesized and studied to demonstrate this inhibition of hydrogen bonding. This directed inhibition of hydrogen bonding thus allows the disconnection of hydrogen bonds in the recognition of polycarboxylic acid with a polypyridine amide receptor by simple conversion into the *N*-oxide derivative in order to alter the supramolecular structure of the complex. This study is in progress in our laboratory.

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7. *Synthesis of **1** and **2***: Compound **3** (350 mg, 1 mmol) was taken in a round bottomed flask containing glacial acetic acid (3 mL) and hydrogen peroxide (2 mL, 30%). It was stirred for 6 h at 50 °C. With respect to starting material, two more polar spots (products) are generated. Solid $NaHCO_3$ was added slowly and carefully to neutralize the mixture at room temperature, which was then extracted with chloroform. The organic layer was washed with water, dried and purified over silica gel by preparative TLC using 5% methanol in chloroform. Compound **1** was isolated as a white solid (140 mg, 38%, mp 205–206 °C). Compound **2** was obtained from the more polar spot [130 mg, 34%, mp 250°C(d)].
8. The ^{1}H NMR spectrum of compound **3** was found to be identical to that reported earlier.[1b]
*Receptor **1***: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 11.25 (s, 1H), 8.60 (br s, 1H), 8.49 (d, 1H, J = 7.5 Hz), 8.19 (d, 1H, J = 8.1Hz), 8.14 (d, 2H, J = 8.3 Hz), 8.08 (d, 2H, J = 8.3 Hz), 7.68 (t, 1H, J = 7.8 Hz), 7.32 (t, 1H, J = 8.1 Hz), 7.04 (d, 1H, J = 7.0 Hz), 6.97 (d, 1H, J = 7.4 Hz), 2.62 (s, 3H), 2.50 (s, 3H). ESIMS; *m/z* (%) 725.4 ($2MH^+$, 7.3), 363.3 (MH^+, 100), 271.1 (9.1), 239.1 (20). Anal. Calcd for $C_{20}H_{18}N_4O_3$: C, 66.29: H, 5.01: N, 15.46%. Found C, 66.31: H, 4.96: N, 15.46%. *Complex (1:1) of receptor **1** with adipic acid*: ^{1}H NMR ($CDCl_3$, 500 MHz): 11.14 (br s, 1H), 10.93 (br s, 1H), 8.56 (d, 1H, J = 7.5 Hz), 8.36 (d, 1H, J = 8.4 Hz), 8.24 (q, 4H, J = 8.1 Hz), 7.74 (t, 1H, J = 7.9 Hz), 7.45 (t, 1H, J = 8.1 Hz), 7.07 (d, 1H, J = 7.6 Hz), 6.97 (d, 1H, J = 7.4 Hz), 2.65 (s, 4H), 2.63 (s, 3H), 2.49 (s, 3H), 2.40 (s, 4H). *Complex (1:1) of receptor **1** with propionic acid*: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 11.22 (br s, 1H), 10.07 (br s, 1H), 8.51 (d, 1H, J = 8.2 Hz), 8.30 (d, 1H, J = 8.3 Hz), 8.18 (d, 1H, J = 8.2 Hz), 8.14 (d, 1H, J = 8.3 Hz), 7.74 (t, 1H, J = 7.9 Hz), 7.34 (t, 1H, J = 8.1 Hz), 7.04 (d, 1H, J = 7.7 Hz), 6.99 (d, 1H, J = 7.4 Hz), 2.62 (s, 3H), 2.52 (s, 3H), 2.38 (d, 2H, J = 7.5 Hz), 1.16 (t, 3H, J = 7.5 Hz). *Compound **2***: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.19 (br s, 2H), 8.44 (d, 2H, J = 8.7 Hz), 8.09 (s, 4H), 7.26 (t, 2H, J = 8.1 Hz), 6.98 (d, 2H, J = 6.6 Hz), 2.55 (s, 6H). ESIMS; *m/z* (%) 757.4 ($2MH^+$, 16), 706.4 (3.3), 379.4 (MH^+, 100), 328.6 (6), 255.1 (10.6). Anal Calcd for $C_{20}H_{18}N_4O_4$: C, 63.48: H, 4.76: N, 14.81%. Found C, 63.50: H, 4.75: N, 14.82 %. *Complex (1:1) of compound **2** with adipic acid*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.13 (br s, 2H), 8.44 (d, 2H, J = 8.4 Hz,), 8.14 (s, 4H), 7.28 (t, 2H, J = 7.5 Hz), 6.99 (d, 2H, J = 7.8 Hz), 2.55 (s, 6H). *Compound **5***: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.17 (br s, 1H), 8.34 (d, 1H, J = 7.7 Hz), 7.28 (t, 1H, J = 6.5 Hz), 6.99 (d, 1H, J = 6.5 Hz), 2.59 (s, 3H), 2.31 (s, 3H). *Complex (1:1) of compound **5** with adipic acid:* ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.21 (br s, 1H), 8.36 (br s, 1H), 7.20 (br s, 1H), 7.01 (br s, 1H), 2.66 (s, 3H), 2.33 (s, 3H).
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