NMR Study of the Amide Bond-formation Using a Heterocyclic Amine and Acid Receptor

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Recently, a tricyclic receptor capable of binding a carboxylic acid or an amine has been described. A kinetic study of the reaction between benzoic acid and benzylamine to give the amide bond using this heterocyclic receptor has been performed. The results suggest that the receptor plays a significant role in accelerating the amide bond-formation. To gain further information on the complex formation between the host, benzoic acid and benzylamine, NOESY and T-ROESY experiments were performed.

A long-term aim for the organic chemists is to design and prepare artificial receptors capable of catalyzing reactions for their study or use in organic synthesis.[1] For several years, our research group has been interested in the synthesis of carboxylic acids and amines receptors.[2] In a previous paper,[2e] we described the design and synthesis of a new heterocyclic receptor **1** capable of binding with acids or amines according to a 1/1 stoichiometry and good values for the association constants were obtained. Some NMR experiments associated with molecular modeling were performed to emphasize the binary complexation of the receptor either with acids or amines. The present study is a part of an extensive research work on the design of a receptor capable of promoting within a supramolecular process, the reaction between an amine and a carboxylic acid to create an amide bond. In this article, both the efficiency of the designed receptor in the amide bond-formation and the actual ternary host–guests interactions will be discussed by using NMR spectroscopy experiments.

To investigate the amide bond-formation, we decided to carry on our research work[3,5] in $CDCl_3$ at 293 K with benzoic acid (**2**) and benzylamine (**3**) as reactants to lead to *N*-benzylbenzamide (**4**). First, it was necessary to confirm that this increasing

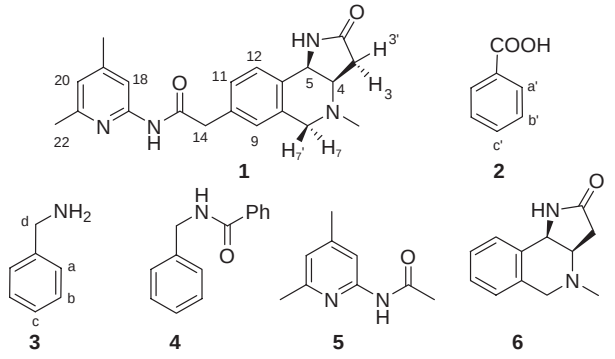

Figure 1. Heterocyclic receptor **1**, substrates **2** and **3**, product **4** and components parts **5** and **6** of the heterocyclic receptor **1**.

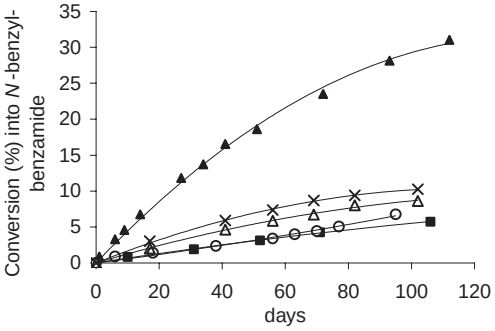

Figure 2. Plots of the conversion into *N*-benzyl-benzamide (**4**) determined by 1D ^{1}H NMR ($CDCl_3$, 400.13 MHz) in the presence of **1** (▲), **5** (○), **6** (×), **5** + **6** (△) and with no host (■) at 293 K.

of the reaction rate is the result of a molecular recognition process arising from the whole host **1** and not only from a general catalysis effect coming from a part of it. We accomplished three kinetic experiments with fragments **5**[6] and **6** (Figure 1) of the heterocyclic receptor **1** in addition to those done with the complete host **1** and without it. The results giving the conversion into the amide after 80 days (Figure 2) clearly shows that the whole host **1** is responsible for the improvement observed in the amide bond-formation. Only weak to moderate effects were observed with compounds **5** or **6** and an equimolar mixture of fragments **5** and **6**. Thus, the conversion rate into *N*-benzylbenzamide (**4**) via the activated pathway with host **1** is about 5.5 times higher than that of the unactivated pathway.

It was now essential to prove the existing interactions of both benzoic acid (**2**) and benzylamine (**3**) with the host **1**. After 80 days of reaction, the sample was first cooled down by step of 10 to 235 K and 1D ^{1}H, 2D NOESY, T–ROESY[5,7,8] experiments were recorded. For the lower temperature, the line width of many signals is increased (Figure 4). This property is commonly interpreted as the result of a slowing down of the molecular movements (increase of τ_c). The fact that signals of both **1**, benzoic acid (**2**) and benzylamine (**3**) become broad whereas the signals of the *N*-benzylbenzamide (**4**) do not change significantly, seems to indicate that molecules of acid **2** and amine **3** are bound to the receptor whereas the amide **4** formed is ejected from the host **1** (as in catalytic cycle conditions) and is present free in solution. This observation is supported by the negative NOE cross signals of the *N*-benzylbenzamide (**4**) ($\omega\tau_c \ll 1$), indicating fast movement, comparatively to the positive NOE cross signals ($\omega\tau_c \gg 1$), indicating slow down movement, observed for the other protagonists (Figure 3, left). Finally, we also conducted NOESY and T-ROESY experiments on a sample at 280 K after only 8 days of reaction (Figure 3, middle and right). In this case

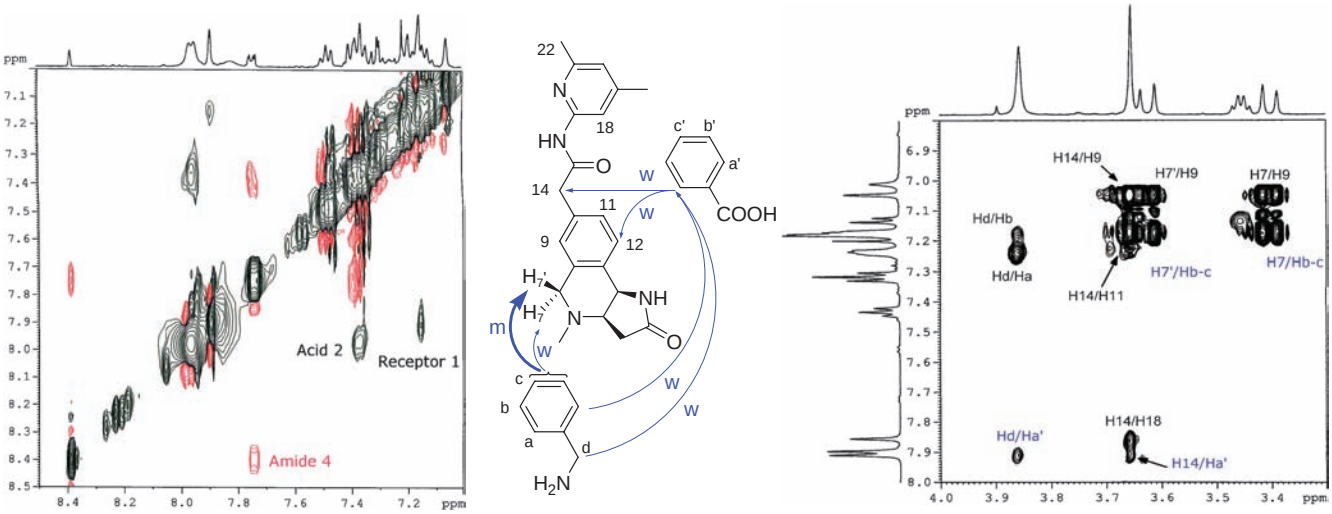

Figure 3. Left: example of the aromatic part of a 2D NOESY experiment with **1**, **2**, and **3** conducted at 248 K after 80 days of reaction (red: negative cross signals; black: positive cross signals; $CDCl_3$, 600.13 MHz). Middle and right: example of a 2D NOESY experiment with **1**, **2**, and **3** conducted at 280 K after 8 days of reaction ($CDCl_3$, 600.13 MHz).

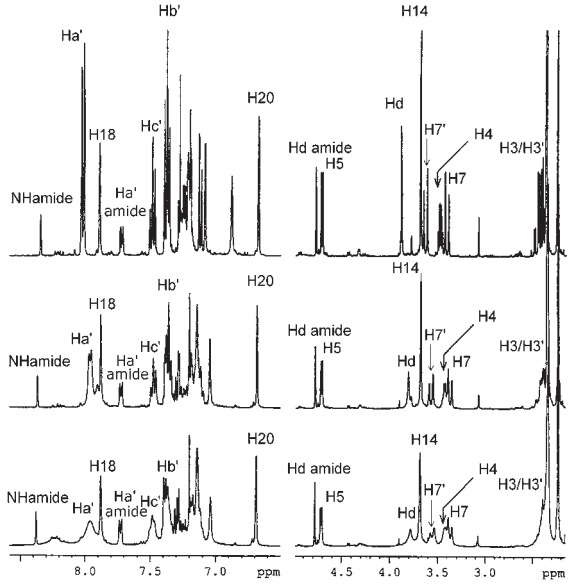

Figure 4. 1D ^{1}H NMR ($CDCl_3$, 400.13 MHz) obtained at 298 K (top), 280 K (middle), and 235 K (bottom) after 80 days of reaction.

all signals were in the $\omega\tau_c \ll 1$ domain and few intermolecular dipolar interactions between amine **3**, acid **2**, and the hetero cyclic receptor **1** were observed.

In a previous reported study,[2e] with host **1** and individual guests, we showed a spatial relationship between benzoic acid (**2**) and both H_{14} and H_{22} of the acetamidopyridine moiety of the receptor **1**. In the present case, when benzoic acid (**2**) is together with host **1** and benzylamine (**3**), the interactions are rather with H_{14} and H_{12}. These findings assume that this time, benzoic acid (**2**) is closed to both the tricyclic part of the receptor and so, to the benzylamine (**3**). The intermolecular NOE also confirmed the closeness between benzoic acid (**2**) and benzylamine (**3**) themselves ($H_{a'}$ and $H_{a,d}$). It must be pointed out that, to explain these interactions, the distance between benzylamine (**3**) and benzoic acid (**2**) must be less than 5 Å and that both the association constant of the ternary complex is sufficient and the exchange process is slow enough to detect the NOE effects. So, the NMR study is in accordance with the kinetic study in which we show that the heterocyclic receptor plays a role by increasing the rate of the amide bond-formation.

References and Notes

1 See for example: J. H. Hartley, T. D. James, and C. J. Ward, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3155.
2 a) P. Charpentier, J.-F. Brière, G. Dupas, G. Quéguiner, and J. Bourguignon, *Tetrahedron*, **52**, 10441 (1996). b) J.-F. Brière, P. Charpentier, G. Dupas, G. Quéguiner, and J. Bourguignon, *Tetrahedron*, **53**, 2075 (1997). c) J.-F. Brière, G. Dupas, G. Quéguiner, and J. Bourguignon, *Heterocycles*, **52**, 1371 (2000). d) G. Moore, V. Levacher, J. Bourguignon, and G. Dupas, *Tetrahedron Lett.*, **42**, 261 (2001). e) J.-F. Brière, G. Dupas, G. Quéguiner, and J. Bourguignon, *Tetrahedron*, **56**, 8679 (2000).
3 To obtain reliable integrations, the ^{1}H spin–lattice relaxation times (T_1) were estimated using inversion–recovery experiment.[4] Then, the relaxation delay as well as the pulse angle were respectively fixed to 5 s and 70° and known concentration of an external reference substance was used (1,2-dichloroethane). All spectra were recorded in $CDCl_3$ (spectroscopic grade) with a sample of 14.7 mM of **1** (or **5** and/or **6**), a starting concentration of 15.1 mM of benzoic acid and 14.7 mM of benzylamine.
4 J. Kowalewski, G. C. Levy, L. F. Johnson, and L. Palmer, *J. Magn. Reson.*, **26**, 533 (1977).
5 NMR measurements were carried out on a BRUKER ARX 400 spectrometer for 1D experiments equipped with a 5 mm QNP ^{1}H/^{13}C/^{31}P/^{19}F probe interfaced to an Silicon Graphics INDIGO2 workstation or a BRUKER AVANCE DMX 600 spectrometer for 2D experiments equipped with a 5 mm *xyz*-shielded gradient TXI ^{1}H/^{13}C-^{15}N probe interfaced to a Silicon Graphics O2 workstation.
6 R.-P. Mariella and E.-P. Becher, *J. Am. Chem. Soc.*, **74**, 1916 (1952).
7 D. Neuhaus and M. P. Williamson, in "The Nuclear Overhauser Effect in Structural and Conformational Analysis," 2nd ed., Wiley-VCH, Chichester (2000).
8 NOESY and T-ROESY (with TOCSY suppression) were used concomitantly to crosscheck for peaks resulting from coherent or mixed magnetization transfer or loss of NOE information in $\omega\tau_c = 1$ domain. Several NOESY spectra with different mixing times (τ_m) in the range of T_1 were acquired for drawing NOE build-up curve of the interprotons cross-peaks. Then all NOESY and T-ROESY experiments were performed with a mixing time in the linear part of the NOE build-up ($\tau_m = 800$ ms).

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