Pergamon

Tetrahedron Letters, Vol. 37, No. 38, pp. 6947-6950, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01524-9

Catalysis of Nucleophilic Addition of Pyrrolidine to 2-(5*H*)-Furanone through Chromenone Cleft-Type Receptors

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Abstract: Several H-bonding receptors are shown to significantly catalyze the nucleophilic addition of pyrrolidine to 2-(5*H*)-furanone to a significant extent. Combination of these receptors with a sulfonamide group affords a further increase in the catalytic effect of these molecules.

Hydrogen bonds are able to catalyze organic reactions[1] and, as recently proposed, may be of great importance in enzyme catalysis[2]. Artificial hydrogen bonding receptors are also able to influence the outcome of organic reactions[3], in several cases showing promising catalytic effects[4].

Receptor **1** (Figure 1) can provide three hydrogen bonds[5]; it is however, essentially unable to increase the rate of the nucleophilic addition of pyrrolidine to acrylamide[6]. In an enolate-like transition state, two of the H-bonds in the complex should be stronger due to the presence of a negative charged oxygen atom, but the third one set by the acrylamide NH becomes weaker due to the loss of activation of its carbonyl group. This reduces the gain in energy on passing from the ground to the transition state, diminishing the expected catalytic effect. Moreover, early proton transfer from the pyrrolidine NH to the acrylamide carbonyl may occur during the addition[7], preventing a large build-up of negative charge built up in the carbonyl group, a factor which again reduces the effect of the hydrogen bonds.

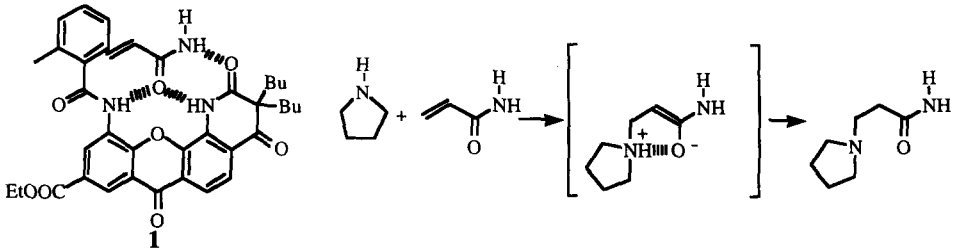


Figure 1: Complex between receptor 1 and acrylamide and the probable reaction path of pyrrolidine and acrylamide.

The complex between receptor **2** and 2-(5*H*)-furanone **3**[8] (Figure 2) does not show these drawbacks in the reaction with pyrrolidine[9]. All three hydrogen bonds in the complex should increase their strength on passing to an enolate-like transition state, while geometric reasons prevent the pyrrolidine from delivering its proton directly to the lactone carbonyl. Accordingly, an improved catalytic effect is expected for receptor **2** with respect to receptor **1**.

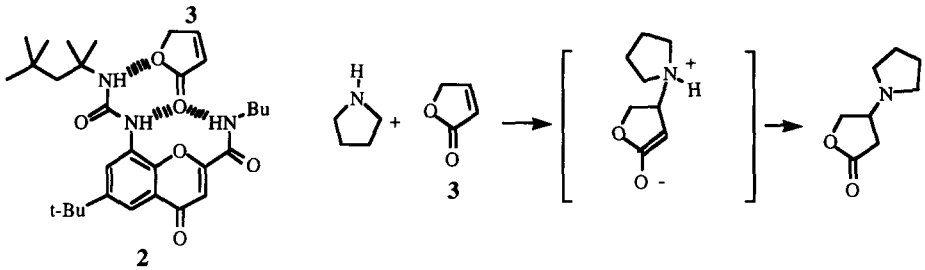


Figure 2: Complex between receptor **2** and lactone **3** and the probable reaction path of pyrrolidine and lactone **3**.

Receptor **2** is indeed able to speed up the addition of pyrrolidine to the butenolide **3** in chloroform. A small amount of this compound (10% mol with respect to lactone **3**) is able to reduce the reaction half life from 380 to 50 minutes (Table 1). Catalysis seems to be related to complex formation because a similar compound **4**, which lacks the amide NH, provides only a small reduction in half life (Table 1). By contrast, no catalytic effect due to receptor **2** is observed in the presence of a highly competitive guest such as tetraethyl ammonium benzoate[10] (Table 1). This receptor, however, does have an important drawback; its association constant with butenolide **3** in chloroform is small, and lactone association is further reduced due to receptor dimerization (Figure 3) ($Kd=1.0x10^2\ M^{-1}$)[8].

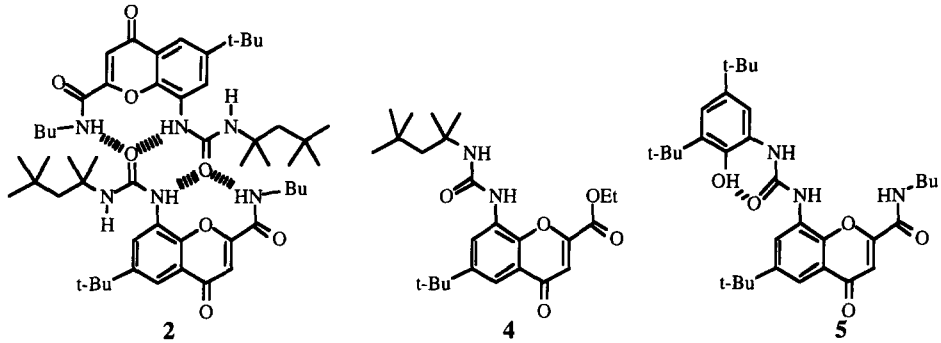


Figure 3: Proposed dimer for receptor **2** and structures for receptors **4** and **5**.

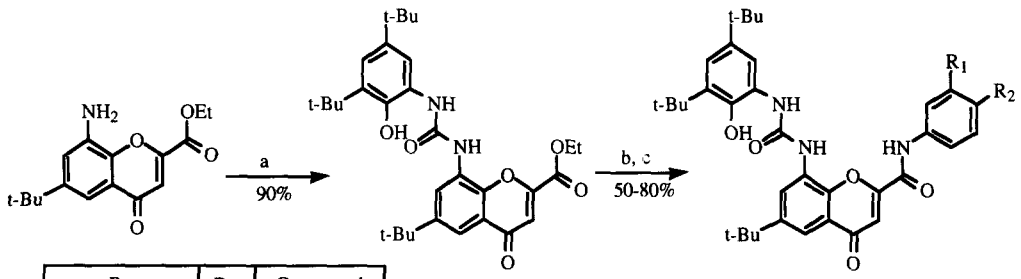
Receptor self-association can be reduced by favoring the right urea conformation with an intramolecular hydrogen bond[8]. Host **5** (Figure 3) has a $Kd = 30\ M^{-1}$. This low value permits measurement of the association constant with butenolide **3** ($Kass = 30\ M^{-1}$). Host **5** should be able to associate a larger amount of lactone **3** in the reaction mixture than the previous compound **2** and should therefore show better activity. In this case, the reaction half-life is reduced to 10 minutes (Table 1).

If H-bonds were responsible for the catalytic effect one would expect more acidic protons to increase the activity of the receptors. Substitution of the butyl chain for a tolyl residue yields host **6** (Figure 4), which leads to a longer half-life (13 minutes) despite the more acidic amide NH. Both the association and dimerization constants are higher in the tolyl derivative, making it difficult to explain the reduction in catalytic activity. A more acidic NH could eventually outweigh small handicaps due to self-association, leading again to more active receptors. This is probably the case of host **7** (Figure 4), which affords a half life of 7 minutes. Unfortunately, this point could not

be confirmed due to the lack of the solubility of this host in chloroform, preventing accurate measurements of Kd and Kass (Table 1).

Receptor	$t_{1/2}$ (min.)	Kass (M^{-1})	Kd (M^{-1})
2	50		$1.0x10^2$
4	320		
5	10	30	30
6	13	83	$1.7x10^2$
7	7		
8	10	72	$1.5x10^2$
9	1.5	71	$2.0x10^3$
10	1.3	67	$1.6x10^3$
TEAB (20%)	110		
TEAB (20%)+**2**	110		
no receptor	380		

Table 1. Association and dimerization constants and catalytic effects of the receptors. (TEAB= Tetraethylammonium benzoate).



R_1	R_2	Compound
H	Me	**6**
H	NO_2	**7**
$CH_2OCH_2OCH_3$	H	**8**
SO_2NEt_2	H	**9**
SO_2NiPr_2	H	**10**

a) Phosgene / 3,5-di-t-butyl-2-hydroxyaniline, b) sodium hydroxide
c) substituted aniline / DCC

Figure 4. Synthesis of receptors **6** to **10**.

The receptors considered so far only interact with the negative charge developed in the butenolide carbonyl group during the reaction. Better catalytic activity is to be expected if the positive pyrrolidine nitrogen is also stabilized in the complex[11]. Host **8** (Figure 4) carries a flexible polyether chain which can lie close to the pyrrolidine nitrogen in the transition state. Both the association and self-association constants are similar to those of host **6**. The activity, however, is only slightly improved ($t_{1/2}$= 10 minutes) (Table 1). Sulfonamides provide better results; in host **9**, this group accounts for a 8 fold increase in catalytic activity with respect to the methyl-substituted ring of host **6**, reducing the reaction half-life to only 1.5 minutes; i.e., 250 times shorter than the uncatalyzed reaction. This result is very promising because lactone association in receptor **9** is strongly handicapped due to the presence of a specially stable dimer (Kd = $2.0x10^3$ M^{-1}). A possible structure for this dimer is shown in figure 5.

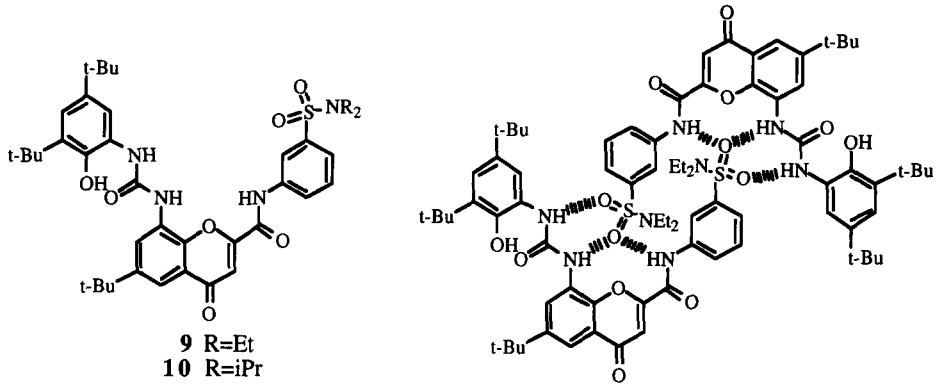


Figure 5. Structure of receptors **9** and **10** and proposed dimer for compound **9**.

CPK molecular models suggest that this dimer would be sensitive to steric hindrance due to the sulfonamide dialkylamino group. However, compound **10**, which includes a diisopropylamine group, has only a small reduction in the dimerization constant (Kd = 1.6×10^3 M^{-1}), the catalytic effect being increased to $t_{1/2}$= 1.3 min. (Table 1). Further attempts to increase the catalytic activity of these receptors are now underway.

Acknowledgments: We thank the "Dirección General de Investigación Científica y Técnica" (DGICYT Grant PB 92-0286) for its support of this work. C. R. also thanks the MEC for a fellowship.

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(*Received in UK* 10 *July* 1996; *revised* 29 *July* 1996; *accepted* 1 *August* 1996)