The Effect of Chromenone Receptors on the Selectivity of the Reaction between Pyrrolidine and 5-Hydroxymethyl-2-(5*H*)-furanone

César Raposo, Marta Almaraz, Mercedes Martín, Victoria Alcázar, Mª Cruz Caballero, and Joaquín R. Morán
Depto. de Química Orgánica, Universidad de Salamanca, Plaza de los Caídos 1-5, E-37008, Salamanca, Spain

(Received October 7, 1996)

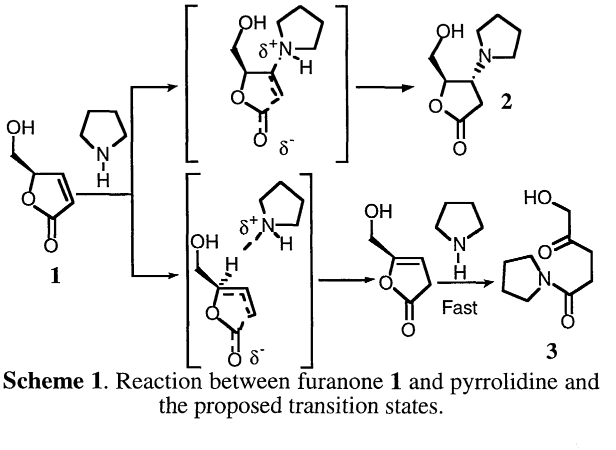
Several chromenone-based receptors have been prepared. Despite the self-association of these hosts in $CDCl_3$ they are able to bind hydroxymethylfuranones with a Kass of around 1000 M^{-1}.

These compounds are able to accelerate the rate of the reaction of butenolide with pyrrolidine together with the increase of the selectivity.

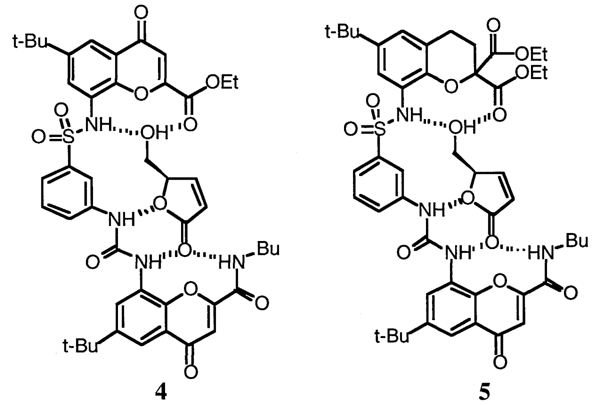
A major drawback of organic reactions is their lack of selectivity and therefore the low yield in which the target product is obtained. The success of enzymes lies not only in their strong catalytic activity but also in the dramatic effect they induce in the selectivity of organic procedures. This kind of effect is also desirable in artificial receptors.[1-4] One reaction amenable to this kind of study takes place between pyrrolidine and 5-hydroxymethyl-2-(5*H*)-furanone **1**. Two products are obtained from this reaction: the conventional nucleophilic adduct **2**[5] and the amide **3** (Scheme 1), which is probably produced through the well-known rearrangement of the double bond[6] and aminolysis of the vinyl ester.[7] Moreover furanone **1** is readily associated with chromenone based receptors,[8] providing a system to study the influence of complex formation in the rate and selectivity of its reaction with pyrrolidine.

The previously published receptor **4** is not, however, suitable for this work due to the high acidity of its sulfonamide proton, which is readily lost in the presence of pyrrolidine. A second receptor **5** (mp= 180°C), in which the acidity of the sulfonamide NH is reduced through substitution of the chromenone moiety by a chromane ring with less electron-withdrawing potential, does not show this drawback (Scheme 2).

Like other chromenone receptors, compound **5** is partially dimerized in $CDCl_3$ solutions.[8] Its Kd can be easily measured at 20°C and shows a value of 2.2×10^2 M^{-1}. Once the self-association is known, the association constant with the butenolide **1** can be calculated as Kass=8.8×10^2 M^{-1}. As expected, these two values are lower than those corresponding to receptor **4** (Kass=6.7×10^3 M^{-1}) owing to the weaker sulfonamide H-bond and the higher mobility of the receptor **5** chromane esters. Nevertheless, the association properties of receptor **5** are in the right range to complex butenolide **1**. Receptor **5** therefore was chosen for a kinetic study.



Scheme 1. Reaction between furanone **1** and pyrrolidine and the proposed transition states.



Scheme 2. Receptors **4** and **5** and their complexes with 5-hydroxymethyl-2-(5*H*)-furanone.

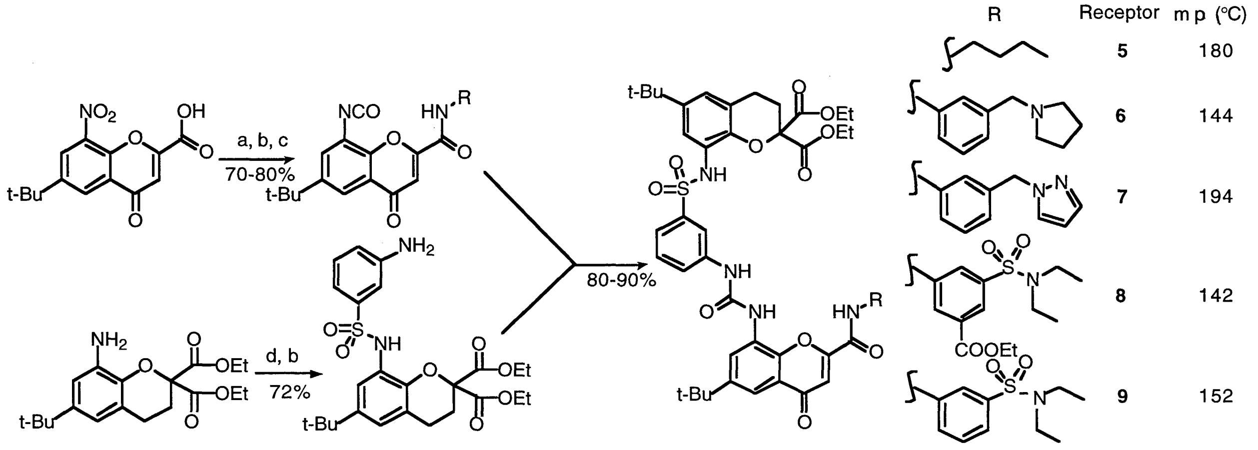
Reactions were carried out in $CDCl_3$ solutions at 20 °C containing 0.1 M pyrrolidine, 0.05 M furanone **1** in the presence or absence of 0.005 M receptor **5**. The butenolide half-life was measured by ^1H NMR integration of furanone signals, showing that receptor **5** exerts a significant catalytic effect. The formation of both pyrrolidine adducts **2** and **3** is accelerated by receptor **5**; however, catalysis in the formation of the 1,4-addition product is more efficient than the lactone aperture. For an enolate-like mechanism, as proposed in Scheme 1, the catalytic effect of receptor **5** can be explained in terms of stronger hydrogen bonds in the transition state complex,[9-11] due to the negative charge developed in the carbonyl oxygens. This is expected for both reaction pathways, and indeed the speed of formation of compounds **2** and **3** increases (Table 1).

Better results are expected for receptors in which not only the negative carbonyl group but also the positive charge developed on the pyrrolidine nitrogen are stabilized.[12-14] Four receptors were therefore prepared in which non-bonding electron pairs were placed in the complex close to the incoming nucleophile in the 1,4 addition pathway.

Additional catalytic groups in receptors **6** (mp= 194°C) and **7** (mp= 144°C) include a pyrazole and a pyrrolidine respectively. The pyrazole receptor **6** showed the expected dimer formation constant and butenolide association in the same range as receptor **5**. Accurate constants cannot be easily measured for the pyrrolidine receptor **7** due to broad signals in its ^1H NMR spectrum. However, the values are probably similar to those of

Table 1. Kass and kinetic results for receptors **5** to **9**

Receptor	Kd (M^{-1})	Kass (M^{-1})	$t_{1/2}$ (min)	Ratio **2/3**
			300	2.8
5	$2 \times 2 \times 10^2$	8.8×10^2	51	9
6	3.7×10^2	7.7×10^2	25	15
7			32	15
8	4.5×10^3	1.3x103	22	15
9	5.5×10^2	1.2×10^3	13	18



a) Pivaloyl chloride / triethylamine / RNH$_2$, b) Tin (II) chloride, c) Phosgene, d) 3-nitrobenzenesulfonyl chloride

Scheme 3. Synthesis of receptors **5** to **9**.

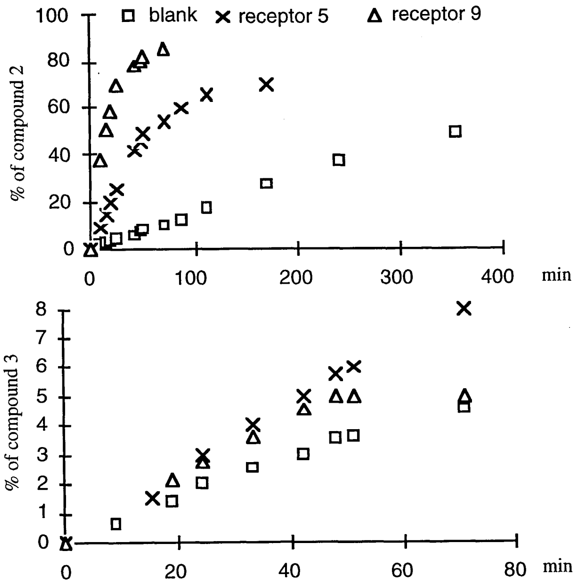


Figure 1. Kinetic plot for the production of compound **2** (top) and **3** (bottom) in the presence of receptors **5** and **9**.

receptors **5** and **6**.

Kinetic studies with these receptors afford better catalytic properties than for receptor **5**, the effect is only moderate.

Better results are obtained from non-bonding electrons of sulfonamide oxygens. This is the case of receptors **8** (mp= 142°C) and **9**[15], in which a 10% molar amount reduces the butenolide half-life to 22 and 13 min., respectively. Surprisingly, the presence of the ethoxycarbonyl group in compound **8** decreases its catalytic efficiency. This group apparently favors the formation of a stronger dimer which handicaps the lactone association, thus reducing catalytic activity under the reaction conditions. The sulfonamide group also increases the dimerization, although to a lesser extent, which is also compensated by a larger association constant with the butenolide (Table 1). To confirm that the complex is the active species, an experiment in the presence of 20% tetraethylammonium benzoate was carried out. Essentially the catalytic activity of receptor **9** was inhibited ($t_{1/2}$=180 min). The reaction half-life reduction is due to the presence of the carboxylate which shows a small catalytic activity itself ($t_{1/2}$=190 min).

The most interesting effect of the sulfonamide **9** lies in its reaction selectivity.[16,17] Essentially the decrease in the lactone half life-due to the sulfonamide can be attributed only to pyrrolidine nucleophilic addition, while butenolide rearrangement is not catalyzed by this group (Figure 1). Whereas the receptor hydrogen bonds should stabilize the negatively-charged transition states of both reaction pathways, the geometry of receptor **9** places the sulfonamide group close to the incoming pyrrolidine but far away from the γ-proton. The sulfonamide non-bonding electron can therefore only favor the nucleophilic addition step.

We thank the "Dirección General de Investigación Científica y Técnica" (DGICYT Grant PB 95-0951A) for its support of this work. C. R. also thanks the MEC for a fellowship and Anna Lithgow for the 400 MHz NMR titrations.

References and notes

1 R. Breslow and A. Graff, *J. Am. Chem. Soc.*, **115**, 10988 (1993).
2 S. W. Tam-Chang, L. Jimenez, and F. Diederich, *Helv. Chim. Acta*, **76**, 2616 (1993).
3 P. J. Smith, E. Kim, and C. S. Wilcox, *Angew. Chem., Int . Ed. Engl.*, **32**, 1648 (1993).
4 J. Wolfe, A. Muehldorf, and J. Rebek Jr, *J. Am. Chem. Soc.*, **113**, 1453 (1991).
5 K. Tomioka, T. Ishiguro, Y. Iitaka, and K. Koga, *Tetrahedron*, **40**, 1303 (1984).
6 K. Nakanishi, in "Natural Products Chemistry," ed by K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, Kodansha Scientific, Tokyo (1974), Vol. 1, Chap. 6, p 462.
7 J. B. Jones and J. M. Young, *Can. J. Chem.*, **44**, 1059 (1966).
8 C. Raposo, M. Almaraz, N. Pérez, M. Martín, V. Weinrich, M. Grande, M. C. Caballero, and J. R. Morán, *Tetrahedron Lett.*, **37**, 1485 (1996).
9 J. Wolfe, D. Nemeth, A. Costero, and J. Rebek Jr., *J. Am. Chem. Soc.*, **110**, 983 (1988).
10 V. Jubian, R. P. Dixon, and A. D. Hamilton, *J. Am. Chem. Soc.*, **114**, 1120 (1992).
11 J. Smith, K. Ariga, and E. V. Anslyn, *J. Am. Chem. Soc.*, **115**, 362 (1993).
12 R. Breslow, A. W. Czarnik, M. Lauer, R. Leppkes, J. Winkler, and S. Zimmerman, *J. Am. Chem. Soc.*, **108**, 1969 (1986).
13 V. Jubian, A. Veronese, R. P. Dixon, and A. D. Hamilton, *Angew. Chem., Int. Ed. Engl.*, **34**, 1237 (1995).
14 F. M. Menger and A. C. Vitale, *J. Am. Chem. Soc.*, **95**, 4931 (1973).
15 mp=152°C, ^{1}H NMR δ (ppm), J (Hz): 8.50 (d, 1H, J=2.2), 8.16 (s, 1H), 7.90 (d, 1H, J=8.0), 7.82 (d, 1H, J=2.2), 7.5-7.4 (m, 2H), 7.47 (d, 1H, J=8.0), 7.35 (d, 1H, J=2.4), 7.4-7.2 (m, 4H), 6.69 (d, 1H, J=2.4), 4.18 (c, 4H, J=7.0), 3.20 (c, 4H, J=7.0), 2.60 (t, 2H, J=6.6), 2.23 (t, 2H, J=6.6), 1.36 (s, 9H), 1.16 (t, 6H, J=7.0), 1.15 (s, 9H), 1.08 (t, 6H, J=7.0).
16 D. P. Curran and L. Kuo, *J. Org. Chem.*, **59**, 3259 (1994).
17 D. P. Curran and L. Kuo, *Tetrahedron Lett.*, **36**, 6647 (1995).