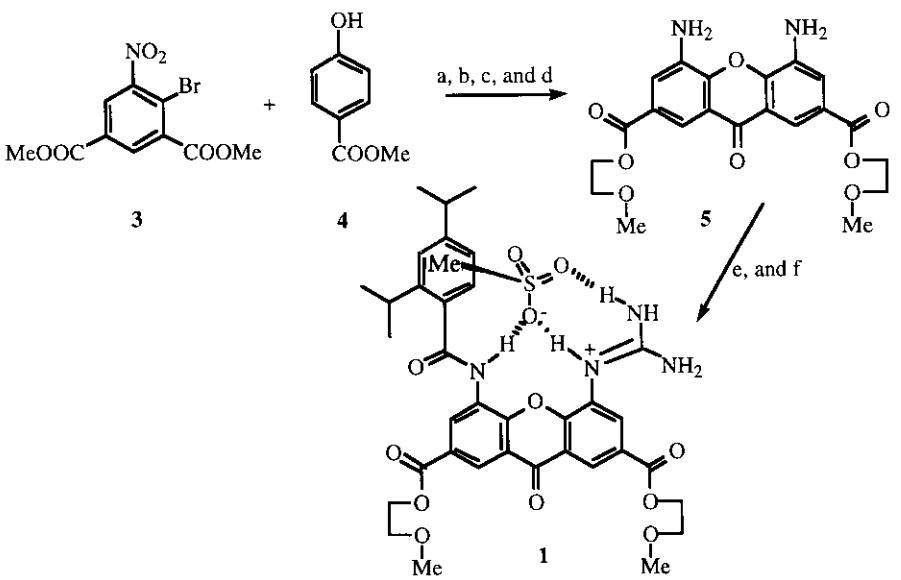
XANTHONE RECEPTORS FOR CARBOXYLIC ACIDS AND CARBOXYLATES

Mercedes Martín, Marta Almaraz, José V. Hernández, Antonio Tejeda, Mª Cruz Caballero, and Joaquín R. Morán*

Departamento de Química Orgánica, Universidad de Salamanca Plaza de los Caídos, 37008 Salamanca, Spain

Abstract- Large association constants have been obtained in $CDCl_3$ for carboxylic acids and a xanthone receptor linked to a guanidine. Protonation of the guanidine with carboxylic acids has been studied in DMSO. Association of the guanidine receptor and monochloroacetic acid may be observed in this highly competitive solvent.

Guanidiniums are very suitable receptors for carboxylic acids.[1] Two strong hydrogen bonds and electrostatic interactions favour complex formation. In order to further improve association, receptor (**1**) (Scheme 1) includes a third H-bond from the xanthone NH and possible stacking interactions with the diisopropylbenzoate residue. The synthesis of this receptor is outlined in Scheme 1.



a: K_2CO_3/DMF/Δ (98%); b: 1) H_2SO_4/140ºC, 2) HNO_3/80ºC (95%); c: methoxyethanol/H_2SO_4 (95%); d: $SnCl_2$/EtOH (83%); e: 2,4-diisopropylbenzoyl chloride (48%); f: cyanamide/methanesulfonic acid (32%)

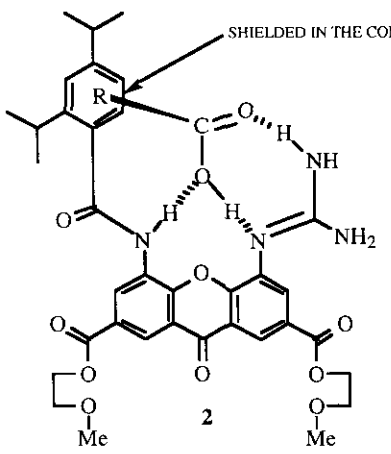
Scheme 1

The ^1H NMR spectrum of compound (**1**) in $CDCl_3$ shows the methyl group of the methanesulfonate strongly shielded, that is in good agreement with the proposed geometry, in which this methyl group may lie in the shielding cone of the diisopropylbenzoate residue.

Addition of tetramethylammonium acetate (a better guest than the sulfonate) to the NMR tube leads to a large shift of the methanesulfonate signal, ending in the expected chemical shift for the free compound. However, attempts to titrate tetramethylammonium acetate in $CDCl_3$ with receptor (**1**) did not afford the expected pattern for movement of the acetate methyl group. At the beginning of the titration, shielding is observed (from 2.08 ppm to 1.55 ppm) but in a later stage a down field shift takes place (from 1.55 ppm to 1.85 ppm). Attempts to titrate other carboxylates in DMSO with the same receptor yielded downfield shifts instead of the expected shielding of the carboxylate α groups. These results are in agreement with a proton transfer from the guanidinium to the carboxylate. No complex is formed in DMSO between the neutral species, because the final chemical shifts of all guests correspond well to those of the carboxylic acids in DMSO.

A further clue pointing to the acidity of guanidinium (**1**) is that the neutral guanidine (**2**) can be obtained by washing the ethyl acetate solution with aqueous sodium hydrogencarbonate.

Even though no complex formation is expected for conventional carboxylic acids in DMSO, CPK models show that structure (**2**) may be a very suitable receptor for them (Figure 1). As in the case of Hamilton amidopiridine receptors,[2] the basicity of the nitrogen atoms may strongly favour association with the acidic carboxylate hydrogen. In a less competitive solvent such as $CDCl_3$ association takes place with decanoic acid with a K_{ass}= $6x10^4$ M^{-1}. In this case the expected shielding of the methylene group does take place (from 2.26 to 1.55 ppm).



K_{ass} (M^{-1})		Guest		δ-free	δ-complex
$1.4x10^9$		dichloroacetic		5.98	4.52
	22				
$6.5x10^7$		chloroacetic		4.14	2.66
			15		
$4.3x10^6$		thiophenylacetic		3.69	2.34
	8.5				
$5.1x10^5$		diphenylacetic		5.08	4.6
			2.6		
$2.0x10^5$		toluic	8.5	2.43	2.13
	3.3				
$6.0x10^4$		decanoic		2.26	1.55

Figure 1: Proposed structures for the guanidinium (**2**) complex and K_{ass} values in $CDCl_3$ based on the competitive method of Whitlock[5]

If the acidity of the guest matches that of the guanidine, a very strong hydrogen bond should arise. Under these conditions the complex formation constant may be of interest to current discussion about the impact of low barrier hydrogen bonds[3] in enzyme catalysis. Therefore, the association constants of several acids of increasing pK_{as}[4] were measured by means of a competitive scale.[5] The results are shown in Figure 1. More than a thousand fold increase were observed on passing from decanoic acid (pK_a= 4.9) to monocloroacetic acid (pK_a= 2.86).

To rule out the possibility that proton transfer might be interfering in the K_{ass} measurement, a study of the UV spectra of receptor (**2**) was undertaken. To reduce complex formation, which could complicate data interpretation, DMSO was used as the solvent. Because a solvent with a high dielectric constant would favour proton[6] transfer between neutral compound, if no such transfer is observed in DMSO, it would not be expected to occur in $CDCl_3$ either.

The UV spectra of both the methanesulfonate and the trifluoroacetate of receptor (**2**) in DMSO overlap, showing bands at 278 nm and 305, 347nm. The neutral guanidine (**2**) shows a different spectrum with a intense band at 285 nm followed by others of lower intensity which are not resolved and fill the gap up to 400 nm. A terminal absorption leaves a yellow colour in the neutral compound which vanishes upon protonation. While acetic or decanoic acids yield no change in the UV spectra of receptor (**2**), and whereas dichloroacetic acid leads to the protonated guanidine, the addition of 1.5 equivalents of monochloroacetic acid ($2x10^{-3}$ M) affords a spectrum which is similar to that of the protonated species but not superimposable. Larger amounts of monochloroacetic acid (5 eq.) do not further change the spectrum. In our opinion, this could be due to complex formation. Indeed, titration of receptor (**2**) with monochloroacetic acid in DMSO furnishes a Kass=$1.8x10^4$ M^{-1}. The shifts for the receptor aromatic protons are shown in Table 1. Strong deshielding is observed for proton H6 ($\Delta\delta$ = 0.53 ppm) adjacent to the guanidine group. When saturation is reached, the addition of either dichloro or trichloroacetic acid further shifts proton 6, in agreement with the final guanidinium protonation (Table 1).

Protons	Free Receptor (ppm)	Receptor (**2**) + chloroacetic acid	Receptor (**2**) + dichloroacetic acid
H1	8.54	8.54	8.70
H3	8.87	9.10	8.80
H6	7.75	8.28	8.35
H8	8.24	8.54	8.60
H9	7.74	7.44	7.50
H10	7.29	7.16	7.22
H11	7.33	7.30	7.32

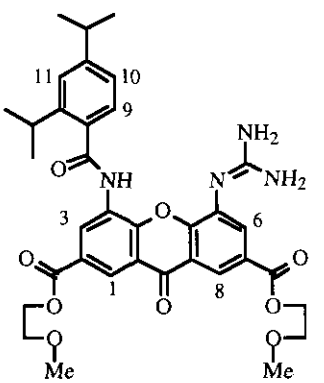


Table 1: Aromatic proton shifts in DMSO (c= $2x10^{-3}$ M)

We therefore believe that monochloroacetic acid associates with receptor (**2**) in a very competitive solvent such as DMSO and that, under these conditions, small differences in the acid pK_a may yield to large changes in the association constants.

Another interesting aspect about receptor (**2**) is the fact that it should not be able to associate primary amides. Carboxylic acids and amides have similar geometries, and most receptors discriminate poorly between them.[6] In compound (**2**) steric hindrance should arise between the NHs in the case of an amide guest, as shown in Figure 2.

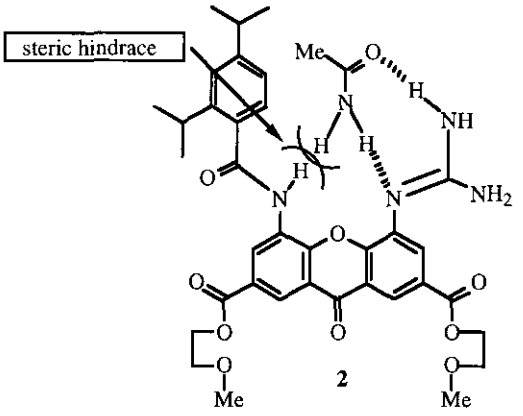


Figure 2: Steric hindrance between NHs of acetamide and receptor (**2**)

To check this hypothesis, acetamide was added to a 10^{-3} M solution of receptor (**2**) in $CDCl_3$. No complex formation could be detected as judged from the ^1H NMR shifts under these conditions.

ACKNOWLEDGEMENTS

We thank the " Dirección General de Investigación Científica y Técnica" (DGICYT Grant PB 95-0951) for its support of this work. Anna Lithgow is thanked for conducting the 400 MHz NMR experiments and the MEC is acknowledged for a fellowship (M. A.).

REFERENCES

1. A. Galán, A. Andreu, A. M. Echevarren, P. Prados, and J. de Mendoza, *J. Am. Chem. Soc.*, 1992, **114**,1511; W. Peschke, P. Schiessl, F. P. Schmidtchen, P. Bissinger, and A. Schier, *J. Org. Chem.*, 1995, **60**, 1039.

2. F. García-Tellado, J. Albert, and A. D. Hamilton, *J. Chem. Soc., Chem. Commun.*, 1991, 1761; C. Vicent, E. Fan, and A. D. Hamilton, *Tetrahedron Lett.*, 1992, **33**, 4269.

3. W.W. Cleland and M. M. Kreevoy, Science , 1994, **264**, 1887; P. A. Frey, S. A. Whitt, and J. B. Tobin, *Science* , 1994, **264**, 1927; A. Warshel, A. Papazyan, and P. A. Kollman, *Science* , 1995, **269**, 102; M. Almaraz, M. Martín, J. V. Hernádez, M. C. Caballero, and J. R. Morán, *Tetrahedron Lett.*, 1998, **39**, 1811.

4. N. S. Isaacs," Physical Organic Chemistry", ed. by Longman Scientific & Technical, Singapore, 1995, pp. 238-239.

5. B. J. Whitlock and H. W. Whitlock, *J. Am. Chem. Soc.*, 1990, **112**, 3910.
6. M. Crego, C. Raposo, M. C. Caballero, E. García, J. G. Saez, and J. R. Morán, *Tetrahedron Lett.*, 1992, **33**, 7437.

Received, 8th June, 1998