

## THE AGGREGATION OF 8-FORMYLAMINO-2-CARBOXAMIDOCHROMENONE HETEROCYCLES IN SOLUTION

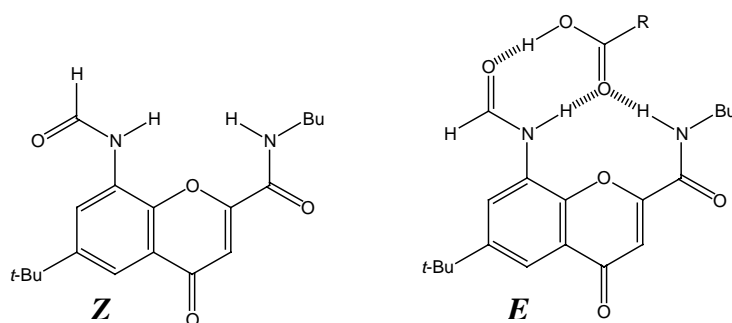
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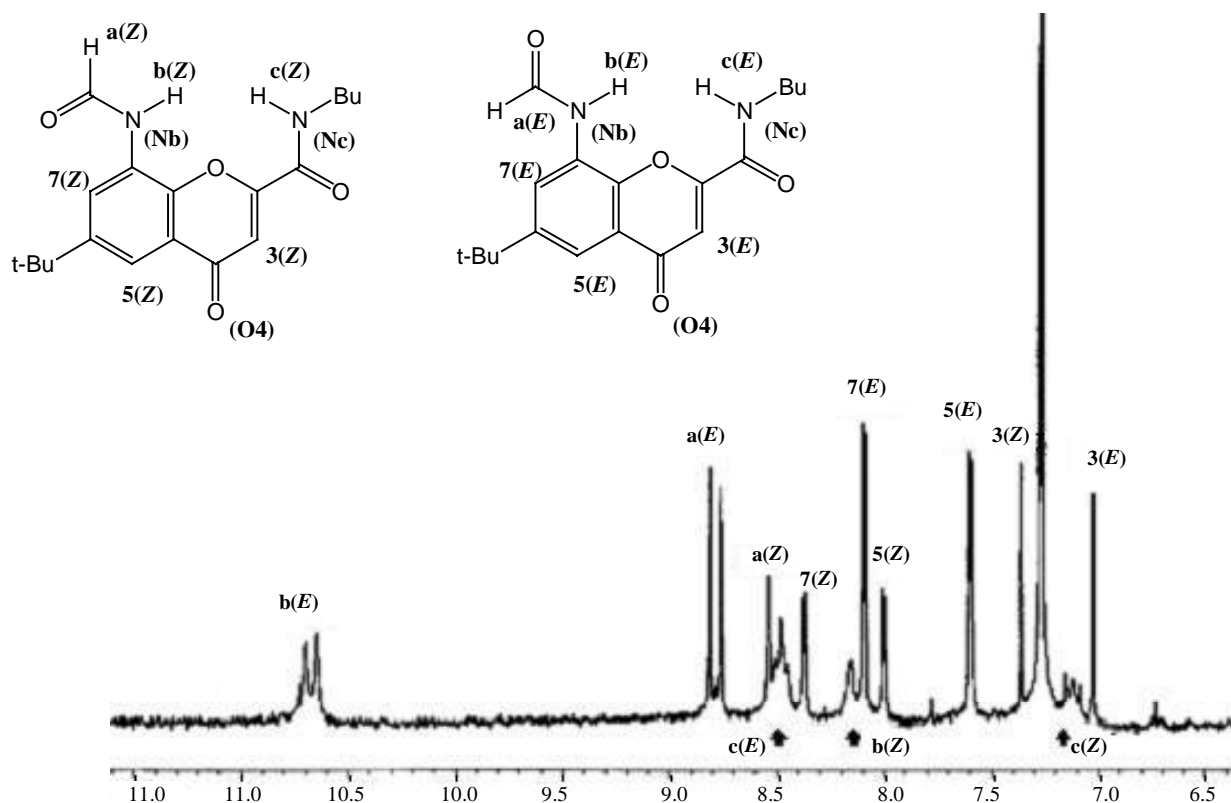
**Abstract** - Formyl-substituted chromenone receptors have been prepared and their self-association process were studied in chloroform solutions. The structure of the aggregates depends on the configuration of the formyl group. The *Z/E* ratio dependence with the molar concentration and X-Ray crystallographic data is used to discuss the structure of the associates.

Association processes are of great importance in biological systems. Artificial receptors<sup>1</sup> based on chromenone heterocycles have been shown to associate carboxylic acids and amides in chloroform solution well.<sup>2</sup> However, conventional titrations, carried out to assess the association constants are tedious and we thought that the use of formamides could be helpful in this respect. Formamides show usually two *E* and *Z* conformations, which can be easily identified in the NMR spectra;<sup>3</sup> receptors in which only one of these conformations fits in the complex should yield a change in the conformer relative proportions, from which it should be easy to deduce the stability of the complex.<sup>4</sup> We expected chromenone receptor (**1**) to meet the above conditions, since only the *E* form can set three hydrogen bonds with a suitable guest like a carboxylic acid (Figure 1).



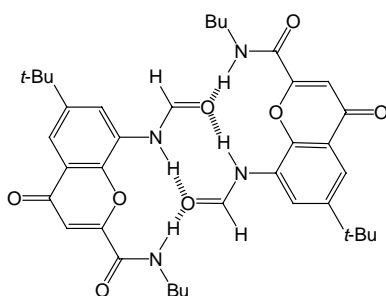
**Figure 1:** *E* and *Z* conformations of receptor (**1**) and the expected complex with a carboxylic acid.

Preparation of compound (**1**) is straightforward from the known aminochromenone<sup>5</sup> and formic acid. In CDCl<sub>3</sub> its NMR spectrum shows the expected signals for the *E/Z* mixture. The large coupling constant (10 Hz) between the *E* formamide proton (8.78 ppm) and the NH proton (10.80 ppm) affords a simple way to recognize these NMR signals; the formamide proton of the *Z* form appears at 8.53 ppm, showing no split due to the NH proton (8.78 ppm) (Figure 2)



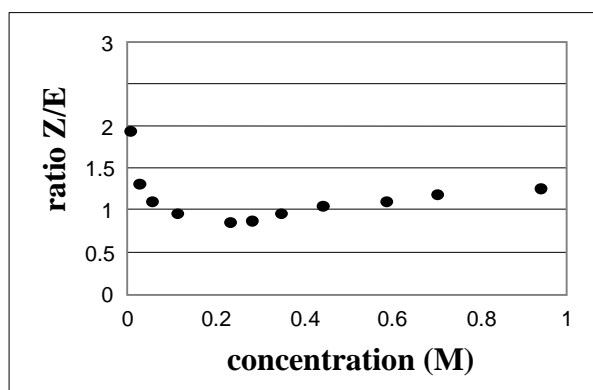
**Figure 2:** NMR spectra of the *E* and *Z* receptors. Total concentration was: 0.004 M.

No shifts in the signals were observed when carboxylic acids (acetic, benzoic, dinitrobenzoic) were added to **1** in chloroform solution, showing that no association was taking place with the chromenone molecule. CPK model inspection revealed that this could well be the case, because the *E* formamide could easily dimerize (Figure 3) into an associate that sets four hydrogen bonds. Since the carboxylic acid alone can provide 3 H-Bonds, the chromenone dimer may be more stable and is the preferred way to obtain association in the solution.<sup>6</sup>



**Figure 3:** Dimer of the *E* formamide forming 4 hydrogen bonds.

An attempt to establish the *E* form dimerization constant, through dilution<sup>7</sup> of compound (**1**) in chloroform, showed that this was probably not the only aggregate in the solution. Dimerization of the *E* form should stabilize this compound with respect to the *Z* conformer. Therefore, at high concentrations, in which a large amount of the *E* dimer was present, we expected a large proportion of this form, while in diluted solutions the more stable *Z* conformation should prevail.<sup>8</sup> While in diluted solutions the behavior of this system was as expected, as the concentration was raised the relative amount of the *E* form revealed a maximum at 0.22 M. After this point an increase in the *Z* form was observed in the NMR spectra until this conformation became the major compound in the spectrum (Figure 4). This result suggests that the *Z* form also aggregates in solutions but that the complex is built up from more than two chromenone molecules.

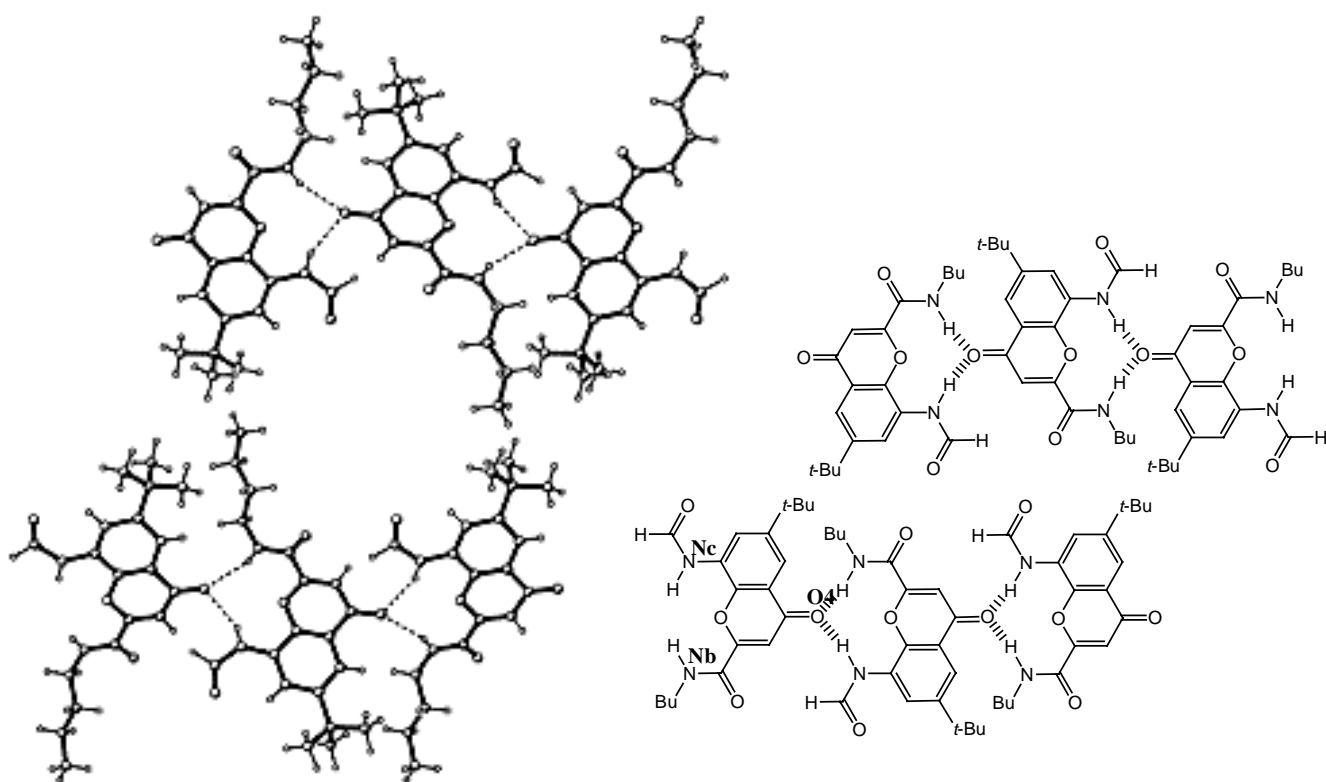


**Figure 4:** Variation of the *Z/E* ratio with the concentration of the receptor. Measurements were performed by integration of the formyl proton signal of the *Z* and *E* forms.

Since from molecular models the geometry of this new associate was not evident, we thought that the crystal structure of compound (**1**) might resemble that of the aggregates of the concentrated solution. Accordingly an X-Ray analysis was undertaken.

Crystallization of compound (**1**) after slow evaporation of a methylene chloride solution yielded yellow crystals suitable for X-Ray analysis.<sup>9</sup>

The solid-state structure of **1** shows only the *Z* conformer, in which neither the formyl nor amide carbonyl group act as hydrogen bond acceptors; this role is played only by the pyrone carbonyl. Other structures that form two H-bonds with carbonyl groups have been described.<sup>10</sup> This structure must therefore be formed by long rows of chromenone units linked to each other by four H-bonds (Figure 5). This kind of aggregation suggests that the associates in the concentrate solutions may be oligomers, consisting of rows of chromenones linked through their pyrone carbonyl groups. From the spectroscopic data, it is clear that the *Z* conformer is the major contributor to this kind of associate. However molecular models do not allowed us to rule out the presence of the *E* form; all these possible equilibria make it specially difficult to accurately measure their thermodynamic constants and the number of molecules of each complex.



**Figure 5:** The crystalline structure of **1**: the molecular packing shows how consecutive molecules of the title compound are connected by intermolecular N-H...O hydrogen bonds forming chains parallel can be observed two interactions: Nb...O4 = 2.98(1) Å, and Nc...O4 = 2.97(1) Å.

Polar solvents, which compete with H-bond formation, reduce the effect of self-association. In these cases, the *Z* form is usually the preferred conformer (Table 1), and no changes in the proportions are observed in the NMR spectra upon concentration. An exception to this rule is trifluoroacetic acid; here, the *E* conformer shows a large concentration, probably because the carboxylic acid fits well in its cleft. The effect of trifluoroacetic acid can be studied in methanol solution showing an increase in the *E* form when this acid is added (in Methanol/Trifluoroacetic acid 2:1 the *Z/E* ratio is 1.72:1).

| Solvent              | <i>Z/E</i> ratio      |
|----------------------|-----------------------|
| Acetone              | 2.73:1.00             |
| Dimethyl sulfoxide   | 2.40:1.00             |
| Methanol             | No E form is observed |
| Trifluoroacetic acid | 1:1.36                |

**Table 1:** Effect of the solvent on the *Z/E* ratio.

## ACKNOWLEDGMENTS

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## REFERENCES AND NOTES:

- <sup>1</sup> E. A. Archer, H. Gong, and M.J. Krische, *Tetrahedron*, 2001, **57**, 1139.
- <sup>2</sup> M. Almaraz, C. Raposo, M. Martín, M.C. Caballero, and J.R. Morán, *J. Am. Chem. Soc.*, 1998, **120**, 3516.
- <sup>3</sup> L.A. Planche and M.T. Rogers, *J. Am. Chem. Soc.*, 1964, **86**, 337.
- <sup>4</sup> M. Crego, J.J. Marugan, C. Raposo, M.J. Sanz, V. Alcazar, M.C. Caballero, and J.R. Morán, *Tetrahedron Lett.*, 1991, **32**, 4185.
- <sup>5</sup> C. Raposo, M. Crego, M.L. Mussons, M.C. Caballero, and J.R. Morán, *Tetrahedron Lett.*, 1994, **35**, 3409.
- <sup>6</sup> C. Raposo, M. Almaraz, N. Pérez, M. Martín, V. Weinrich, M. Grande, M. C. Caballero, and J. R. Morán, *Tetrahedron Lett.*, 1996, **37**, 1485.
- <sup>7</sup> I. M. Dlotz, ‘Ligand Receptor Energetics: a Guide for the Perplexed’, Wiley Interscience, New York, 1997; L. Fieding, *Tetrahedron*, 2000, **56**, 6151.
- <sup>8</sup> E. L. Efiel, and S. H. Wilen, ‘Stereochemistry of organic compounds’, p. 620, John Wiley & Sons, Inc, 1994, New York.
- <sup>9</sup> CRYSTALLOGRAPHIC DATA: C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>, M= 344.40, orthorhombic, space group Pbca (no. 61), a = 14.779(2), b = 8.2336(11), c =30.373(4) Å, V = 3696.0(8) Å<sup>3</sup>. Z = 8, D<sub>c</sub> = 1.238 Mg/m<sup>3</sup>, m(Cu-Kα) = 0.087 mm<sup>-1</sup>, F(000) = 1472. Data (8744 collected reflections, 2809 and unique reflections [I > 2σ(I)]) were measured on a Siemens Smart CCD diffractometer equipped with a normal focus 2.4 kW sealed tube X-Ray source (Mo- Kα radiation, λ = 0.71073 Å) operating at 40 kV and 30 mA. The structure was solved by direct method and the non-hydrogen atoms were refined anisotropically by full-matrix least squares based on F<sup>2</sup> to give the agreement factors R<sub>1</sub> = 0.0462, ωR<sub>2</sub> =0.0904. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Center as supplementary material (CCDC 181802). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (e-mail: deposit@ccdc.cam.uk).
- <sup>10</sup> O. Saied, M. Simard, and J.D. Wuest, *J. Org. Chem.*, 1998, **63**, 3756; T.R. Kelly, P. Meghani, and V.S. Ekkund, *Tetrahedron Lett.*, 1990, **31**, 3381.