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Three Complexing Agents for Ureas and Formamides

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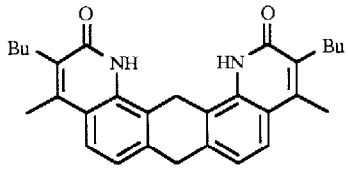
Abstract:Three cleft type hydrogen bonding receptors were prepared, with slightly different geometries due to the presence of either methylene, oxygen, or sulfur All three are able to complex urea, one with the methylene group being the best suited Benzyl formamide, probably due to its smaller cleft, is better associated to the oxygen compound

In view of their simplicity and predictable geometry, hydrogen bonding complexes of organic molecules offer a good opportunity to develop new enzyme -like reagents. A major problem of such complexes is, however, their weakness when there are not many hydrogen bonds interacting simultaneously. A synthetically simple receptor is highly desirable, because the introduction of active groups will complicate the synthesis, thereby making the new reagent less attractive. In order to develop new receptors for amides or esters, with a minimum number of hydrogen bonds, it is necessary to know the optimun geometry of the receptor, thus allowing one to form several strong hydrogen bonds at the same time

To simplify the problem, we have started with the more symmetrical receptors for ureas, which permit the formation of an extra hydrogen bond and promise higher association constants.

Compounds from **1** to **4** (Scheme 1) are able to form four hydrogen bonds with ureas (Scheme 2). The dihydroanthracenes **1** and **2** show a cleft with a parallel geometry. The shorter C-O distance as compared to the C-C bond make the cleft in the xanthone derivative to converge, and the non-bonding electrons of the oxygen atom are able to weaken the complex through intramolecular hydrogen bonds. The sulfur atom in **4** should display weaker intramolecular bonds, although the greater C-S distance as compared to the C-C one causes the cleft to diverge



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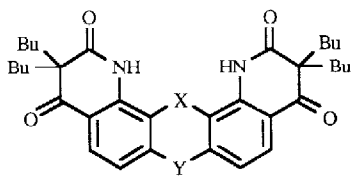
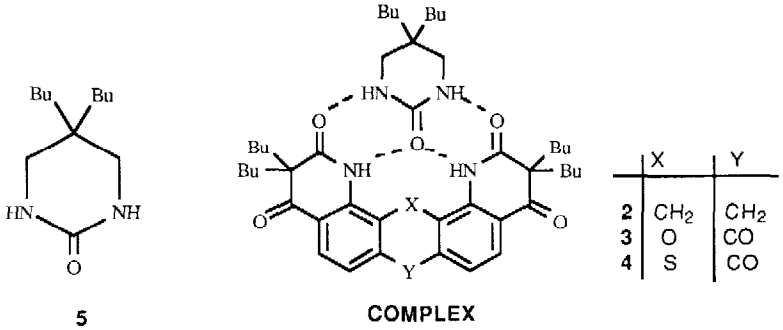


	X	Y
2	CH_2	CH_2
3	O	CO
4	S	CO

Scheme 1

We started out with dihydroanthracene **1**. This compound can be prepared from the known 9,10-dihydro-1,8-diaminoanthracene[1]. Treatment of the diamino compound with butyl acetoacetic acid and

dicyclohexyl carbodiimide yields a diamide, which cyclizes under the classic Knorr conditions in sulfuric acid. This substance, probably due to its planarity, is a highly crystalline compound which decomposes unmelted over 300°, and is almost insoluble in chloroform. To make the ^1H NMR titration easier we made use of the cyclic urea **5**, which is easily prepared from malononitrile through alkylation, treatment with $LiAlH_4$ and phosgene.



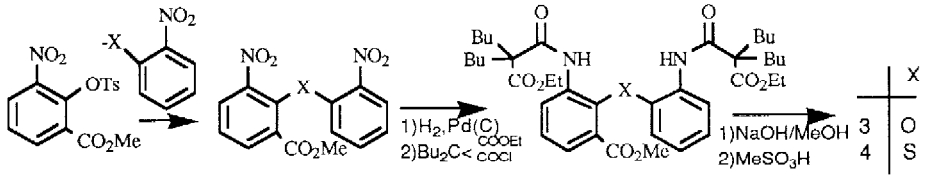
Scheme 2

^1H NMR experiments adding receptor **1** to a known amount of the urea **5**, showed that only one equivalent of the receptor can be dissolved. Plotting the chemical shifts of the methylenes of **5** against the amounts of **1** added, resulted in a straight line, indicating a large association constant.

Compound **2**[2]was obtained from the foregoing dihydrodiaminoanthracene and the chloride of the monoethyl ester from dibutylmalonic acid, followed by acid ring closure (55% yield).

The non-planar geometry of compound **2** (mp=142°C) made it easier to deal with. It is a readily chloroform soluble solid. Its association constant with the urea **5** in $CDCl_3$ is also too high to be measured with our 200 MHz spectrometer. However, by changing to a more polar solvent, such as acetone-d_6, and again following the displacements of the methylene signals in **5**, we were able to measure a Ks of $8x10^4$ M^{-1} (curve fitting). We also estimated the association constant in the very polar MeOH around 30, but the lack of solubility of the receptor in this solvent means that this value is uncertain.

The synthesis of xanthone and thioxanthone derivatives **3**[3] (mp= 164°C) and **4**[4] (mp=254°C), was accomplished starting from methyl 3-nitrosalicylate. Tosylation yielded a crystalline substance (90%yield) which undergoes direct displacement with sodium 2-nitrothiophenolate (90% yield). Formation of the pyridinium salt from the tosylate and pyridine is mandatory for coupling the nitrosalicylate with 2-nitrophenolate as its potassium salt[5] affording the diphenyl ether in 40% yield. Reduction of the nitro groups either with hydrogen/palladium , or tin chloride yielded the amines, which can be readily acylated with the chloride of the monoethyl ester dibutylmalonic acid. Hydrolysis and treatment with a mixture of methanesulfonic acid and P_2O_5 performed a triple cyclization[6] to yield receptors **3** (40% yield) and **4** (70% yield)(Scheme 3).



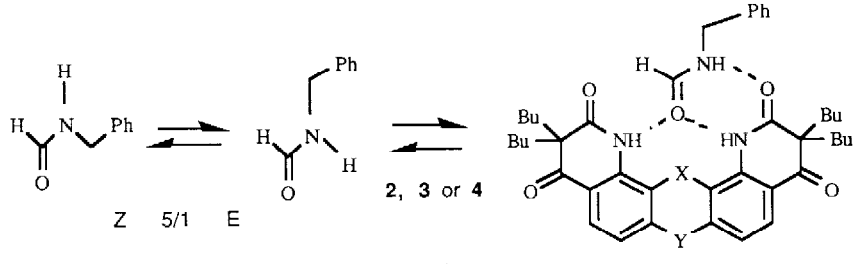
scheme 3

With the urea **5** the oxygen compound **3** shows the smallest association constants both in $CDCl_3$ Ks= $3x10^5$ M^{-1} and acetone-d_6 Ks= $1x10^4$ M^{-1} while the sulfur compound had a Ks= $2x10^6$ M^{-1} in $CDCl_3$ and a Ks= $2x10^4$ M^{-1} in acetone-d_6.

Due to its possible interest in REDY dialysis systems and in order to compare this with other urea complexing agents[7] we also measured the binding constants with urea itself An aqueous urea solution (1ml, 0.171M) was extracted with receptor **2** in chloroform (200µl, 0.037M) Urea was analyzed in the water phase using of the bioMerieux® commercial colourimetric procedure, showing a 0.117M concentration. The distribution constant for the partition of urea between chloroform and water is approximately $9x10^{-5}$ M^{-1}, hence, the K_S for the urea complex may be calculated as $4x10^4$ M^{-1}. A similar procedure showed Ks= $8x10^3$ M^{-1} and $3x10^3$ M^{-1} for the sulfur and oxygen analogues. This was the same trend as with the cyclic urea **5**; however the values are lower owing to the presence of water

Whereas the urea **5** shows the optimum geometry to be complexed, dibenzyl urea has to associate in an unfavorable conformation in which both benzyl methylenes have to press against each other. This reduces the association constant with receptor **2** to a K_S of only $6x10^2$ M^{-1}

Amides should form three hydrogen bonds with these receptors (Scheme 4), however the amide's α-methylene group is too bulky to fit into the cleft The small formamides do not have this drawback and they offer a very easy way to measure the association constants. Formamides have E and Z conformations in rapid equilibrium, both conformers can be seen as different compounds in their ^1H NMR spectrum[8]. When a receptor is added only the signals of the E conformer which fits into the cleft are shifted, while the Z signals remain at a constant shift (Scheme 4).



Scheme 4

The equilibrium is also shifted to the E compound; the more receptor added, the smaller the Z peaks become. Once the E to Z equilibrium constant is known, integration of the E and Z signals, allows to calculate the association constant, because the free E form can be calulated from the Z conformer and the equilibrium constant. For example, a $2x10^{-2}$M benzyl formamide solution in chloroform with 1 25 equivalents of the

oxygen receptor **3** shows in its ^1H NMR spectrum a 2/1 E/Z ratio. Knowing that under these conditions the equilibrium between E and Z conformers of benzyl formamide favours the Z one in a 5/1 proportion, it is possible to calculate a Ks= $7x10^2$ M^{-1}. The same procedure showed for benzyl formamide and the dihydroanthracene derivative **2** a Ks= $5x10^2$ M^{-1} and a very small Ks for the sulfur analogue **5**. In this latter case, no shift or increase of the E signals could be observed.

This change in the trend of the constants seems to indicate, that intramolecular hydrogen bondings are not very important in these molecules, and that the small change in cleft geometry is decisive. Small geometry changes have already been recognized as important[9].

The convergent cleft in the xanthone derivative **3,** is too small to comfortably accommodate an urea molecule; a smaller formamide is, however, better complexed. The sulfur analogue shows a cleft which is too large, either for ureas or formamides, while the dihydroanthracene cleft shows a good geometry for ureas, although still too large for formamides.

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2) ^1H-NMR-data (200 MHz, $CDCl_3$); Compound **2:** δ= 7.93 (d, 2H, J=8 Hz), 7.12 (d, 2H, J=8 Hz), 4.24 (s, 2H), 4.14 (s, 2H), 2.10 (m, 8H), 1.20 (m, 16 H), 0.73 (t, 12H, J=6 Hz)

3) ^1H-NMRdata (200 MHz, $CDCl_3$); Compound **3:** .δ= 8.10 (d, 2H, J=8 Hz), 8.01 (d,2H,J=8) Hz), 2.05 (m, 8H), 1.10 (m, 16H), 0.65 (m, 8H).

4) ^1H-NMR-data (200 MHz, $CDCl_3$); Compound **4**: δ= 8.39 (d, 2H, J=8 Hz), 8.16 (d, 2H, J=8 Hz), 2.10 (m,8H), 1.20 (m, 16H), 0.79 (t, 12H, J=6 Hz)

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