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Benzimidazole Receptors for Carboxylic Acids

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Abstract: Combination of an aminobenzimidazole with a chromenone unit provides a receptor for carboxylic acids or primary amides. This host is highly selective for carboxylic acids with K_{ass} above 10^6 M^{-1} while amides only bind weakly with association constants in the order of hundreds of M^{-1}.

Amidopyridines, widely used by Hamilton[1] and others,[2] have proved to be very successful as binding arms for carboxylic acid receptors. Large association constants have been obtained, especially with dicarboxylic acids thanks to the presence of the strong acid-base H-bond between the pyridine nitrogen and the acid carboxylic group. The basic nature of benzimidazole[3] also promises a strong H-bond with carboxylic acids, which may give rise to good receptors for these guests. This may be the case of host **1**, in which the basic benzimidazole is combined with a chromenone unit, to provide a third H-bond in the association (Figure 1).

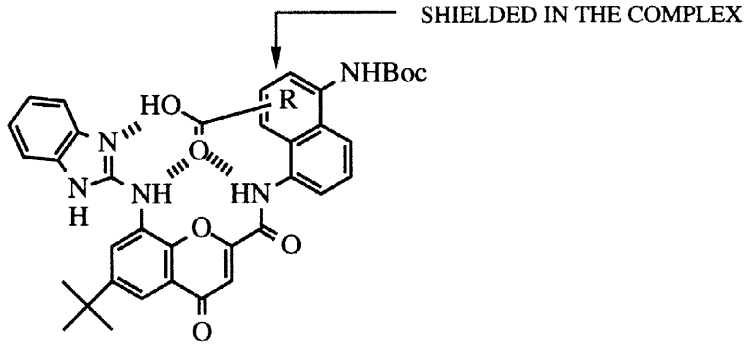

Figure 1. Complex of host **1** with a carboxylic acid.

Compound **1** can be prepared as shown in scheme 1. Treatment of the known aminochromenone **2**[4] with thiophosgene yields the expected isothiocyanate, which readily reacts with phenylenediamine. Attempts to cyclize the thiourea **3** to the benzimidazole produced large amounts of the aminochromenone **2**. The best conditions were found to be methyl iodide and DBU at -30°C, which rapidly lead to isothiourea **4**, followed by work up and cyclization in refluxing toluene.

CPK models show a good fit between the acids in cleft **1**, with the α-carbon lying over the naphthyl ring in the receptor (Figure 1). This provides an easy way to carry out NMR titrations since α-hydrogens in the guests are strongly shielded in the complex (Table 1).

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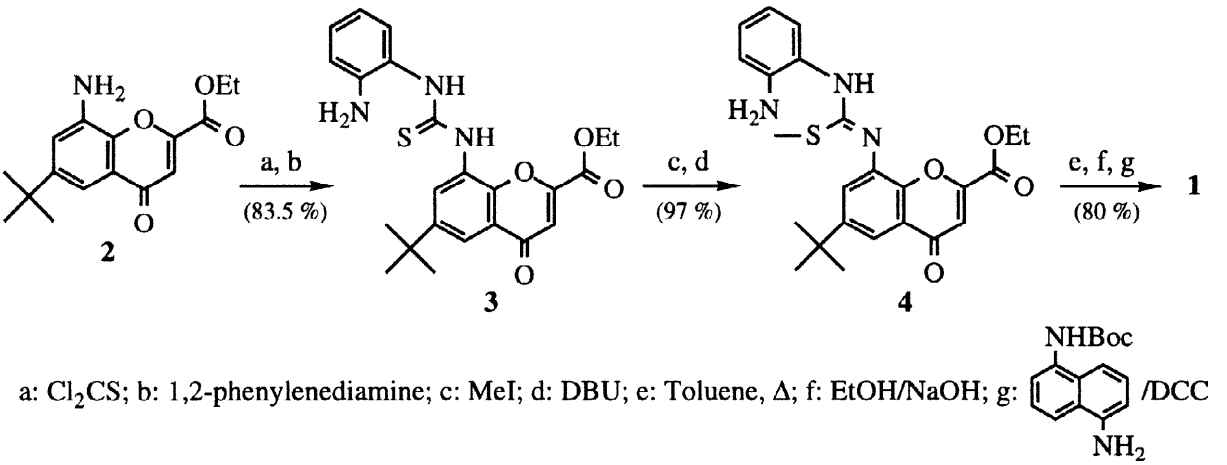

a: Cl_2CS; b: 1,2-phenylenediamine; c: MeI; d: DBU; e: Toluene, Δ; f: EtOH/NaOH; g:

/DCC

Scheme 1

For example, NMR titrations provide K_{ass}= $8.3x10^3$ M^{-1} and K_{ass}= $1.6x10^5$ M^{-1} for pivalic and diphenylacetic acid, respectively. The t-butyl group in pivalic acid is shifted from 1.23 ppm to 0.53 ppm in the complex while the diphenylacetic proton moves 1.31 ppm upfield (Table 1).

Current discussion of the impact of low barrier hydrogen bonds[5] in enzyme catalysis is related to finding out how strong the complex can be when the donor and acceptor basicities of the hydrogen bond in the complex are the same. Since we found it difficult to differentiate between proton transfer and complex formation working in $CDCl_3$ with host **1**, two different approaches were used to study the proton transfer event. Polar solvents such as DMSO compete strongly for receptor hydrogen bonds and therefore disfavor complex formation. ^{1}HNMR spectra show that host **1** is essentially indifferent to chloroacetic acid in DMSO; dichloroacetic acid shows partial protonation while trifluoroacetic acid yields the completely protonated benzimidazole. The lack of a strong shielding effect in the dichloroacetic α proton suggests that complex formation is very weak, if indeed it occurs at all. The ester **5** does not complex acids strongly due to the lack of the third H-bond and probably due to the repulsion of the non-bonding electrons between the oxygens of the host and guest.

Compound **5** shows a yellow colour due to the presence of a weak band (386 nm, ε = $3.5x10^3$ l cm^{-1} mol^{-1}) in its UV spectra in $CHCl_3$. Protonation with trifluoroacetic acid makes the yellow colour vanish, the UV band shifting from 386 nm to 330 nm. Again, dichloroacetic acid provides only partial protonation since both bands are observed together in the UV spectrum of **5** when this acid is added.

Initial experiments revealed that the association constant of host **1** and dichloroacetic acid in $CDCl_3$ exceeds the limits of NMR methods. This constant was therefore evaluated from a competitive scale,[6,7] similar to the reactivity scales developed by Huisgen.[8] Competitive experiments were performed with $3x10^{-3}$ M guest solutions to which pure host was added until saturation was reached. Proton shifts of guests were recorded for each experiment and plotted against one another. A Monte Carlo non-linear curve fitting method based on equation (1) was used to evaluate the relative association constants.

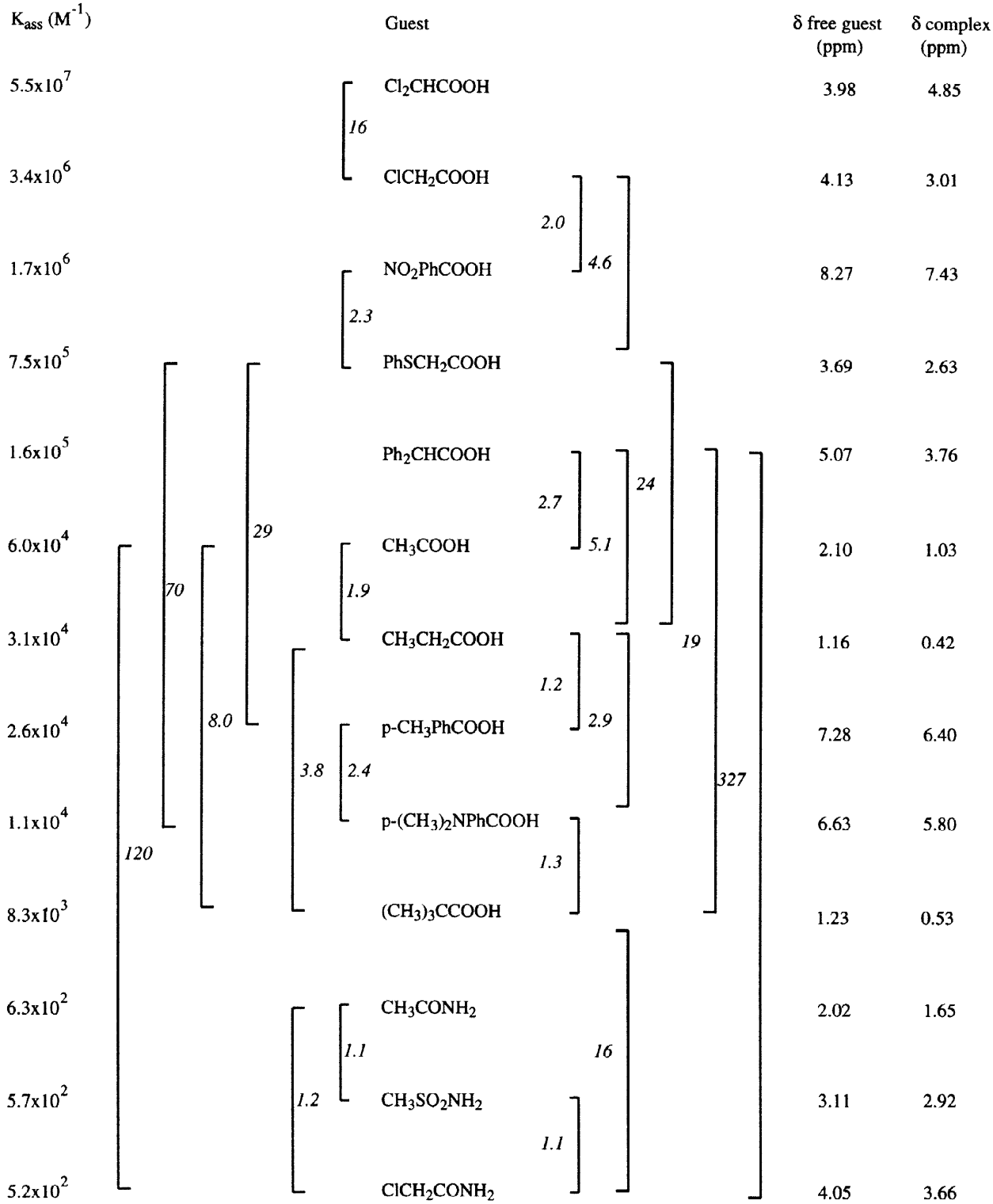

Table 1. Association constants of receptor **1** with several acids, its relative constants in $CDCl_3$ at 20°C and free guest and complex chemical shifts. K_{ass} correspond to averages between several experiments. Relative constants beyond 20 may be affected by large errors.

$$K_{ass,1}/K_{ass,2} = (\delta_1-\delta_{f1})(\delta_{c2}-\delta_2) / (\delta_2-\delta_{f2})(\delta_{c1}-\delta_1)$$

Equation (1). δ_f: chemical shift of free guest, δ_c: chemical shift of complexed guest, δ: observed chemical shift.

Table 1 shows the K_{ass} values of all the guests studied, pointing to an impressive 106.000-fold increase (6.8 Kcal) on passing from the neutral chloroacetamide to dichloroacetic acid.

The association constants in the upper part of table 1 are strongly related to the guest pKa. Exceptions may be aromatic acids, which show slightly weaker complexes than expected. Steric hindrance may account for this behavior since the pivalic acid complex is 10 times weaker than that formed with acetic acid. Weaker complexes do not seem to be very strongly affected by the guest acidity; acetamide, chloroacetamide and sulfonamide, all show complexes with similar stabilities, despite the different NH pKa.

Even if the gain in energy on passing from a neutral guest complex to dichloroacetic is far below the 20 Kcal increase from conventional low-barrier hydrogen bonds,[5] use of these strong acid-base H-bonds seems promising in the field of Molecular Recognition.

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