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Lactone Receptors with Catalytic Activity

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Abstract: *Three cleft-type receptors have been prepared that associate 2(5H)-furanone in benzene. These complexes show greater reactivity toward pyrrolidine nucleophilic addition than the furanone itself, probably due to stronger hydrogen bonds in going to the transition state.*

Several carboxylate group receptors have been published recently[1]. Chromone **1** is able to set three hydrogen bonds with carboxylate groups and therefore form strong associates with them. The association constant with tetraethylammonium benzoate[2] in $CDCl_3$ is over 10^5 M^{-1}. Lactones have the right geometry for complexing[3] with receptor **1**, although the association constant is however far smaller. γ-butyrolactone, for example, forms a weak complex with receptor **1** (Figure 1) in the same solvent (Ks= 30 M^{-1}).

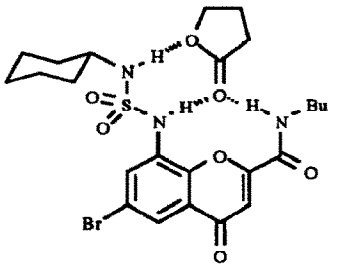

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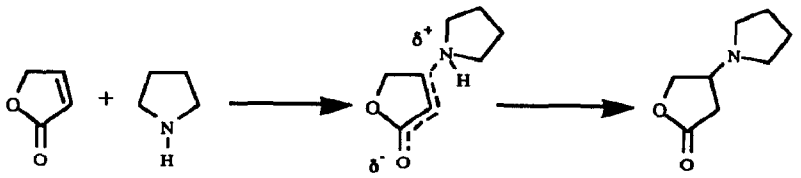
Figure 1: Complex between butyrolactone and chromone **1**.

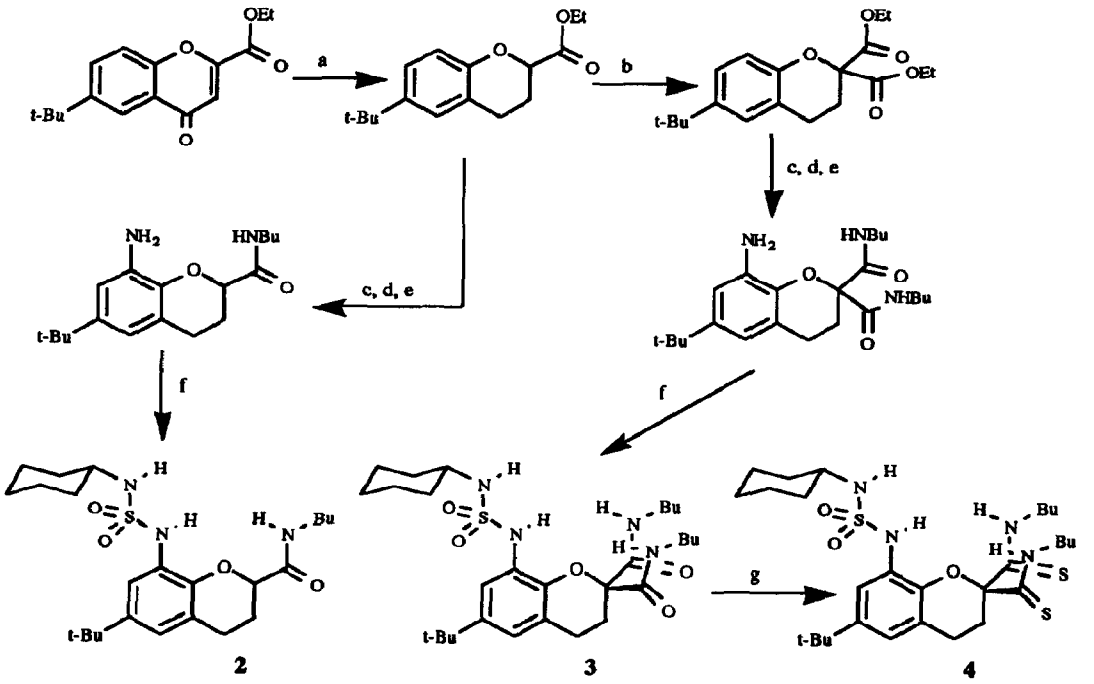
This large difference in association constants suggest that lactone complexes could show catalytic activity in reactions in which, in the transition state, negative charge develops in the carbonyl oxygen atom. This will increase the association constant in going to the transition state and consequently should catalyze the reaction[4]. Synthetic receptors have already been found to show catalytic activity in nucleophilic addition

to carbonyl conjugated double bonds[5], and amines are known to add readily to butenolides[6]. We therefore studied the nucleophilic addition of pyrrolidine to an unsaturated lactone such as 2(5*H*)-furanone.



Scheme 1: Reaction of pyrrolidine and 2(5*H*)-furanone.

Receptor **1** is however not suitable for this work because the aromatic sulfuryl amide hydrogen is lost in the presence of bases like triethylamine or pyrrolidine, preventing complex formation. Therefore, a new receptor, **2**, was prepared.



a) H_2/ Pd (C), b) LDA/ THF, Ethyl chloroformate, c) HNO_3/ Ac_2O, d) $SnCl_2$/ EtOH, e) $BuNH_2$, f) N-Cyclohexylsulfamoyl chloride/ triethylamine, g) Lawesson reagent.

Scheme 2: Synthesis of receptors **2** to **4**.

Hydrogenation of the chromone skeleton[7] yields a benzopyrane in which the lack of the carbonyl group reduces the acidity of the sulfuryl amide. Furthermore a t-butyl group is included in the molecule to increase its solubility in apolar solvents. Compound **2** does not form a salt with pyrrolidine and is therefore a good candidate for study of its catalytic effect.

The association constants of receptor **2** are smaller than for receptor **1**. Probably a more rigid frame in **1**, combined with stronger hydrogen bonds, could explain this effect. Receptor **2** is indeed a very weak lactone binder in chloroform. To increase the association constant with the 2(5*H*)-furanone, benzene d_6 was used as the solvent; this leads to an association constant of Ks= 68 M^{-1}, which is high enough to ensure complexation under the reaction conditions.

Receptor **2** shows catalytic activity in this nucleophilic addition. When a 1/10 molar ratio between receptor and lactone is added, the reaction half life is reduced from 125 min to 51 min[8] (Table 1).

Receptor	Ks (M^{-1}) with tetraethylammonium benzoate in DMSO d_6.	Ks (M^{-1}) with 2(5*H*)-furanone in benzene d_6.	$t_{1/2}$ (min) for reaction of pyrrolidine with 2(5*H*)-furanone
2	$4.2x10^1$	68	51
3	$9.6x10^1$	4	22
4	$2.1x10^2$	19	16
No receptor			125

Table 1: Association constants and kinetic results[9] for receptors **2** to **4**.

The carbonyl oxygen of esters can only form two strong hydrogen bonds. The corresponding enolates, however, can possibly set three strong hydrogen bonds because their X-ray structures show the carbonyl oxygen coordinated to three lithium atoms[10]. Molecular models show that four hydrogen bonds can be set between receptor **3** and an enolate-like transition state.

While the presence of the four hydrogen bonds increases the association constant with tetraethylammonium benzoate (Table 1), the receptor **3** lactone associate is surprisingly weak, yielding only a Ks= 4 M^{-1}. This low value can may due to an intramolecular six-member ring hydrogen bond in the ground state of receptor **3**, which sets an inappropriate conformation for binding. Interestingly the catalytic activity of this receptor is better than for receptor **2**, reducing the reaction half life to 22 min. The higher ratio between the association constants of the carboxylate and the neutral lactone possibly explains this result[11] (Table 1).

Thioamides are known to be better hydrogen bond donors than amides[12] and therefore receptor **4** was prepared by treatment of receptor **3** with Lawesson reagent. As expected, the association constant is higher than for receptor **3** both for tetraethylammonium benzoate and 2(5*H*)-furanone (Table 1). The better complexing properties of this compound readily account for its increased catalytic activity, the reaction half life being reduced to 16 min.

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8 Catalysis due to the receptor functional group has been ruled out because N-butyl acetamide shows no rate increase under these conditions, and the sulfuryl amide is essentially the same in all the receptors, while the catalytic activities are different.

9 Reactions were performed in benzene d_6 at a lactone concentration of 0.27 M, pyrrolidine 0.29 M and receptors 0.027 M at 20°C.

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11 Accurate measurements of the carboxylate association constants is not possible in either benzene d_6 or $CDCl_3$. However, DMSO d_6 allows easy comparison of these constants.

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