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Cleft Type Receptors with Catalytic Activity in Amide Deuteration

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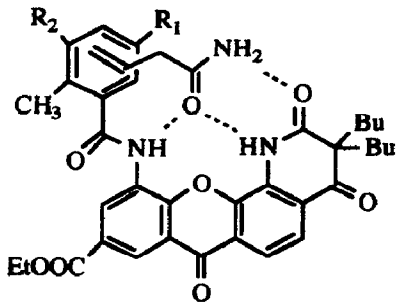
Abstract: Cleft type receptors have been prepared with a significant activity in amide deuteration. Charge-transfer and hydrogen bonds seems to be responsible for the catalytic activity.

Cleft type receptors for simple functional groups could be the frame for new enzyme-like reagents[1]. Compound **1** is able to set three H-bonds with acids or amides and associate them in $CDCl_3$[2] (Fig.1). In these complexes charge-transfer seems to be very important. This effect increases the stability of the complexes from a value of $1.5x10^3$ M^{-1} for isophthalic acid monomethyl ester to $1.5x10^6$ M^{-1} for the better electron donor 4-dimethylaminobenzoic acid[2]. A reaction whose transition state is more strongly associated by a receptor than its ground state should be catalyzed, in agreement with Pauling[3]. This could be the case of reactions which take place through negatively charged intermediates if charge-transfer to the electron poor receptor **1** aromatic ring is possible.

The rearrangement of vinylacetamide to the corresponding crotonamide should take place through the enolate. Negative charge develops in the amide α-carbon going on to the transition state. In the complex this carbon is close to the 3,5-dinitrotoluic group of receptor **1**, and charge-transfer should therefore stabilize this intermediate enolate.



	R_1	R_2
1	NO_2	NO_2
2	H	H
3	SO_2NHBu	H
4	$SO_2N(Et)_2$	H
5	SO_2NHBu	NO_2

Figure 1: Complexes of receptors **1-5** with vinylacetamide

Complexation and kinetic studies were carried out in ^1H NMR with $CDCl_3$ as the solvent. And association of vinylacetamide with receptor **1** (Table 1) was confirmed in this solvent.

TABLE 1

RECEPTOR	(Ks, M^{-1}, vinylacetamide)	(Ks, M^{-1}, 4-methoxy-3-pyrrolin-2-one)
1	$1.7x10^3$	$1.3x10^5$
3	$3.0x10^2$	$4.0x10^3$
4	$4.0x10^2$	$3.5x10^3$
5	$4.0x10^2$	$1.4x10^4$

Association constants for receptors **1**, **3**, **4** and **5** with vinylacetamide and 4-methoxy-3-pyrrolin-2-one with $CDCl_3$ at 20° C

Initial attempts to study the vinylacetamide rearrangement reaction, making use of 1,8-diazabicyclo[5.4.0]-undec-7-ene(1,5-5) (DBU) as base, showed that the deuteration reaction, due to the acidic deuterium of $CDCl_3$, was competitive with the rearrangement. Owing to this drawback we preferred to study the α deuteration reaction, which should take place through the same enolate intermediate.

Acetone-d6 was added (2%) to improve the deuterium donor properties of the solvent. Under these conditions making use of a receptor/vinylacetamide 3/10 ratio, a four fold decrease in the reaction half life time was observed (Table 2), while no catalysis was observed with receptor **2** which lacks the nitro groups. This result shows that charge-transfer is probably responsible for the catalysis.

Saturated aliphatic amides do not undergo deuteration under these conditions, however, due to higher acidity of its protons, the commercially available 4-methoxy-3-pyrrolin-2-one, is deuterated faster (Table 3). The better geometry of this guest and the charge-transfer effect increases the stability of the receptor **1** complex to a Ks= $1.3x10^5$ M^{-1}(Table 1).

TABLE 2

RECEPTOR	$t_{1/2}$ (minutes)
without receptor	535
1	160
3	180
4	480
5	115

Deuteration half life times of vinylacetamide (0.1 M) in the presence of DBU (0.2 M) in $CDCl_3$/Acetone-d_6 98/2 at 20° C and **1**, **3**, **4** or **5** receptor (0.03M)

TABLE 3

RECEPTOR	$t_{1/2}$ (minutes)
without receptor	150
1	50
3	80
5	40

Deuteration half life times of 4-methoxy-3-pyrrolin-2-one (0.1 M) in the presence of DBU (0.2M) in $CDCl_3$/Acetone-d_6 98/2 at 20° C and **1**, **3** or **5** receptor (0.03 M)

The catalytic effect of receptor **1** in the deuteration of this guest (Table 3) is, however, smaller than for vinylacetamide. The presence of charge-transfer in the ground state accounts well for this effect because the energy difference between the transition and ground state will probably be smaller.

A receptor in which new H-bonds can be set in the transition state should also display catalytic activity. Seebach[4] has shown that in amide enolates the nitrogen atom is pyramidalized and that its non-bonding electrons can set strong hydrogen bonds. In receptor **3** the sulfonamide group is set to exploit this possible new hydrogen bond. CPK models show that the sulfonamide NH is placed behind the amide nitrogen atom, and if this nitrogen pyramidalizes, a new hydrogen bond could be set.

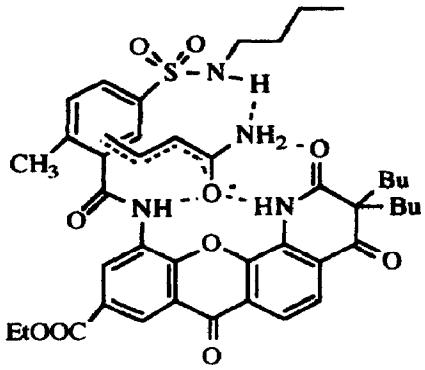


Figure 2: Proposed structure for the complex of receptor **3** and vinylacetamide enolate, showing a possible hydrogen bond between the sulfonamide and the vinylacetamide enolate nitrogen

Association constants of this receptor **3** with vinylacetamide and 4-methoxy-3-pyrrolin-2-one (Table 1) are smaller than expected, probably because the large N-butylsulfonamide group can hinder the guest. Receptor **3** shows a slightly smaller catalytic activity than receptor **1** both for vinylacetamide (Table 2) and 4-methoxy-3-pyrrolin-2-one (Table 3). The presence of the sulfonamide NH is necessary for this activity because the N-diethylsulfonamide receptor **4** (Table 2) is almost inactive. However, the mere presence of this group is not sufficient to induce deuteration because N-butyltoluensulfonamide, which cannot associate the guest, does not induce any rate increase. Once again, catalysis is better for vinylacetamide than for 4-methoxy-3-pyrrolin-2-one; in this latter compound, the amide nitrogen probably does not pyramidalize easily because of the pyrrol structure of the enolate.

To combine the charge-transfer effect with the presence of a new hydrogen bond in the transition state a nitro group was included in receptor **5**. The association constant with vinylacetamide is similar to those, of receptors **3** and **4** (Table 1). However, the complex with 4-methoxy-3-pyrrolin-2-one is much more stable, which indicates a better charge transfer. The catalytic activity is, as expected, better than for the foregoing receptors (Tables 2 and 3).

The best results are obtained however when a Schwesinger phosphazene[5] [tert-octylimino-tris(dimethylamino)phosphorane] is used as the base. Under these conditions an 8 fold decrease in the reaction half life time is obtained for the deuteration of vinylacetamide and receptor **5** (Table 4). Once again the results with 4-methoxy-3-pyrrolin-2-one, which does not pyramidalize well, are poorer (Table 5) and almost no benefit is obtained from the receptor **5** nitro group. The presence of the two nitro groups in receptor **1** does not allow the use of phosphazene bases because decomposition takes place.

TABLE 4

RECEPTOR	$t_{1/2}$ (minutes)
without receptor	2050
3	360
4	2000
5	260

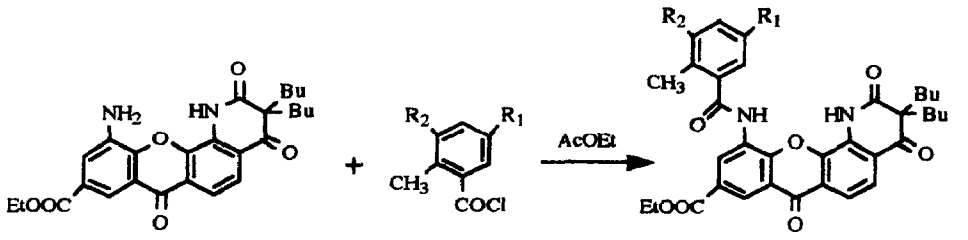
Deuteration half life times of vinylacetamide (0.1 M) in the presence of tert-octylimino-tris(dimethylamino)phosphorane (0.1 M) in $CDCl_3$/Acetone-d_6 98/2 at 20° C and receptor 3, 4 or 5 (0.03 M)

TABLE 5

RECEPTOR	$t_{1/2}$ (minutes)
without receptor	220
3	110
5	100

Deuteration half life times of 4-methoxy-3-pyrrolin-2-one (0.1 M) in the presence of tert-octylimino-tris(dimethylamino)-phosphorane (0.1M) in $CDCl_3$/Acetone-d6 98/2 at 20° C and receptor 3 or 5 (0.03 M)

Preparation of all these receptors was carried out by reacting amine 6[2] with the proper acid chloride, as shown in scheme 1.



RECEPTOR	R_1	R_2	yield (%)	m.p.(°C)	solvent
1	NO_2	NO_2	86	313 (dec.)	methanol
2	H	H	95	245-247	ethanol
3	SO_2NHBu	H	72	274-277	ethyl acetate
4	$SO_2N(Et)2$	H	75	145-146	chloroform-hexane
5	SO2NHBu	NO_2	67	311-313	chloroform-hexane

Scheme 1

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