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A Receptor for Aromatic Acids and Amides

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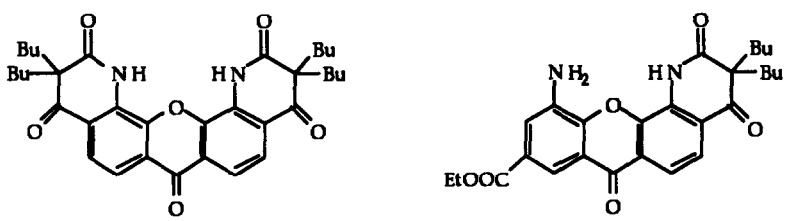
Key Words: Molecular recognition, cleft type hydrogen bonding receptor, aromatic acids and amides,charge-transfer

Abstract: *A dinitrotoluic residue has been introduced onto an hydrogen bonding aromatic acid receptor to achieve stacking and charge-transfer interactions. This new receptor shows large differences in association constants with aromatic guests in $CDCl_3$ ranging from 1.6 x 10^3 with isophthalic acid methyl ester to 1.5 x 10^5 with p-dimethylamino benzoic acid.*

Carboxylic acids are readily complexed in apolar solvents by making use of guanidines or amidopyridines [1,2]. Amides are not so easily complexed due to the lack of the strong acid-base interaction. In order to increase the strength of acid as well as neutral molecule complexes, it is desirable to increase the amount of hydrogen bonds and to include stacking[3,4] and charge-transfer interactions[5]. The xanthone derivative 1 (fig. 1) has the correct geometry to complex the carbonyl group of ureas and formamides[6]. Its cleft is, however, too small to accommodate sterically demanding acids or amides due to the steric hindrance between the α group and one of the receptor carbonyls.

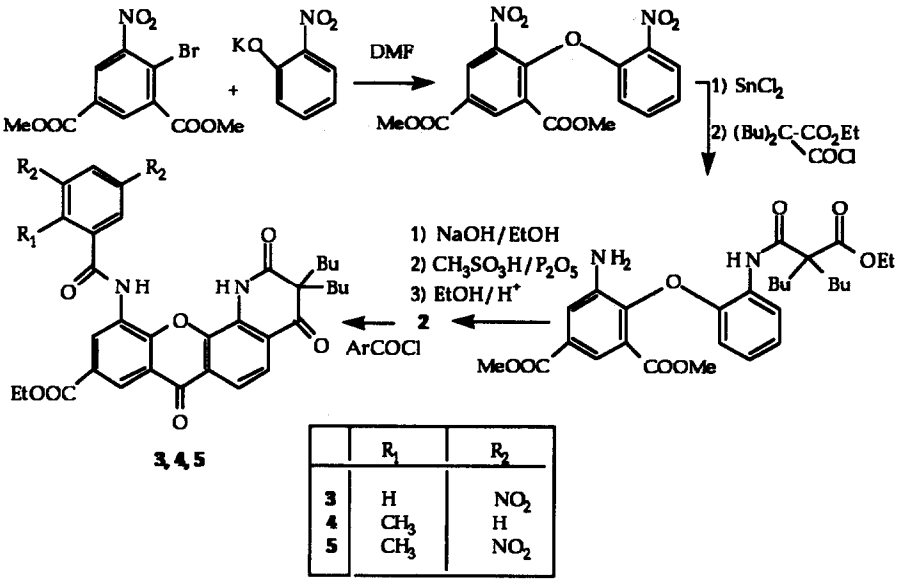


1 **2**

Fig. 1

Compound 2 (fig. 1) has a wider cleft, the poor amine NH hydrogen bond, however, yields weak complexes in chloroform, either with dodecanoic (K_s= 3 x 10^2 M^{-1}) or cinnamic acids (K_s= 4 x 10^2 M^{-1}). Acyl derivatives of 2 should be better carboxyl complexing agents, due to the stronger amide NH hydrogen bond. If an aromatic amide is prepared there exists the possibility of beneficial stacking and charge-transfer

interactions. Compounds 3 to 5 are crystalline solids which can be readily prepared starting from 4-bromo-5-nitrodimethylisophthalate and potassium nitrophenolate (scheme 1)



	R_1	R_2
3	H	NO_2
4	CH_3	H
5	CH_3	NO_2

Scheme 1

Receptor 3 (m.p.= 234°C, 45% yield) shows rather small association constants with either 4-ethoxybenzoic acid (Ks= 1.5 x 10^3 M^{-1}) or 3,4,5-triethoxybenzoic acid (Ks= 1.8 x 10^3 M^{-1}). 2,4-diethoxybenzoic acid is even more weakly complexed (Ks= 7 x10^1 M^{-1}) probably due to its intramolecular hydrogen bond. In our opinion the small charge transfer contribution to the complex is due to a poor overlapping of the aromatic clouds. CPK models (fig. 2) and modeling studies suggest that the geometry of the complex can be improved by including an ortho methyl group in the dinitrobenzamide ring. This produces a twist between the carbonyl group and the aromatic cloud, leaving both aromatic rings from host and guest almost parallel with no large loss of conjugation energy.

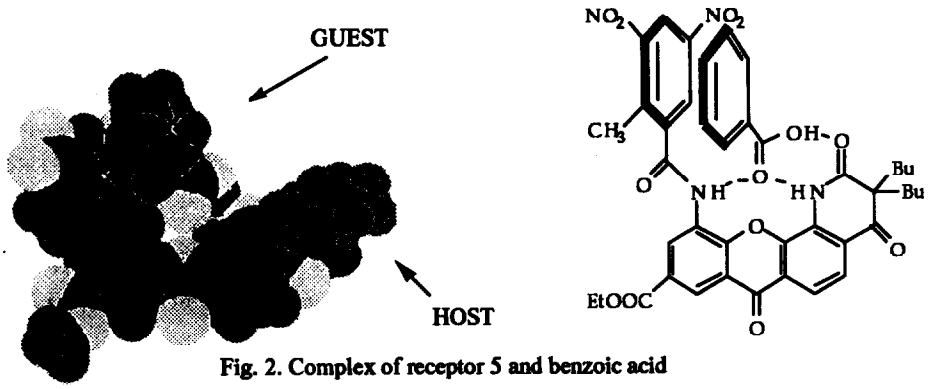


Fig. 2. Complex of receptor 5 and benzoic acid

While the tolyl derivative 4 (m.p.= 259°C, 38.5% yield) has a small association constant with 4-ethoxybenzoic acid (8.1 x 10^2 M^{-1}), thanks to the charge-transfer contribution the dinitrotolyl derivative 5[7] (m.p.=296°C, 31.5% yield) forms a complex over 100 times stronger (table 1).

A similar twist in the guest geometry, making use of 2-toluic acid and host 5, does not improve the binding (table 1).

The stability of receptor 5 complexes is highly dependent on the guest substituents (table 1). The expected increase in complex strength is observed on passing from isophthalic acid monomethyl ester to benzoic and ethoxybenzoic acid.

TABLE 1

GUEST	Ks (M^{-1})
3-Ethoxycarbonylbenzoic ac.	1.47 x 10^3
2-Toluic ac.	3.52 x 10^4
Benzoic ac.	6.00 x 10^4
4-Ethoxybenzoic ac.	1.53 x 10^5
3,4-Methylenedioxybenzoic ac.	1.58 x 10^5
3,4,5-Trimethoxybenzoic ac.	2.41 x 10^4
3-Dimethylaminobenzoic ac.	8.21 x 10^5
4-Dimethylaminobenzoic ac.	1.56 x 10^6

Receptor 5- association constants with aromatic acids.[9]

TABLE 2

GUEST	Ks (M^{-1})
Benzamide	2.79 x 10^4
4-Ethoxybenzamide	4.63 x 10^4
2,4-Diethoxybenzamide	7.75 x 10^4
3,4,5-Trimethoxybenzamide	6.24 x 10^3
4-Dimethylaminobenzaldehyde	2.60 x 10^2

Receptor 5- association constants with aromatic amides and aldehydes

The effect of further meta alkoxide groups on the guest aromatic ring is small. This could be consistent with the study of Staab and coworkers[8] on donor-acceptor cyclophanes, because the para oxygen corresponds to the "pseudogeminal" orientation with respect to the receptor nitro group, while the meta substitution is closer to "pseudoortho".In the case of gallic acid trimethyl ether, the new meta alkoxide diminishes the strength of the complex.(tabla 1) Probably the conjugation of the important para oxygen is handicapped by the two meta methoxy groups.

Benzamides follow a similar trend (table 2). While 4-ethoxybenzamide shows a higher association constant than benzamide itself, the 3,4,5-trimethoxy derivative forms a weaker complex. The presence of an intramolecular hydrogen bond with an ortho oxygen is, in the case of amide, beneficial, 2,4-diethoxybenzamide showing a better value than the preceding ones.

The presence of dimethylamino substituents yields the best complexes. The best conjugation of the 4-dimethylamino group has the greatest effect, with an association constant above 10^6 M^{-1}, significantly higher than the meta derivative.

Aldehydes are also associated; however, the loss of one hydrogen bond in the complex and the less polarized carbonyl group yield poor binding even in the case of 4-dimethylaminobenzaldehyde (table 2)

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7) ^{1}H-NMRdata (200 MHz, $CDCl_3$); Compound 5: .δ= 10.41 (s, 1H), 10.20 (s, 1H.), 9.30 (s, 1H), 9.03 (s, 1H), 8.95 (s, 1H, J= 2.2 Hz), 8.47 (s, 1H, J= 2.2 Hz), 8.14 (d, 1H, J= 8.6 Hz), 7.94 (d, 1H, J= 8.6 Hz), 4.51 (c, 2H, J= 7.0 Hz), 2.85 (s, 3H), 1.86 (m, 4H), 1.52 (t, 3H, J= 7.0 Hz), 0.76 (m, 8H,), 0.30 (m, 6H) ppm.

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9) NMR titrations were carried out using constant 10^{-3}M $CDCl_3$ host solutions, following the butyl CH_3 signals, which typically move from 0.30 ppm to 0.82 ppm in the complex. Data were evaluated using a non-linear Montecarlo curve fitting program.

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