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Thiourea versus the oxyanion hole as a double H-bond donor

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ABSTRACT

A novel receptor based on the 4,5-diamine-9,9-dimethylxanthene skeleton functionalised with triflamides has been developed and its hydrogen-bonding donor ability is examined and compared with that of thiourea groups. The novel receptor also shows its potential as an organocatalyst.

Organocatalysis is a field in rapid expansion.[1] One of the key elements of an organocatalyst is its ability to associate substrates with a carbonyl group or another good H-bond acceptor.[2] Many of these compounds rely upon the presence of groups, such as ureas or thioureas, capable of double hydrogen-bond donation.[3]

Nevertheless, natural enzymatic systems show a preference for linear H-bonds in the oxyanion-hole structure,[4] instead of the angular H-bonds of urea or thiourea groups.

Although many thiourea derivatives have recently been developed as organocatalysts,[5] no comparison between the association properties of thioureas and oxyanion hole mimics has been carried out.

The carbonyl group of ketones or aldehydes affords, as guests, only weak complexes,[6] and accurate measurement of the association constants (NMR titrations) is difficult. Therefore, a better H-bond acceptor would be desirable. Our initial results in the search for more suitable guests amongst ketones, sulfoxides, phosphine oxides and triphenylarsine oxide clearly showed that this latter compound yielded the strongest complexes. Additionally, triphenylarsine oxide has other practical advantages: it is a commercially available stable solid, it is easy to handle, and it is very soluble in chloroform.

Several substituted thioureas (**1–4**, Table 1) were tested to screen their binding properties with the substrate of our choice: triphenylarsine oxide. We also prepared seven receptors for oxyanion hole mimics: receptors **5** and **6**, derived from *meta*-xylylenediamine; receptors **7** and **8**, derived from isophthalic acid and receptors **9–11**, derived from 4,5-diamine-9,9-dimethylxanthene. The association constants were measured in $CDCl_3$ at 293 K.

From the above complexation studies it was clear that thioureas are highly efficient. Given the availability of thiourea derivatives, the great success of organocatalysts based on this functional group is not surprising.

Thioureas **1–4** showed better association constants than *m*-xylylene bis-acetamide **5** (9 M^{-1}). This latter skeleton probably presents too many degrees of freedom to become a good scaffold. An effective comparison of the contribution of the different scaffolds to the binding process is nevertheless difficult, because the influence of the substituents is of great importance. Isophthalic acid dibutylamide **7** showed a higher association constant (entry 7, 23 M^{-1}) than dimethyl thiourea **1** (16 M^{-1}), but substitution of one of the methyl groups by a tolyl unit transformed the thiourea **1** into a better receptor (entry 2, 47 M^{-1}). As expected, the more rigid xanthene derivatives enhanced the hydrogen bonding ability of the NH groups, showing higher association constants that ranged from 2.0×10^3 M^{-1} (receptor **9** functionalised with 4,5-bis-acetamide groups) to 6.0×10^3 M^{-1} (receptor **10** with 4,5-bis-thioacetamide moieties).

However, the most spectacular effect was related to the incorporation of the electron-withdrawing trifluoromethyl group. The replacement of a single methyl group in dimethyl thiourea **1** by a bis(trifluoromethyl)phenyl group (receptor **3**) increased the association constant from 16 M^{-1} to 5.3×10^2 M^{-1} (33-fold), and substitution of the second methyl afforded the Schreiner thiourea **4**, with an association constant of 1.0×10^5 M^{-1} (nearly 200 times better

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Table 1
Structure of receptors **1**–**11** and their association constants with triphenylarsine oxide in $CDCl_3$

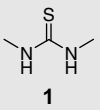
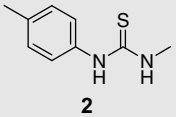
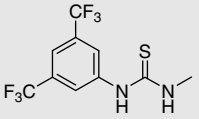
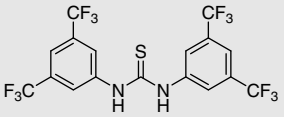
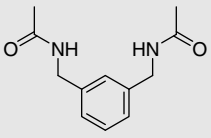
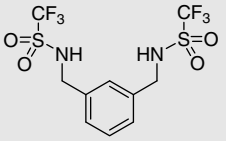
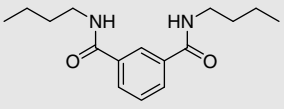
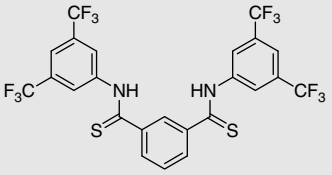
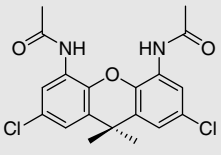
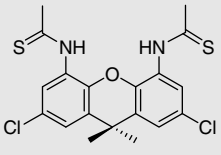
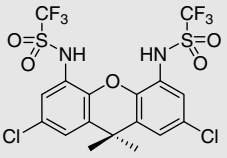
Entry	Receptor	K_{ass} (M^{-1})
1	 **1**	16
2	 **2**	47
3	 **3**	5.3×10^2
4	 **4**	1.0×10^5
5	 **5**	9
6	 **6**	4.5×10^2
7	 **7**	23
8	 **8**	4.2×10^4
9	 **9**	2.0×10^3
10	 **10**	6.0×10^3

Table 1 (*continued*)

Entry	Receptor	K_{ass} (M^{-1})
11[a]	 **11**	4.5×10^5

[a] The association constant was estimated from competitive titration with **4**.

than the monomethyl thiourea **3**). Discovery of the Schreiner thiourea[3h] is in this respect an outstanding achievement.

We also evaluated the remarkable changes in binding when *m*-xylylenediamine, isophthalic acid and 4,5-diamine-9,9-dimethylxanthene skeletons were modified using the trifluoromethyl group. The flexible *m*-xylylenediamine receptor now functionalised with triflamides (**6**) displayed an association constant as high as $4.5 \times 10^2\ M^{-1}$ (50-fold compared to **5**). An even more impressive effect was observed for the binding of receptor **8** and triphenylarsine oxide: the previously reported $K_{ass} = 23\ M^{-1}$ for the isophthalic acid dibutylamide **7** increased up to $4.2 \times 10^4\ M^{-1}$ (1800-fold) when bis(trifluoromethyl)phenyl groups were introduced through thioamide junctions.

Also as expected, receptor **11** with triflamide moieties on the xanthene framework provided the highest complexation constant, yielding a complex **4** times stronger than the Schreiner thiourea.

Given the excellent binding properties of receptors **11** and **4** with triphenylarsine oxide, we decided to extend our study to other guests, performing competitive titrations (Table 2):

In most cases, the xanthene triflamide **11** proved to be a better H-bond donor than the Schreiner thiourea, affording stronger complexes. Nevertheless, receptor **11** had a hindered cleft, and in the case of the sterically demanding triphenylphospine oxide the thiourea **4** formed a stronger associate (Table 2, entry 3). The data reported for As–O and P–O bond distances[7] support these experimental results: the shorter P–O bond involves steric hindrance between the phosphine oxide phenyl rings and the xanthene receptor **11**, hindering the binding process. However, when the less sterically hindered substrate trioctylphosphine oxide was used, the bistriflamide receptor **11** formed a stronger complex than the Schreiner thiourea (sixfold). The absolute association constants for the phosphine and arsine oxides were in the range of $10^5\ M^{-1}$–$10^4\ M^{-1}$.[8]

Sulfoxides and ketones are poorer H-bond acceptors, displaying lower association constants that change from $7.8 \times 10^3\ M^{-1}$ (tetramethylenesulfoxide and receptor **11**) to only $53\ M^{-1}$ (cyclohexanone and receptor **4**). In all cases, there is excellent agreement between the absolute association constants and the data obtained from competitive titrations.

Since the Schreiner thiourea proved to be a good catalyst of the Diels–Alder reaction and since receptor **11** was able to bind ketones, we examined the reaction between methyl vinyl ketone (**12**) and cyclopentadiene (**13**) under conditions similar to those reported by Schreiner[9] (Fig. 1).

Table 2
Competitive binding studies with receptors **11** and **4** in $CDCl_3$

Entry	Guest	K_{rel} (K_{11}/K_4)
1	$Ph_3As{=}O$	4.3
2	$Oc_3P{=}O$	6
3	$Ph_3P{=}O$	0.43
4	Tetramethylenesulfoxide	7.1
5	Cyclohexanone	1.9

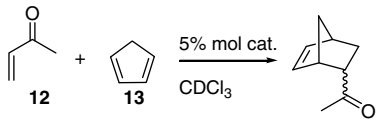


Figure 1. Diels–Alder reaction between methyl vinyl ketone and cyclopentadiene.

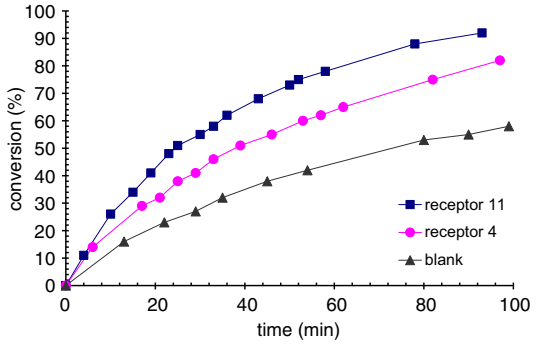


Figure 2. Kinetic studies for the Diels–Alder reaction between **12** and **13**.

The Diels–Alder reactions were carried out in a standard NMR tube containing a solution 0.1 M methyl vinyl ketone, 1.0 M cyclopentadiene and 5×10^{-3} M of catalyst (5 mol %, as referred to the ketone concentration).

Analysis of the kinetic data revealed that receptor **11** was a slightly better catalyst than the Schreiner thiourea for the reported reaction, reducing the half-life time of the reaction by a factor of 1.6 (25 min with catalyst **11** vs 40 min for catalyst **4**) (Fig. 2).

In sum, the xanthene receptor **11** reveals the efficiency of the oxyanion-hole geometry for the association of H-bond acceptors. The combination of this core with the bis(trifluoromethyl)phenyl group is currently underway in our laboratory as part of our search for bifunctional catalysts.

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