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Synthesis and NMR Binding Studies towards Rational Design of a Series of Electron-Withdrawing Diamide Receptors/Organocatalysts

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A related series of bisamides have been evaluated for rational correlation between anion complexation and organocatalysis: remarkable enhancement of hydrogen bonding to anions was observed along with significant increases in catalytic activity in the Baylis–Hillman reaction. In addition, X-ray crystallography showed a large degree of pre-organisation was observed in one receptor by incorporation of bis-(trifluoromethyl)aniline groups along with a thioamide functionality. A novel bifunctional amide/*N*-acylsulfonamide within the series gave the best catalytic profile.

Introduction

The recognition of anions is an ever-expanding field.[1] Many hosts incorporating functional groups such as indoles, pyrroles, sulfonamides, ureas and amides have been successful in selectively complexing a range of anionic guests via hydrogen bonding.[2] Often, these receptor molecules are designed with some degree of pre-organisation in mind, for example creating a cleft-like structure.[3,4] The use of metal-free organic molecules to catalyse reactions has also received intense interest.[5] The catalytic activity of several such organocatalysts involves coordination of groups such as those listed above via hydrogen bonding to highly negative or anionic intermediates.[6] Considering a major objective of both receptor and organocatalyst design is the molecular recognition of anions, much can be gained from taking a cooperative view between both areas, giving rise to the potential of dual application of molecular receptors for anion recognition and organocatalysis.[7]

Our interest lies in the rational design of receptors for selective anion binding and catalysis, specifically reactions where hydrogen bonding and electrophile activation play key mechanistic roles. Instead of the lengthy and potentially troublesome synthesis of transition state analogues for binding studies, we look to the binding characteristics of our target receptors with anions as a guide to catalytic mechanisms and in some cases, use anion binding properties as a mechanistic probe into organic reactions.

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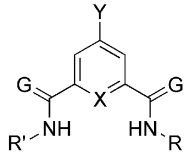
Results and Discussion

We assessed compounds **1**–**7** (Figure 1), based on the simple, flexible, minimally pre-organised motif first evaluated by Crabtree for anion binding, using binding characteristics to predict their applicability as efficient organic catalysts.[8] The well known receptor building blocks of iso-



1: X = CH; G = O; Y = H; R = *n*Bu
2: X = CH; G = O; Y = H; R = 4-$(CF_3)C_6H_4$
3: X = CH; G = O; Y = H; R = 3,5-$(CF_3)_2C_6H_3$
4: X = N; G = O; Y = H; R = 3,5-$(CF_3)_2C_6H_3$
5: X = CH; G = S; Y = H; R = 3,5-$(CF_3)_2C_6H_3$
6: X = CH; G = O; Y = NO_2; R = 3,5-$(CF_3)_2C_6H_3$
7: X = CH; G = O; Y = H; R = 3,5-$(CF_3)_2C_6H_3$; R' = $SO_2$3,5-$(CF_3)_2C_6H_3$

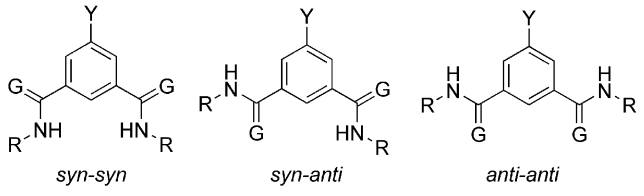


Figure 1. Structure of receptors **1**–**7** and their possible conformations.[11]

phthalic acid and 2,6-pyridinedicarboxylic acid[8] were used to generate a series of open-cleft bisamides **2**–**7** while **1** was used as a reference starting point.[9,10]

Each receptor differed by the nature of the groups attached to the amide skeleton, altering amide acidity and structural rigidity. To increase the acidity of the amide N–H groups and therefore increase hydrogen bonding,[12,13] the highly electron-withdrawing 4-trifluoromethylphenyl group (see **2**), 3,5-bis(trifluoromethyl)phenyl group (see **3**–**7**)[12] and also an additional *p*-nitro group (see **6**) were incorporated into the diamide structure. In addition, receptor **4** was designed to hold a degree of cleft pre-organisation and was expected to preferentially exist in the *syn-syn* conformation (Figure 1) most suitable for binding.[11,14] To circumvent the H-bond accepting properties of amides,[15] thioamide **5**, which is less likely to self associate[16] was also evaluated. This receptor might exist in the *syn–syn* conformation due to intramolecular interactions between acidic aromatic C–H groups and the sulfur atom as observed for some thiourea molecules.[13] Finally, a bifunctional hybrid amide/*N*-acylsulfonamide **7** was prepared incorporating both increased hydrogen bond donating properties and also the possibility to deprotonate the sulfonyl N–H; a potentially useful feature where proton transfer may occur and/or where activation of an electrophile plays a key role in the catalytic cycle.[17,18] In this paper, we report the synthesis, comparative anion binding properties, X-ray structure of **5** and preliminary catalytic and kinetic results in the Baylis–Hillman reaction.[19]

Receptor **1** was prepared according to literature procedures[20] while **2**–**6** were synthesised in a single step in good yields from commercially available starting materials. A four step synthetic sequence was employed for **7** (Scheme 1).

Initial binding studies conducted in $CDCl_3$ indicated strong association but were hindered by low solubility in some cases; therefore CD_3CN was used for further studies. The anion complexation properties were evaluated with tetra-*n*-butylammonium salts of bromide, chloride, acetate and benzoate. These anions represent different topologies (spherical vs. coplanar) and sizes and were chosen to give good indications of receptor selectivity and catalytic potential.

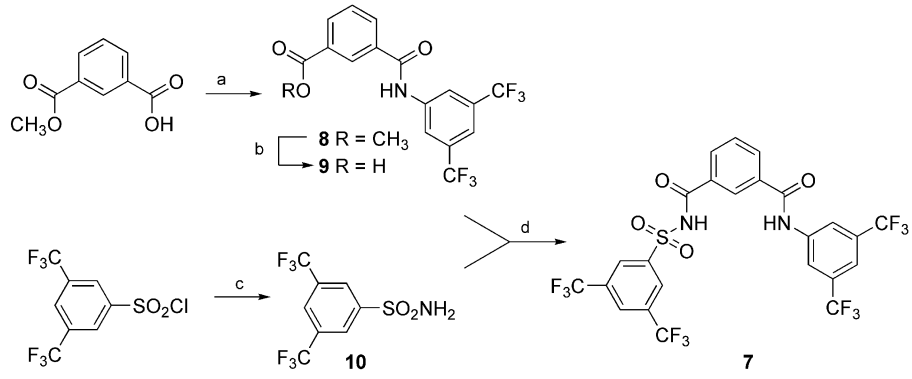
Standard ^1H NMR titration in CD_3CN at 298 K was employed with titration continued up to the addition of 10 equiv. of anion relative to receptor. Stability constants were obtained using the WINEQNMR2 program[21] (Table 1). JOB plot analysis was carried out for all receptors revealing 1:1 binding in most cases. The JOB plot for compound **6** with acetate and chloride possessed a minor contribution from 2:1 receptor: anion stoichiometry as observed by a small shoulder on the plot at 0.65 mol fraction receptor; however 1:1 stoichiometry was deemed to dominate. Interestingly, JOB plot analysis of **7** with chloride and bromide pointed solely to 2:1 receptor: anion stoichiometry. In the cases of **5** and **7** with acetate and benzoate, binding could not be accurately fitted to a 1:1 isotherm. This will be discussed later.

Table 1. Binding constants K_a (M^{-1}) for receptors **1**–**7** with bromide, chloride, acetate and benzoate as tetrabutylammonium salts at 298 K in CD_3CN. K_a values calculated based on N–H proton.

Receptor	Bromide	Chloride	Acetate	Benzoate
1	80	260	920	650
2	700	8,900	4,900	12,100
3	4,700	10,800	14,300	19,200
4	290	3,800	8,700	3,800
5	5,900	17,500	_[a,b]	_[a,b]
6	6,100	11,100	16,600	21,000
7	$K_a^{1:1}$ 900 $K_a^{2:1}$ 6,100	$K_a^{1:1}$ 4,000 $K_a^{2:1}$ 3,700	_[a,b]	_[a,b]

[a] Deprotonation prevented the calculation of an accurate association constant. [b] Did not reliably fit to a 1:1 model.

Receptor **1** was observed to bind all anions with association constants in the range 80–950 M^{-1}. Significantly enhanced anion complexation was found for receptors **2**–**6**, for example a 73-fold increase in binding strength in the case of **6** with bromide. A second notable example was thioamide **5** with chloride where, a 66-fold increase in K_a



Scheme 1. Synthesis of bifunctional receptor **7**. (a) 3,5-bis(trifluoromethyl)aniline, EDCI, DMAP, dichloromethane, room temp., 16 h, 92% (b) NaOH, methanol, reflux, 1 h, 77% (c) NH_3, Et_3N, DMF, room temp., 16 h, 98% (d) EDCI, DMAP, 50:50 dichloroethane:*tert*-butyl alcohol, room temp., 16 h, 43%.

was achieved; 17,500 M^{-1} for **5** compared to 260 M^{-1} for **1**. Receptor **6** gave the best 1:1 binding characteristics with strong binding to all anions studied.[22]

In all cases, the receptors were more efficient for chloride than bromide and this was ascribed to differing hydrogen bond capabilities[23] and also the size constraint of bromide as previously observed by Crabtree et al.[8] Receptors **3**, **4** and **6** gave highly efficient binding for the coplanar acetate and benzoate ions, particularly for benzoate with receptors **3** and **6** exhibiting 30- and 33-fold increases respectively in benzoate binding over the control **1**.

When comparing binding affinity for each of the anions with structural variation and amide acidity, **3** yielded significantly enhanced binding constants compared to the monotrifluoromethyl variant **2**. The more acidic thioamide **5** and also *p*-nitro derivative **6** gave even superior anion binding. However, the less flexible, more pre-organised **4** gave considerably lower K_a values, possibly due to electrostatic repulsion.[8]

Receptor **7** with bromide and chloride produced an excellent fit to a 1:1 and 2:1 receptor: anion species (Table 1).[24] We postulate these high 2:1 receptor: anion K_a values were due to the formation of a stable complex in which one anion is complexed between two receptors, with the higher 2:1 K_a for **7** with bromide ascribed to the large size of the bromide anion better able to accommodate this stoichiometry. Similar binding stoichiometries were previously reported by others.[25]

Receptors **5** and **7** produced interesting titration curves with acetate and benzoate as illustrated in Figure 2. For example in the case of **5** with acetate, the N–H signal disappeared and the titration was tracked using the isophthaloyl H2 proton between the thioamide groups. Initially, a minor upfield shift was observed followed by a significant downfield shift, with a second minor upfield shift upon addition of 1 equiv. acetate followed by significant downfield migration once again. We suggest this is due to initial desolvation of the receptor,[26] followed by strong hydrogen bonding to the anion, indicated by the subsequent downfield shift. The minor upfield shift at 1 equiv. anion poses two possibilities. With the increased acidity of the thioamide N–H, proton transfer to the carboxylate from the receptor could account for the chemical shift perturbation. Alternatively, the observed behavior may purely be a consequence of changing complex stoichiometries as the titration proceeds which may be facilitated by the more acidic receptor **5**. In either case a subsequent conformational change could allow for further binding events resulting in migration downfield of the H2 signal. Similar behavior was observed in the case of **5** with benzoate.

A similar but more pronounced effect was observed in the case of the more acidic **7** with both acetate and benzoate. As the sulfonyl N–H was not visible in the NMR spectrum, the titration was monitored using the amide N–H proton. Addition of up to 0.5 equiv. anion caused a downfield shift of the N–H resonance. Upon addition of a further 0.5 equiv. anion an upfield shift occurred, with an almost linear downfield migration upon further additions. Furthermore, the isophthaloyl H2 and the H4 protons of the bis(trifluoromethyl)phenyl rings broadened significantly up to addition of 1 equiv. anion but subsequently sharpened. We suggest this was due to an overall equilibrium process involving binding of the first 0.5 equiv. of anion generating a 2:1 receptor:anion complex followed by deprotonation of the highly acidic sulfonyl N–H which is known to have a similar pK_a to carboxylic acids.[17] This equilibrium process may account for the broadened signals up to 1 equiv. anion with the equilibrium driven to a single complexed species by addition of further anion. A conformational change may have occurred following the addition of

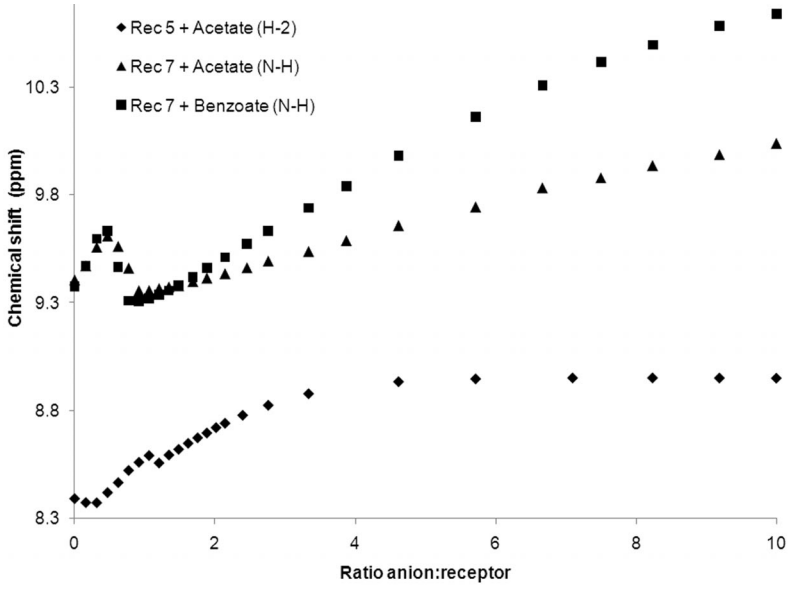


Figure 2. Binding curves of **5** with acetate and **7** with acetate and benzoate.

1 equiv. of anion allowing the amide N–H and isophthaloyl H4 to further bind anionic species. A similar trend involving deprotonation was observed for sulfonamide functionalised urea compounds[27] with evidence of conformational change allowing further binding events reported by Crabtree et al.[8] and Kilburn et al.[28]

In a number of cases, K_a values in excess of 10^4 M^{-1} were obtained for the most efficient receptors **2**, **3**, **5** and **6** with several anions. These titrations were repeated in the more competitive [D_6]DMSO and K_a values calculated (Table 2).[21]

Table 2. Binding constants K_a (M^{-1}) for strong binding systems in [D_6]DMSO at 298 K. 1:1 stoichiometry was observed in all cases.

Receptor	Chloride	Acetate	Benzoate
2	100	480	160
3	120	1,370	720
5	80	2,700[a]	2,540[a]
6	100	5,200	800

[a] Calculated based on isophthaloyl H2 signal.

For titrations conducted in [D_6]DMSO, the receptors appeared to possess a degree of selectivity for acetate, in particular receptor **6**. We suggest the increase in K_a values for **2**–**6** with acetate is linked to the increased acidity of the N–H bond as discussed earlier. Interestingly, **5** appeared to bind strongly to benzoate compared to **2**, **3** and **6**. This may be due to proton transfer as indicated by the broadening and subsequent loss of amide N–H signal after the addition of 1 equiv. of anion. In addition, conformational change is likely to play a role in accommodating the benzoate anion. Overall our results highlight the key role of solvent in binding and selectivity.

Gratifyingly, diffraction grade crystals of **5** (Figure 3) through slow evaporation of a chloroform/methanol mixture revealed its structure, with a crystallographic twofold axis through the middle of the molecule. The two nitrogen atoms are twisted in opposite directions out of the plane to minimise steric conflict and enable hydrogen bonding to a neighboring sulfur atom (Figure 3, b). In addition, **5** was found to exist in the solid state in its *syn-syn* conformation, possibly due to internal interactions with the polarized C–H bonds (H-7) ortho to the CF_3 group and the Lewis basic sulfur atom.[13] Further evidence supporting this conformation came from ^{1}H NMR spectroscopy. The chemical shift of this proton (H-7) lay further downfield in the case of thioamide **5** (δ = 8.53 ppm for **5**; 8.38 ppm for **3**), suggesting possible H-bonding interactions. Moreover, the proton *ortho* to both amide moieties (H2) was further upfield for **5** compared to the corresponding proton on **3**. This is in agreement with previously reported similar systems in which isophthaloyl H2 existed most upfield for an isophthalamide in the *syn-syn* conformation.[4] Therefore, it appears that a remarkable level of pre-organisation was achieved in this receptor, comparable to similar preorganisation effects which make some thiourea molecules effective for binding and catalysis.[13]

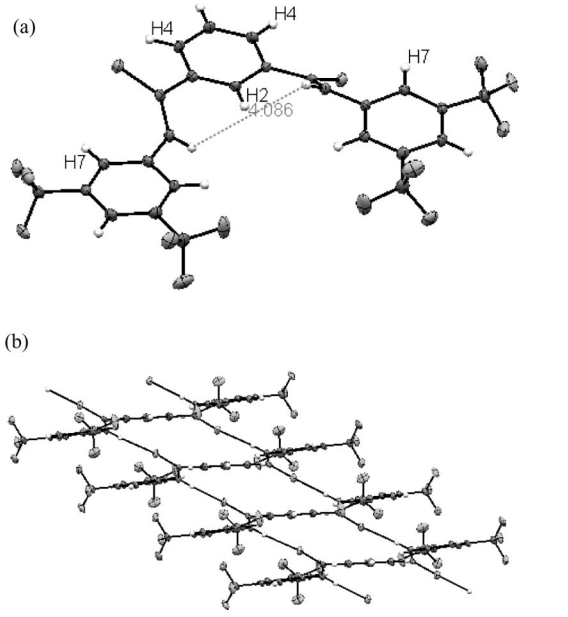
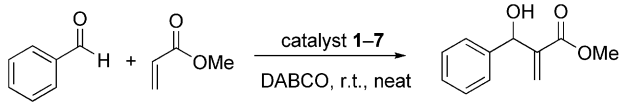


Figure 3. (a) X-ray crystal structure of **5** showing measurements between protons in the proposed anion binding cleft. (b) Crystal packing of **5**.

With the strong affinity of **2**–**7** for the acetate and benzoate anions in particular, they were applied as organocatalysts in the DABCO catalysed Baylis–Hillman reaction of benzaldehyde with methyl acrylate (Scheme 2).[19] It was envisaged that the oxyanion binding ability of these receptors would facilitate the catalysis of this highly useful reaction through stabilisation of the negative oxyanion intermediates of the reaction. In addition possible proton transfer steps could be accelerated by deprotonation of the catalyst as in the case of **5** and **7**.



Scheme 2. Baylis–Hillman reaction of methyl acrylate and benzaldehyde.

Initial reactions conducted in acetonitrile gave inferior yields to those under neat reaction conditions (Table 3). Under neat conditions in all cases, yield and rate enhancements were observed. Reaction yield after 20 h was determined after product isolation by column chromatography. A kinetic study by ^{1}H NMR spectroscopy using (*E*)-stilbene as an internal standard was undertaken in order to calculate the rate constant (k_{obs}) during the initial stages of the reaction (< 20% conversion). Receptor **7** gave the largest yield and rate constant, producing a 76% yield, a 2.2-fold increase in product formation, a factor of 3.9 times greater rate constant than the uncatalysed process (Figure 4). In addition, in the case of **7** it was possible to recycle the catalyst 3 times with less than a 5% reduction in catalytic activity.

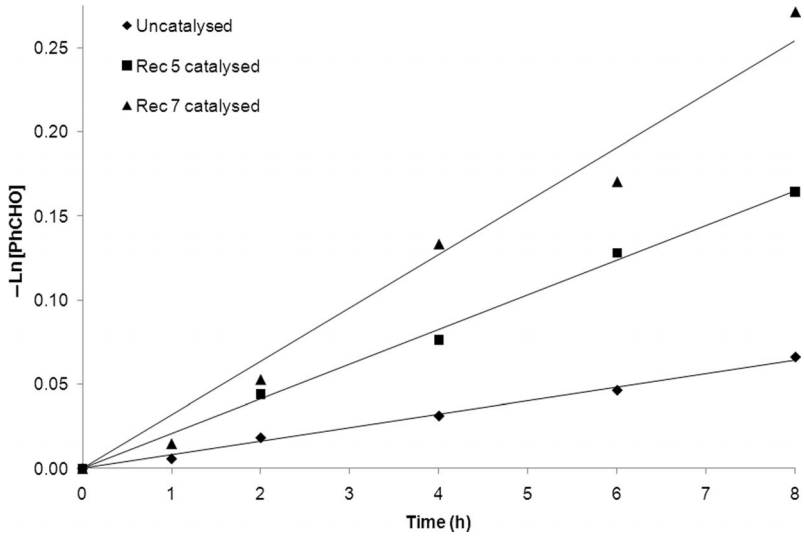


Figure 4. Kinetic plots and least square fits of –Ln[PhCHO] vs. time for receptor **5** and **7** catalysed Baylis–Hillman reaction. The uncatalysed reaction is also shown.

Table 3. Catalysis of Baylis–Hillman reaction of benzaldehyde and methyl acrylate using **1**–**7** as H-bond donating organocatalysts.

Receptor	Yield [%][a]	$k_{obsd} \times 10^{-2}$ [h^{-1}][b]	k_{rel}
Uncatalysed	34	0.82	1
1[c]	44	0.77	0.94
2[c]	50	0.55	0.67
3	68	2.38	2.9
4	–[d]	–[d]	–[d]
5	71	2.5	3.1
6	51	2.68	3.3
7	76	3.19	3.9

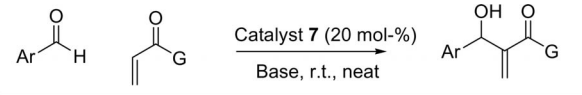
[a] Reagents and conditions: benzaldehyde (1 equiv.). DABCO (1 equiv.), methyl acrylate (3 equiv.), catalyst **1**–**7** (20 mol-%), room temp., 20 h. [b] Initial rates (< 20% conversion), 10 equiv. of methyl acrylate used; (*E*)-stilbene was used as an internal standard for ^{1}H NMR.[30] [c] Poor solubility in kinetic experiment. [d] Not determined due to complete insolubility of **4** in reactants.

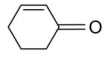
We propose that binding of our anion receptors to the negative intermediates in the reaction medium through the N–H group accelerates the reaction. In general, the increase in amide N–H polarisation of the receptor led to enhanced catalytic activity which was consistent with the findings of the binding studies; in the case of **1**, **2** and **3** there was excellent correlation between acetate K_a and catalytic performance. In addition, pre-organisation of the catalytic site of **5** may have contributed to its catalytic success. In the case of **5** and **7** proton transfer as observed in the binding studies along with increased acidity may account for the further increase in yield and reaction rate, particularly in light of reported mechanistic studies.[29]

Receptor **6** produced a disappointing yield of 51%. However, it produced an initial rate constant of 2.68 h^{-1}, slightly higher than that of the more successful catalysts **3**, **5** and **7**. We propose this is linked to strong binding of one of the several anionic species involved in the reaction cycle causing inhibition. This is supported by the earlier binding studies (Table 1).

In addition, kinetic experiments conducted for **3** and **7** in the presence of 1 equiv. of tetra-*n*-butylammonium benzoate resulted in substantially diminished rate constants; 86% and 50% respectively. This was deemed to be due to competition between the anionic intermediates and benzoate for the H-bonding sites of these catalysts.

Table 4. Baylis–Hillman reaction using a variety of substrates and bases catalysed by **7**.



Ar	G	Base	mol-% **7**	Time (h)	Yield %[a]
C_6H_5	OMe	DABCO	–	20	34
C_6H_5	OMe	DABCO	20	20	76
C_6H_5	OMe	DMAP	–	20	8
C_6H_5	OMe	DMAP	20	20	41
C_6H_5	OMe	DBU	–	20	33
C_6H_5	OMe	DBU	20	20	34
C_6H_5	OMe	PPh_3	–	20	trace
C_6H_5	OMe	PPh_3	20	20	trace
o-$O_2NC_6H_4$	OMe	DABCO	–	1	79
o-$O_2NC_6H_4$	OMe	DABCO	20	1	86
o-MeC_6H_4	OMe	DABCO	–	42	6
o-MeC_6H_4	OMe	DABCO	20	42	22
o-$MeOC_6H_4$	OMe	DABCO	–	72	6
o-$MeOC_6H_4$	OMe	DABCO	20	72	55
p-FC_6H_4	OMe	DABCO	–	42	69
p-FC_6H_4	OMe	DABCO	20	42	82
p-MeC_6H_4	OMe	DABCO	–	36	19
p-MeC_6H_4	OMe	DABCO	20	36	38
p-$MeOC_6H_4$	OMe	DABCO	–	96	4
p-$MeOC_6H_4$	OMe	DABCO	20	96	19
C_6H_5	O-*t*Bu	DABCO	–	20	4
C_6H_5	O-*t*Bu	DABCO	20	20	28
C_6H_5		DABCO	–	38	4
C_6H_5		DABCO	20	38	59

[a] Isolated yield after flash chromatography.

Following on from this work, we examined the generality and scope of our most successful catalyst **7**. Initially variation of the base in the reaction of benzaldehyde with methyl acrylate was examined. Triphenylphosphane, DBU and DMAP were evaluated and in all cases inferior yields compared to DABCO were obtained. Subsequently, with the optimum catalyst and base in hand, we examined the substrate scope of the reaction of methyl acrylate with activated and de-activated aldehydes. Finally, reaction of a number of different Michael acceptors with benzaldehyde were investigated. In all cases, **7** afforded significant yield enhancement compared to the uncatalysed reactions (Table 4) with catalytic effect observed for all substrates and Michael acceptors studied.

Considerable yield enhancement was observed in many cases, particularly in systems where deactivated aldehyde derivatives were employed, e.g. a 4.8- and 9.2-fold increase in product formation for deactivated 2- and 4-substituted methoxybenzaldeyde. Another notable example is reaction of benzaldehyde with 2-cyclohexen-1-one, where a 15-fold increase in product formation was observed. It is also worth noting the ease of recoverability of the catalyst in each reaction. The catalyst could be obtained with high purity during the catalytic product isolation step of flash chromatography.

Further catalytic studies are currently underway in our laboratory including application of the receptors in alternative reactions.

Conclusions

To summarise, we synthesised a series of rationally designed diamides and evaluated their properties as anion receptors and organocatalysts in the Baylis–Hillman reaction. Equilibrium binding was determined by NMR titration and catalytic activity was assessed by product yield and kinetic measurements. X-ray crystal structure of receptor **5** also showed an unexpected level of preorganisation within the flexible thioamide motif. The anion binding constants of the receptor series with increasing hydrogen bond donating capability provided a useful tool to probe the catalytic activity of these receptors. Ongoing work in this area involves further structural modification of the motif along with their application to other reactions.

Experimental Section

Synthesis of New Receptors

Receptor 2: To a solution of 4-trifluoromethylaniline (1.60 g, 9.9 mmol) in DMF (30 mL) was added triethylamine (1.52 g, 15 mmol) and DMAP (1.21 g, 9.9 mmol). The reaction mixture was cooled to 0 °C and isophthaloyl dichloride (1 g, 4.9 mmol) was added in small portions over 2–3 min. The solution was stirred at 90 °C for 20 h. After this time the dark brown mixture was added to water (300 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with 5% lithium chloride solution (2 × 80 mL) and deionised water (2 × 100 mL) to remove DMF. The product was dried with $MgSO_4$ and solvent removed in vacuo. The crude was purified by column chromatography, eluting with 80:20 hexane/ethyl acetate. The solvent was removed in vacuo to give **2** (1.20 g, 54%) as a white solid; m.p. 256–258 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3296, 3144, 1651, 1605, 1537, 1321, 1258, 837 and 715. ^{1}H NMR (400 MHz, CD_3CN, 22 °C): δ = 9.17 (s, 2 H, N–H), 8.53 (t, $J_{H,H}$ = 1.53 Hz, 1 H, 2-H), 8.15 (dd, $J_{H,H}$ = 8.4 and 1.53 Hz, 2 H, 2′-H), 7.97 (d, $J_{H,H}$ = 8.4 Hz, 2 H, 3′-H), 7.76 (d, $J_{H,H}$ = 7.6 Hz, 2 H, 4-H), 7.69 (t, $J_{H,H}$ = 7.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, CD_3CN, 22 °C): δ = 166, 143, 135, 132, 129, 128 126.5, 126.2, 124.2, 121 ppm. LRMS (ES$^+$): *m*/*z* = 453 [M + H]$^+$. HRMS: *m*/*z* for $C_{22}H_{15}N_2O_2F_6$ (M^+) calcd. 453.1038; found 453.1026.

Receptor 4: To a solution of 3,5-bis(trifluoromethyl)aniline (2.27 g, 9.9 mmol) in DMF (30 mL) was added triethylamine (1.52 g, 15 mmol) and DMAP (1.21 g, 9.9 mmol). The mixture was cooled to 0 °C and pyridine-2,6-dicarboxyl chloride (0.99 g, 1 mmol) was in small portions over 4–5 min. The reaction was held at 75–80 °C for 18 h and subsequently poured into a large volume of water (300 mL). The resulting white solid product was isolated from the solvent by filtration. The crude was purified by trituration using ethyl acetate to give the title product **4** (0.96 g, 34%) as a white solid; m.p. 341–342 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3284, 3101, 1686, 1550, 1572, 1472, 1437, 1383, 1279, 1175, 1146, 1068, 1001, 936, 889, 840 and 683. ^{1}H NMR (400 MHz, CD_3CN, 22 °C): δ = 10.51 (s, 2 H, N–H), 8.60 (s, 4 H, 2′-H), 8.50 (d, $J_{H,H}$ = 8.2 Hz, 2 H, 4-H), 8.29 (t, $J_{H,H}$ = 8.2 Hz, 1 H, 5-H), 7.82 (s, 2 H, 4′-H) ppm. LRMS (ES$^+$): *m*/*z* = 590 [M + H]$^+$. HRMS: *m*/*z* for $C_{23}H_{12}N_3O_2F_{12}$ (M^+) calcd. 590.0738; found 590.0716.

Receptor 6: To 5-nitroisophthalic acid (1 g, 4.74 mmol) was added dry dichloromethane (30 mL) under N_2 atmosphere. To this was added DMAP (1.16 g, 9.47 mmol), EDCI (1.82 g, 9.47 mmol) and 3,5-bis(trifluoromethyl)aniline (2.17 g, 9.47 mmol) and the off-white coloured suspension was stirred at room temperature for 16 h. The resulting reaction mixture was washed with 1 M HCl, 10% aqueous sodium hydrogen carbonate, saturated NaCl, and the product dried with $MgSO_4$. The solvent was removed in vacuo to leave a yellow crude oil, 1.48 g. which was purified by flash chromatography (85% hexane:15% ethyl acetate) to give the title compound **6** (1.52 g, 51%) as a white solid; m.p. 310–312 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3245, 3084, 1659, 1549, 1381, 1280, 1179, 1136 and 893. ^{1}H NMR (400 MHz, CD_3CN, 22 °C): δ = 9.53 (s, 2 H, N–H), 8.99 (d, $J_{H,H}$ = 1.5 Hz, 2 H, 4-H), 8.94 (t, $J_{H,H}$ = 1.5 Hz, 1 H, 2-H), 8.38 (s, 4 H, 2′-H), 7.81 (s, 2 H, 4′-H) ppm. ^{13}C NMR (125 MHz, CD_3CN, 22 °C): δ = 163, 148.5, 140, 136, 132.5, 131.5, 125.5, 124.5, 122, 120 ppm. LRMS (ES$^+$): *m*/*z* = 634 [M + H]$^+$. HRMS: *m*/*z* for $C_{24}H_{10}N_3O_4F_{12}$ (M^-) calcd. 632.0480; found 632.0497.

Receptor 7: To mono-methyl isophthalate (1.0 g, 5.55 mmol) in dichloromethane (30 mL) was added DMAP (0.68 g, 5.55 mmol), EDCI (1.06 g, 5.55 mmol) and 3,5-bis(trifluoromethyl)aniline (1.27 g, 5.55 mmol) and the mixture was stirred at room temperature for 16 h. The reaction mixture was then washed with water and 1 M HCl. The white solid precipitate was collected by filtration and purified by flash chromatography (80% hexane:20% ethyl acetate) to give **8** as a white solid, (2.0 g, 92%); m.p. 293–295 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3416, 3271, 3104, 3003, 2958, 1717, 1661, 1569, 1471, 1443, 1382, 1278, 1258, 1172, 1123, 943, 891, 720 and 686. ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C): δ = 8.51 (s, 1 H, 2-H), 8.32 (s, 1 H, N–H), 8.26 (d, $J_{H,H}$ = 7.6 Hz, 1 H, 6-H), 8.23 (s, 2 H, 2′-H), 8.17 [d, $J_{H,H}$ = 7.6 Hz, 1 H, 4-H], 7.68 (s, 1 H, 4′-H), 7.64 (t, $J_{H,H}$ = 7.6 Hz, 1 H, 5-H), 3.98 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, CD_3CN, 22 °C): δ = 166.5, 164.5, 139.2, 134.1, 133.5, 132.3, 130.9, 129.6, 127.6, 124.5, 122, 120, 118, 52.7 ppm. LRMS (ES$^+$): *m*/*z* =

392 $[M + H]^+$. HRMS: *m/z* for $C_{17}H_{10}NO_3F_6$ (M^-) calcd. 390.0565; found 390.0562.

To ester **8** (1.67 g, 4.26 mmol) dissolved in hot methanol (40 mL) was added 1 M NaOH, (20 mL, 20 mmol) and the mixture was refluxed with stirring for one hour. Distilled water (100 mL) was added to the mixture which was then acidified to pH 3 with concentrated aqueous HCl. The mixture was cooled and filtered to give **9** (1.24 g, 77%) as a white solid; m.p. 194–196 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3292, 3092, 2662, 2551, 1690, 1651, 1562, 1470, 1441, 1381, 1305, 1279, 1175, 1146, 943, 893, 728 and 683. ^{1}H NMR (400 MHz; [D_6]-DMSO, 22 °C): δ = 13.3 (br. s, 1 H, OH), 11.02 (s, 1 H, N–H), 8.57 (s, 1 H, 2-H), 8.51 (s, 2 H, 2′-H), 8.21 (d, $J_{H,H}$ = 7.6 Hz, 1 H, 6-H), 8.15, (d, $J_{H,H}$ = 7.6 Hz, 1 H, 4-H), 7.80 (s, 1 H, 4′-H), 7.67 (t, $J_{H,H}$ = 7.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz; [D_6]DMSO, 22 °C): δ = 166.7, 165.4, 134.2, 132.8, 132.2, 130.8, 129.1, 128.5, 124.6, 121.9, 120, 116.6 ppm. LRMS (ES^+): *m/z* = 378 $[M + H]^+$. HRMS: *m/z* for $C_{16}H_8NO_3F_6$ (M^-) calcd. 376.0484; found 376.0423.

Aqueous ammonia (2 mL), triethylamine (3.64 mmol, 0.5 mL) were added to DMF (20 mL), the reaction mixture cooled to 0 °C and to this was added dropwise 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (0.5 g, 1.6 mmol). The reaction mixture was stirred at room temperature for 16 h and to this was added 300 mL distilled water. The basic reaction mixture was acidified to pH 2 by addition of concentrated HCl causing the product to precipitate out of solution. The off-white precipitate **10** (0.46 g, 98%) was collected by filtration; m.p. 184.5–185 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3356, 3262, 3097, 3067, 1862, 1833, 1626, 1531, 1457, 1324, 1197 and 907. ^{1}H NMR (400 MHz; [D_6]DMSO, 22 °C): δ = 8.46 (s, 1 H, 4-H), 8.40 (s, 2 H, 2-H), 7.79 (s, 1 H, NH_2) ppm. ^{13}C NMR (100 MHz; [D_6]DMSO, 22 °C): δ = 147, 131, 127, 124.6, 121.9 ppm. LRMS (ES^+): *m/z* = 294 $[M + H]^+$. HRMS: *m/z* for $C_8H_4NO_2F_6S$ (M^-) calcd. 291.9867; found 291.9864.

Acid **9** (370.5 mg, 0.98 mmol) was dissolved in a 50:50 mixture of dichloroethane:*tert*-butyl alcohol (20 mL) and to this stirred suspension was added DMAP (360 mg, 2.95 mmol), EDCI (472 mg, 2.46 mmol) and 3,5-bis(trifluoromethyl)benzenesulfonamide (**10**) (200 mg, 0.68 mmol). The reaction mixture was stirred for 72 h at room temperature and after this time Amberlyst 15 anion exchange resin (2 g) was added and the mixture was diluted with ethyl acetate (10 mL). This mixture was stirred for a further 2 h and subsequently passed through a plug of silica gel and washed with ethyl acetate. The filtrate was collected and solvent removed in vacuo. The crude product was purified by flash chromatography (98% dichloromethane/2% methanol) to give product **7** (187 mg, 43%) as an off white solid, m.p. 241.5–242.3 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3450, 3318, 3093, 2927, 1667, 1608, 1553, 1471, 1380, 1353, 1179, 888, 844 and 682. ^{1}H NMR (400 MHz, CD_3CN, 22 °C): δ = 9.37 (s, 1 H, Amide N–H), 8.61 (s, 1 H, 2-H), 8.52 (s, 2 H, 2′′-H), 8.33 (s, 2 H, 2′-H), 8.13 (d, $J_{H,H}$ = 7.6 Hz, 1 H, 6-H), 8.09 (s, 1 H, 4′′-H), 7.96 (d, $J_{H,H}$ = 7.6 Hz, 1 H, 4-H), 7.69 (s, 1 H, 4′-H), 7.39 (t, $J_{H,H}$ = 7.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz; [D_6]DMSO, 22 °C): δ = 169, 166, 148, 141, 138, 133, 132, 130, 128, 127.9, 127.6, 124.7, 124.4, 123.9, 122, 121.7, 120, 116 ppm. LRMS (ES^-): *m/z* = 651 $[M - H]^-$. HRMS: *m/z* for $C_{24}H_{11}N_2O_4F_{12}S$ (M^-) calcd. 651.0248; found 651.0242.

CCDC-796511 contains the supplementary crystallographic data for **5**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Full experimental procedures, characterisation data, NMR stack plots and rate plots.

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