Catalysis of aldehyde imination by hydrogen bonding with a simple organic disulfonamide receptor

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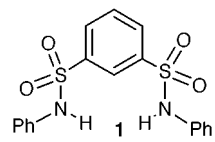
The disulfonamide receptor 1 catalyzes imine formation from aldehyde and amine, apparently by binding the transition state for the rate-determining nucleophilic attack of amine on the aldehyde.

Catalysis by abiotic receptors[1] is a rapidly developing field in supramolecular chemistry, and systems have been developed that mimic enzyme properties by binding preferentially the transition state over the ground (reactant) state.[2] Most compounds developed for that purpose are macrocycles.[3] Molecular clefts with appropriately convergent recognition sites can give unexpectedly strong binding for anionic substrates[4] and some elegant examples of open clefts catalyzing reactions involving anionic transition states *via* hydrogen bonding have been reported.[5] The increased skeleton flexibility in open clefts *vs.* macrocycles can be favorable for catalysis if the open-chain receptor accommodates better the changes along the reaction coordinate.[1b] In other examples, interaction of the anionic intermediate with a metal center[6] rather than with a hydrogen bond donor group is responsible for catalysis. Some of the reported cases[6b–f] involve imine formation catalysis.

Receptor **1** seemed a good choice as an imine formation



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catalyst because it is known[4b] to bind strongly to halide ions as well as acetate [*e.g.* $K_a(M^{-1}) = 2.1 \times 10^4$ for the 1:1 complex with OAc^-]. The reaction of an aldehyde with an amine to give an imine was chosen as the catalytic reaction because the rate determining[7] nucleophilic attack of amine has a R(Nu)HC–O^- transition state that should be bound more tightly than the starting aldehyde. The imine product, having only one lone pair, is not expected to be optimally bound by the receptor, so catalyst poisoning by the imine product should be avoided. We now find that the easily available[4b] disulfonamide **1** catalyzes the reaction of eqn. (1) at −20 °C in CD_2Cl_2 with anhydrous $MgSO_4$ present to remove water (Bn = benzyl).

$$p\text{-}MeC_6H_4CHO + BnNH_2 \rightarrow p\text{-}MeC_6H_4CH{=}NBn + H_2O \quad (1)$$

Initial rate experiments, carried out under pseudo-first order conditions[8] show that **1** (8 mol% *vs.* RCHO) is an effective catalyst for the reaction, causing a 6.1-fold acceleration of imine formation (Figs. 1 and 2) as measured by ^{1}H NMR resonance integrations. The initial rate of imine formation was increased by a factor of 6.1 in the presence of catalyst as compared to the control which did not contain **1**. Eqn. (1) is subject to general acid catalysis, and the most appropriate control is *o*-chlorophenol because it has a pK_a (8.49) most comparable with the disulfonamide **1** (p$K_a \approx 8.05$).[9] As shown in Fig. 1(*c*), even 100 mol% of *o*-chlorophenol only shows a small rate acceleration *versus* 8 mol% of **1** [Fig. 1(*a*)]. 100 mol% of phenol [pK_a = 9.89, Fig. 1(*e*)] gave almost no acceleration. Only much stronger acids, such as *p*-nitrophenol [pK_a = 7.15, Fig. 1(*b*)], gave substantial acceleration.

By analogy with the known[4] mode of association of anions with the receptor, a favorable two point hydrogen bonding interaction of the two convergent sulfonamide groups with the anionic oxygen of the transition state for eqn. (1) (see **2**) may be responsible for catalysis.

The known[4b] binding properties of **1** with oxyanions allow an estimate of the association constant (K_a) for the transition state **2**. For acetate, the observed K_a of 2.1×10^{-4} M^{-1} corresponds to a ΔG of binding of −24.2 kJ mol^{-1}. By transition state theory, often used to predict rate enhancements,[10] the rate acceleration is related to the ratio of the binding constant of the receptor with the transition state *versus* the binding constant with the substrate. We were not able to accurately determine the binding constant with the substrate owing to exchange of the

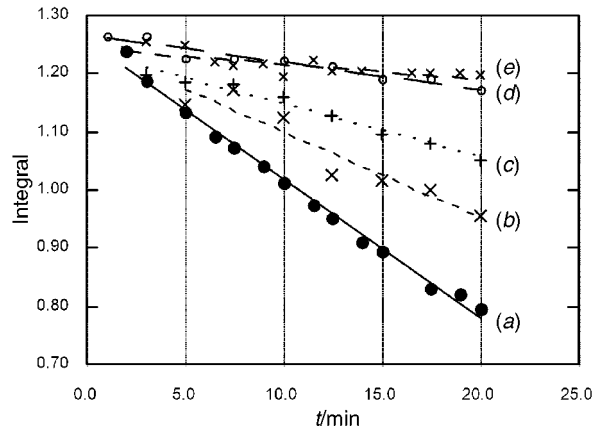

Fig. 1 Initial rate data (change in CHO integral at δ 9.94): (*a*) 8 mol% **1**; (*b*) 8 mol% *p*-nitrophenol, (*c*) 100 mol% *o*-chlorophenol, (*d*) no additive, (*e*) 100 mol% phenol.

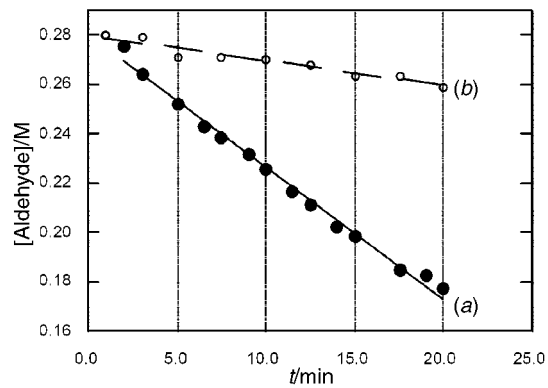

Fig. 2 The decrease of the aldehyde concentration with time (derived from the ^{1}H NMR integral of the aldehyde proton) under pseudo first-order conditions showing (*a*) the catalytic effect of the receptor *versus* (*b*) the uncatalyzed rate.

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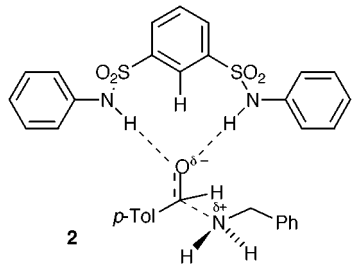

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N–H sulfonamide resonance with trace protic impurity and the chemical shift change for the C–H aromatic resonance being too small to allow accurate titration monitoring. From literature data,[5a] association constants in CH_2Cl_2 for hydrogen bond receptors having two convergent hydrogen bond donor groups with neutral carbonyl substrates are in the range of 1 to 2×10^3 M^{-1}. Assuming that the transition state is bound to the receptor approximately as well as acetate (2×10^4 M^{-1}) an acceleration factor of 10–20 is predicted, a value comparable with the experimental value of 6.1.

Molecular cleft receptors, even very simple ones like **1**, can be catalytically active for reactions such as eqn. (1), where the transition state for the slow step is thought to be bound more strongly than starting materials or products. As a cleft rather than a macrocycle, this receptor is expected to bind the substrate carbonyl group without significantly blocking access of the nucleophile to the carbonyl.

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Notes and references

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8 With excess amine, observing the disappearance of the *p*-Me and CHO resonances of the aldehyde and the appearance of the *p*-Me and CH_2 resonances of the imine. In a typical experiment, a 5 mm NMR tube containing *p*-tolualdehyde (0.025 ml, 0.21 mmol) and anhydrous $MgSO_4$ (5.2 mg, 0.043 mmol) in 0.750 ml of CD_2Cl_2 was introduced into the probe and left at −20 °C to equilibrate. Receptor **1** (6.3 mg, 0.016 mmol) was added and the spectrum recorded, then $BnNH_2$ (0.250 ml, 2.3 mmol) was added and the aldehyde resonances (δ 9.94, 2.45) and the imine resonances (δ 4.80, 2.41) were monitored. Plotting the integration values *vs*. time for the first 20 min and linear fitting of the straight line gave the initial rates.

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