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# Three Hydrogen Bond Donor Catalysts: Oxyanion Hole Mimics and Transition State Analogues

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Supporting Information

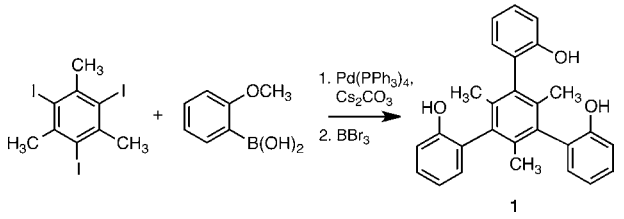
**ABSTRACT:** Enzymes and their mimics use hydrogen bonds to catalyze chemical transformations. Small-molecule transition state analogues of oxyanion holes have been characterized by computations, gas-phase IR and photoelectron spectroscopy, and determination of their binding constants in acetonitrile. A new class of hydrogen bond catalysts is proposed (donors that can contribute three hydrogen bonds to a single functional group) and demonstrated in a Friedel–Crafts reaction. The employed catalyst was observed to react 100 times faster than its rotamer that can employ only two hydrogen bonds. The former compound also binds anions more tightly and was found to have a thermodynamic advantage.

Nucleophilic addition reactions are often catalyzed by oxyanion holes in enzyme-catalyzed processes.[1] Thousands of X-ray crystal structures indicate that nature typically makes use of two hydrogen bonds to facilitate these transformations.[2] Inspired by this observation, chemists have mimicked this behavior and developed a wide variety of hydrogen bond catalysts.[3] The most successful and widely employed of these species are thioureas [RNHC(S)NHR]. These compounds accelerate reactions by binding to a substrate and increasing its electrophilicity or alternatively by coordinating to an anionic leaving group and generating a reactive carbenium ion intermediate.[4] Transition state analogues for these processes are characterized herein, and the first report of a new catalyst class that makes use of three O–H hydrogen bond donors is described.[5,6]

Thioureas have two N–H bonds, which play a critical role in their effectiveness as hydrogen bond catalysts. Their acidities also can be enhanced with substituents, which is important as well because more acidic derivatives are better (i.e., more reactive) catalysts.[7] Oxygen acids are inherently more acidic than their nitrogen analogues, however, because oxygen is more electronegative than nitrogen. Several enzymes that use three hydrogen bonds in their oxyanion holes for catalysis have also been identified.[8] This suggested to us that compounds containing three hydrogen bond donors might be an effective new catalyst class and that candidates with three OH groups are particularly attractive targets.

To explore whether a three hydrogen bond donor can confer an energetic and kinetic advantage over a two hydrogen bond donor, 1,3,5-triarylbenzene **1** was synthesized as illustrated in Scheme 1. In this compound, the peripheral aromatic rings are known to be twisted with respect to the central one.[9] As a result, all three OH groups can be on one side of the central benzene ring or two hydroxyl substituents can be on one side and the third on the other (i.e., syn and anti rotamers, respectively). The rotation barrier is large enough in both cases to prevent the two rotamers from interconverting at room temperature. Isomerization does take place in refluxing mesitylene, and upon cooling, the two isomers can be separated by medium-pressure liquid chromatography.

**Scheme 1. Synthesis of Triarylbenzene 1**




1

The rotamers *syn*- and *anti*-**1** readily form complexes with chloride ion upon electrospray ionization (ESI).[10] These small-molecule clusters can be viewed as transition state analogues for oxyanion holes and hydrogen bond catalysts. To determine whether *syn*-**1**·$Cl^-$ and *anti*-**1**·$Cl^-$ are distinct species or if they interconvert upon ESI, their multiphoton IR action spectra were recorded with a Fourier transform mass spectrometer equipped with an optical parametric oscillator (OPO)/optical parametric amplifier (OPA) laser system that has been described previously (Figure 1).[11] The two spectra are distinct, indicating that the two isomers do not interconvert upon ESI.

An absorbance was observed at 3545 $cm^{-1}$ for *anti*-**1**·$Cl^-$ but not for the syn isomer. This feature corresponds to a free O–H stretch, which would be expected for *anti*-**1**·$Cl^-$ because one chloride anion cannot coordinate simultaneously with all three hydroxyl groups in this compound. The absence of this band, and any other above 3100 $cm^{-1}$, in the spectrum of *syn*-**1**·$Cl^-$ indicates that all three of the OH substituents form hydrogen bonds with the chloride ion in this isomer. In accord with these observations, the most favorable M06-2X/aug-cc-pVDZ-computed structures[12,13] for the *anti*- and *syn*-**1** cluster ions have two and three hydrogen bonds to $Cl^-$, respectively (Figure

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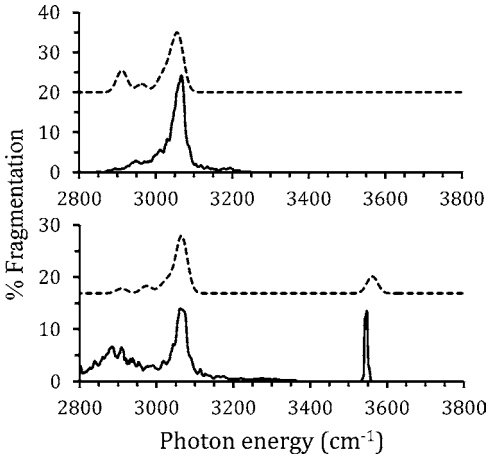


**Figure 1.** IR action spectra of (top) *syn*-**1**·$Cl^-$ and (bottom) *anti*-**1**·$Cl^-$ from 2800 to 3800 $cm^{-1}$. B3LYP/aug-cc-pVDZ predictions are shown as dotted lines; see the Supporting Information for more details.

2). Fragmentation of these complexes to *anti*- or *syn*-**1** and $Cl^-$ were predicted by density functional theory (M06-2X/maug-cc-pVT(+d)Z//M06-2X/aug-cc-pVDZ)[14] to be endothermic by 40.3 and 47.2 kcal $mol^{-1}$ at 298 K, respectively.[15] This 6.9 kcal $mol^{-1}$ difference is largely due to the presence of three hydrogen bonds in the syn complex versus only two in the anti species.

To characterize these cluster ions further and obtain an experimental measure of the hydrogen bond interaction energies with $Cl^-$, photoelectron spectra of PhOH·$Cl^-$, *anti*-**1**·$Cl^-$, and *syn*-**1**·$Cl^-$ generated by ESI were recorded at 20 K using a $F_2$ laser at 157 nm (7.867 eV) (Figure 3).[16] As expected, the spectra of the *anti*- and *syn*-**1** complexes with $Cl^-$ are different, indicating once again that the two ions are distinct and do not interconvert upon ESI. On the basis of the rapidly rising onset energies for all three species, estimates of the adiabatic electron detachment energies (ADEs) of 4.15 (PhOH·$Cl^-$), 4.65 (*anti*-**1**·$Cl^-$), and 4.80 eV (*syn*-**1**·$Cl^-$) were obtained. All of these values are larger than that for $Cl^-$ (ADE = 3.6131 eV)[17,18] and were well-reproduced by M06-2X/maug-cc-pVT(+d)Z//M06-2X/aug-cc-pVDZ computations, which gave values of 3.88, 4.67, and 4.72 eV, respectively. The experimental differences with respect to $Cl^-$ [i.e., ADE(cluster) − ADE($Cl^-$)] are 12.4, 23.9, and 27.4 kcal $mol^{-1}$, respectively,

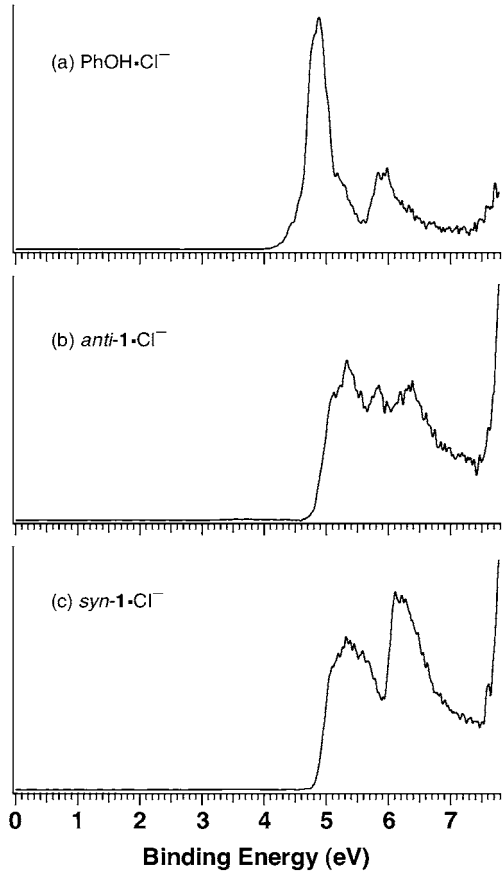


**Figure 3.** Low-temperature (20 K) photoelectron spectra of (a) PhOH·$Cl^-$, (b) *anti*-**1**·$Cl^-$, and (c) *syn*-**1**·$Cl^-$ at 157 nm (7.867 eV).

reflecting the stabilization of the chloride anion by 1−3 hydrogen bonds. These values cannot be equated to the hydrogen bond strengths or the disassociation enthalpies but instead correspond to lower limits for these quantities because electron detachment of the anions leads to neutral clusters that have stabilizing OH−chlorine atom interactions. This is a result of the large difference in the H−Cl (103.2 kcal $mol^{-1}$) and PhO−H (88.1 kcal $mol^{-1}$) bond dissociation energies.[19] As a result, the ADE(PhOH·$Cl^-$) − ADE($Cl^-$) value of 12.4 kcal $mol^{-1}$ is significantly smaller than the measured dissociation enthalpy of 26.0 ± 2.0 kcal $mol^{-1}$ for PhOH·$Cl^-$.[20] The 3.5 kcal

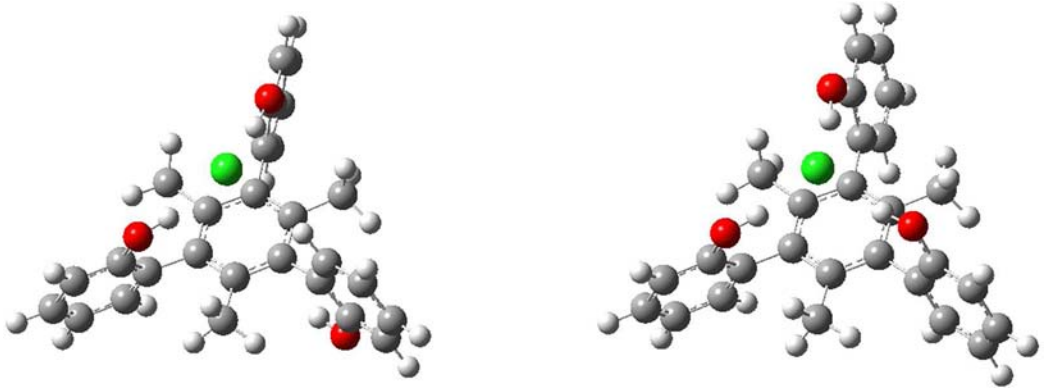

**Figure 2.** M06-2X/aug-cc-pVDZ-computed structures of (left) *anti*-**1**·$Cl^-$ and (right) *syn*-**1**·$Cl^-$. The OH···$Cl^-$ and O···$Cl^-$ distances are 2.116 and 2.121 Å (OH−Cl) and 3.067 and 3.071 Å (O−Cl) for *anti*-**1**·$Cl^-$ and 2.145, 2.145, and 2.146 Å (OH−Cl) and 3.089, 3.089, and 3.090 Å (O−Cl) for *syn*-**1**·$Cl^-$.


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$mol^{-1}$ energy difference between the ADEs of *anti*-**1**·$Cl^-$ and *syn*-**1**·$Cl^-$, however, is a measure of the stabilization resulting from an additional hydrogen bond. It also indicates that there is a thermodynamic preference for the formation of three hydrogen bonds to $Cl^-$ rather than two.

In view of the biological importance of anion binding in ion channels and anion transporters[21] and the physiological role of chloride anion in stabilizing membrane potentials, regulating cell volume, and inhibiting synapses,[22] the association constants of *anti*- and *syn*-**1** with halide anions were measured in acetonitrile by UV or $^1$H NMR spectroscopy at 23 °C (Table 1). The binding constant for *syn*-**1** with $Cl^-$ is $1.3 \times 10^5$ $M^{-1}$,

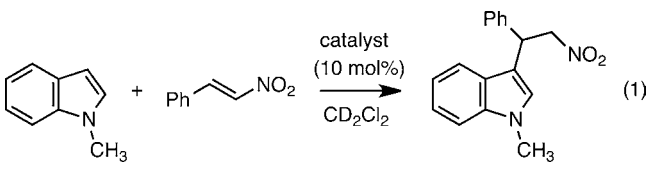
**Table 1. Binding Constants and Selectivities for *syn*- and *anti*-1**

| | $K$ ($M^{-1}$) | | | selectivity | | |
|---|---|---|---|---|---|---|
| cmpd | $Cl^-$ | $Br^-$ | $I^-$ | $Cl^-/Br^-$ | $Cl^-/I^-$ | $Br^-/I^-$ |
| *syn*-**1** | $1.27 \times 10^5$ | 4270 | 102 | 30 | 1250 | 42 |
| *anti*-**1** | 240 | 39 | 4.8 | 6.2 | 50 | 8.1 |
| *syn*/*anti* | 529 | 109 | 21 | 4.8 | 25 | 5.2 |

which is quite large [e.g., ~100 times larger than for catechol ($K$ = 1015 $M^{-1}$) and ~1000 times larger than for resorcinol ($K$ = 145 $M^{-1}$)][23] and reflects a strong association, particularly since acetonitrile is a polar solvent. A much smaller value of 240 $M^{-1}$ was measured for *anti*-**1**, which leads to a syn/anti ratio of 529:1. This preference for syn binding presumably reflects the syn rotamer's ability to form three hydrogen bonds, whereas the anti structure can form only one or two. The difference in the binding free energies for the two rotamers is 3.7 kcal $mol^{-1}$, which is virtually the same as the ΔADE of the cluster ions (i.e., 3.5 kcal $mol^{-1}$).

Bromide and iodide ions were also examined, and the binding constants to *anti*- and *syn*-**1** were determined. All of the association constants are smaller for these less basic halide anions, but the values are larger for the syn isomer, with syn/anti ratios ranging from 529 ($Cl^-$) to 21 ($I^-$). The syn isomer is more selective than the anti isomer, which is important if such a compound is to be used as an anion sensor.[24]

Taken together, our results indicate that *syn*-**1** might be a good hydrogen bond catalyst and should be a better one than *anti*-**1**. That is, a compound capable of forming three hydrogen bonds to a substrate in a reaction transition state may be more effective than an analogous two hydrogen bond donor. To test this possibility, *anti*- and *syn*-**2**,[9] which have 1-pentyl groups para to the three OH substituents in **1**, were used in the Friedel–Crafts reaction between β-nitrostyrene and *N*-methylindole (eq 1);[25] **1** was not used because of its limited solubility.



(1)

Second-order rate constants were measured by $^1$H NMR spectroscopy, and the reaction catalyzed by *syn*-**2** was observed to proceed 100 times faster than that catalyzed by *anti*-**2**; the background reaction occurred ~3 times slower than when *anti*-**2** was used as the catalyst, and correcting for this increased the syn/anti ratio to ~160. This indicates that the three hydrogen bond donor is a more effective catalyst in this instance than its analogous two hydrogen bond donor. This is the first such nonenzymatic report, and it provides a kinetic reason for why enzymes might adopt three hydrogen bonds versus two in their oxyanion holes. Catalysts such as **1** or **2** that can form three hydrogen bonds in the transition state are consequently a promising new class of enzyme mimics and hydrogen bond catalysts.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental and computational sections, binding constant determinations, kinetic data, calculated structures (*xyz* coordinates) and energies, a ChemDraw picture of *syn*-**2**, and complete ref 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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