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Rapid Quantification of the Activating Effects of Hydrogen-Bonding Catalysts with a Colorimetric Sensor

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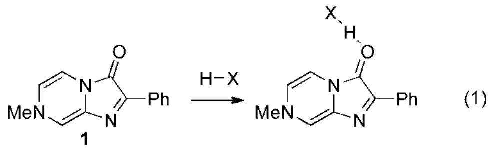
Ⓢ *Supporting Information*

ABSTRACT: A sensor has been developed to quickly and simply assess the relative reactivity of different hydrogen-bonding catalysts. Specifically, blue-shifts seen upon treatment of H-bonding catalysts with the colorimetric compound 7-methyl-2-phenylimidazo[1,2-*a*]pyrazin-3(7*H*)-one correlate well to the K_{eq} of binding to the sensor. The blue-shifts also show a high degree of correlation with relative rates in Diels–Alder reactions of methyl vinyl ketone and cyclopentadiene employing the H-bonding catalysts. The relevance of the sensor blue-shifts to the LUMO-lowering abilities of the H-bonding catalysts is discussed.

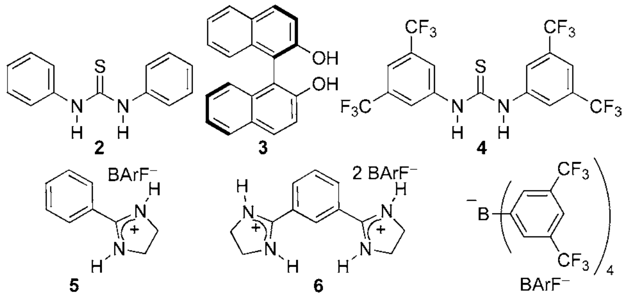
Electrophile activation by small-molecule hydrogen-bond donors has emerged as an important paradigm for enantioselective catalysis.[1] Nonetheless, a thorough understanding of the principles and features that govern the reactivity and selectivity of these catalysts remains incomplete. A number of physical organic measurements have provided scales that can be used to estimate the reactivity, such as pK_a tables,[2] nucleophilicity and electrophilicity parameters,[3] Irving–Williams order,[4,5] etc., but no scales have been made for all categories of hydrogen-bonding catalysts. Contributing to this problem is the large range of H-bond strengths, from 0.2 to 40 kcal/mol.[6] While the strength of a H-bonding interaction can be inferred from ΔpK_a,[7,8] such a measurement gives an incomplete account with respect to catalysis since a water molecule poorly mimics a substrate. As a result, secondary interactions, such as sterics, dual H-bonding,[9] and H-bonding directionality, between a H-bond donor and an electrophilic substrate are not fully incorporated. Here, we present a simple spectroscopic measurement using a colorimetric sensor to determine the effectiveness of H-bonding catalysts in electrophilic activation of a monodentate substrate. The measurement is effective for a range of catalysts encompassing a pK_a window of ~7–20.

We assessed a number of methods to judge the ability of different H-bond donors to activate a carbonyl (LUMO-lowering) but found that methods effective for strong Lewis acids, such as changes in IR or NMR signals, provided insufficient signal or were technically challenging. In search of a simple, easily applied measurement, we elected to use a colorimetric sensor molecule. 7-Methyl-2-phenylimidazo[1,2-*a*]pyrazin-3(7*H*)-one (**1**), which gives good correlations between λ_{max}-shifts and the Fukuzumi parameters for a small number of Lewis acids,[10–12] was discovered to give a readily discernible signal upon coordination (eq 1) with a range of H-bond donors (Chart 1). Figure 1 illustrates the simplicity of the method, with changes in color that are readily visible to the naked eye upon saturation with different H-bonding catalysts.



(1)

Chart 1. Hydrogen-Bonding Catalysts



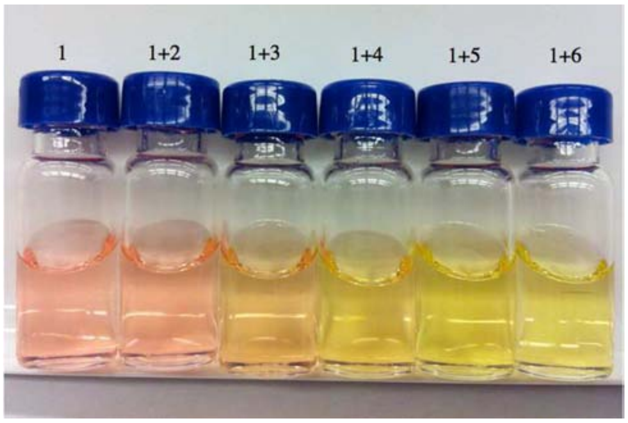


Figure 1. Change in color upon addition of hydrogen-bonding catalysts (see Chart 1) to the pyrazinone sensor **1** in dichloromethane.

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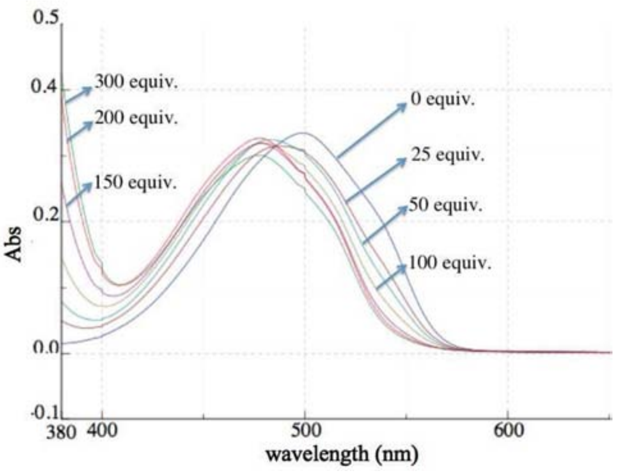


Figure 2. Response of sensor **1** at 2.22 × 10^{-5} M to increasing amounts of *N,N′*-di(3,5-bis(trifluoromethyl)phenyl)thiourea (**4**) in dichloromethane.

Table 1. Hydrogen-Bonding Catalyst Saturated λ_{max} and K_{eq} Values for Binding to 1, along with k_{cat} Values for the Reaction in Eq 2 at 1 mol% Catalyst Loading in Benzene

H-bond catalyst	pK_a (in DMSO)	λ_{max} (nm)	K_{eq} (M^{-1})	k_{cat} (s^{-1})
none		499		–[a]
2	13.4 (ref 7)	490	1.67 × 10	1.26 × 10^{-6}
3	17.1 (ref 15)[b]	487	3.23 × 10	1.80 × 10^{-6}
4	8.5 (ref 7)	477	1.77 × 10^{3}	2.09 × 10^{-5}
5	12.8–13.6 (ref 16)	473	3.34 × 10^{3}	4.90 × 10^{-5}
6	12.8–13.6 (ref 16)[c]	465	3.47 × 10^{5}	1.79 × 10^{-4}

[a] k_{uncat} = 7.50 × 10^{-5} s^{-1}. [b] For 2-naphthol. [c] First pK_a may be 1–2 units lower due to dicationic nature of **6**.

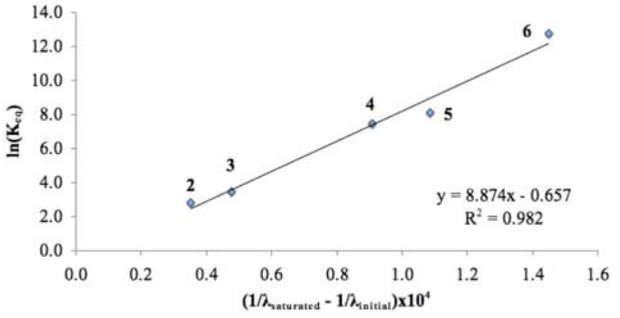
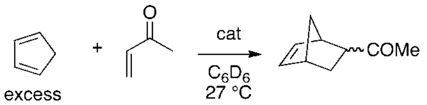


Figure 3. Correlation between wavelength-shift and K_{eq}.

Figure 2 further illustrates the blue-shift in the λ_{max} of the sensor when combined with increasing amounts of a H-bonding catalyst, in this case *N,N′*-di(3,5-bis(trifluoromethyl)-phenyl)thiourea (**4**). With these data, K_{eq} values (Table 1) for the sensor–H-bond donor association[13] could be readily obtained from the corresponding titration curves as illustrated for **4**.[14] The inverse of the λ_{max}-shift obtained upon saturation with **2–6** showed a strong correlation with the K_{eq} value (Figure 3), indicating that this λ_{max}-shift could be used as a reliable indicator of the association between the sensor and a prospective H-bonding catalyst.

Importantly, this sensor coordinates very weakly to water ($\Delta\lambda_{max}$ at saturation = 3.4 nm), which is easily displaced by catalyst. Thus, implementation is simple: sufficient catalyst is added until no further blue-shift is seen. At this point, any water has been displaced, and the sensor is saturated. The λ_{max} obtained at this juncture is then used in the correlations to binding (K_{eq}) and rate (k_{rel}, see below). For example, a measurement can be made using 10 μg of the sensor and ≤10 mg of the catalyst without special precautions to exclude moisture.

Diels–Alder reactions of α,β-unsaturated carbonyl dienophiles are well established to undergo rate acceleration with Lewis acids by LUMO-lowering of the dienophile,[17–20] and a similar activation is believed to operate for H-bonding catalysts.[21] To limit the number of different interactions between the substrates and the H-bonding catalyst, the monodentate substrate methyl vinyl ketone was selected along with a nonbonding diene, cyclopentadiene (eq 2). Rate measurements by NMR[22,23] showed a range of activities for different H-bonding catalysts (Table 1).



(2)

A plot of ln(k_{rel}) (k_{rel} = k_{cat}/k_{uncat}) vs the inverse of the λ_{max}-shift (Figure 4) showed a strong correlation, indicating that the binding to the sensor provides a reasonable account of the LUMO-lowering ability of different H-bonding catalysts. In contrast, the pK_a values do not track well with the reactivity (Table 1, pK_a vs k_{cat}).

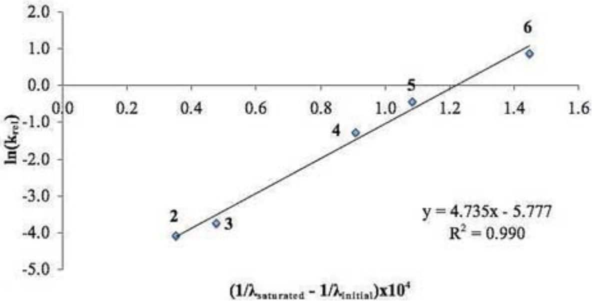


Figure 4. Correlation of Diels–Alder k_{rel} values from different hydrogen-bonding catalysts with the wavelength-shifts of sensor **1**.

In conclusion, pyrazinone sensor **1** was found to rapidly provide a read-out of the relative reactivity of hydrogen-bonding catalysts in the Diels–Alder reaction of methyl vinyl ketone and cyclopentadiene. Namely, catalysts that cause a greater blue-shift at saturation of the sensor are more reactive. Thus, it appears that the interaction between hydrogen-bond donors and the carbonyl of the sensor provides a good approximation of the LUMO-lowering potential available via H-bonding. These preliminary results support the use of sensor **1** as a tool to gauge the relatively reactivity of new H-bonding catalysts and to further the understanding of why some H-bonding catalysts are more effective than others. Exploration of additional H-bonding donors and Lewis acids with the pyrazinone sensor and with other reactions is underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, kinetics results, and spectral data. 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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