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

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### Abstract

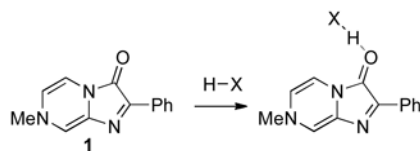
A sensor to quickly and simply assess the relative reactivity of different hydrogen bonding catalysts has been developed. Specifically, blue shifts seen upon treatment of hydrogen bonding catalysts with the colorimetric compound, 7-methyl-2-phenylimidazo[1,2-a]pyrazin-3(7H)-one, correlate well to the  $K_{eq}$  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 hydrogen bonding catalysts. The relevance of the sensor blue shifts to the LUMO lowering abilities of the hydrogen bonding catalysts is discussed.

Electrophile activation by small-molecule hydrogen bond donors has emerged as an important paradigm for enantioselective catalysis.<sup>i</sup> 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 the  $pK_a$  table,<sup>ii</sup> the nucleophilicity and electrophilicity parameters,<sup>iii</sup> the Irving – Williams order<sup>iv,v</sup> etc but no scales have been made for all categories of H-bonding catalysts. Contributing to this problem is the large range of hydrogen bond strengths, from 0.2–40 kcal/mol.<sup>vi</sup> While the strength of a hydrogen bonding interaction can be inferred from  $\Delta pK_a$ ,<sup>vii,viii</sup> 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 hydrogen bonding,<sup>ix</sup> and hydrogen bonding directionality, between a hydrogen 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 hydrogen bonding catalysts in electrophilic activation of a monodentate substrate. The measurement is effective for a range of catalysts encompassing a  $pK_a$  window of approximately 7–20.

We assessed a number of methods to judge the ability of different hydrogen 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(7H)-one (**1**), which gives good correlations between  $\lambda_{max}$  shifts and the Fukuzumi parameters for a small number of Lewis acids<sup>x,xi,xii</sup> was discovered to give a readily discernable signal upon coordination (eq 1) with a range of hydrogen bond donors (Chart 1). Figure 1 illustrates the simplicity of the method with changes in color, which are readily visible to the naked eye, upon saturation with different hydrogen bonding catalysts.

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Supporting Information. Experimental procedures, kinetics results, and spectral data. This information is available free of charge via the Internet at <http://pubs.acs.org/>.

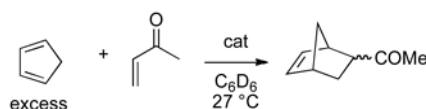


(1)

Figure 2 further illustrates the blue shift in the  $\lambda_{\max}$  of the sensor when combined with increasing amounts of a hydrogen bonding catalyst, in this case *N,N'*-di(3,5-bis(trifluoromethyl)phenyl)thiourea. With this data,  $K_{\text{eq}}$  values (Table 1) for the sensor – hydrogen bond donor association<sup>xiii</sup> could be readily obtained from the corresponding titration curves as illustrated for *N,N'*-di(3,5-bis(trifluoromethyl)-phenyl)thiourea.<sup>xiv</sup> The inverse of the  $\lambda_{\max}$  shift obtained upon saturation with **2–6** showed a strong correlation with the  $K_{\text{eq}}$  value (Figure 3) indicating that this  $\lambda_{\max}$  shift could be used as a reliable indicator of the association between the sensor and a prospective hydrogen 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  $\lambda_{\max}$  obtained at this juncture is then used in the correlations to binding ( $K_{\text{eq}}$ ) and rate ( $k_{\text{rel}}$ , see below). For example, a measurement can be made using 10  $\mu\text{g}$  of the sensor and 10 mg of the catalyst without special precautions to exclude moisture.

The Diels-Alder reactions of  $\alpha$ ,  $\beta$ -unsaturated carbonyl dienophiles is well established to undergo rate acceleration with Lewis acids by LUMO lowering of the dienophile<sup>xvii,xviii,xix,xx</sup> and a similar activation is believed to operate for hydrogen bonding catalysts.<sup>xxi</sup> In order to limit the number of different interactions between the substrates and the hydrogen bonding catalyst, the monodentate substrate methyl vinyl ketone was selected along with a nonbonding diene, cyclopentadiene (eq 2). Rate measurements by NMR<sup>xxii,xxiii</sup> showed a range of activities for different hydrogen bonding catalysts (Table 1).



(2)

A plot of  $\ln(k_{\text{rel}})$  ( $k_{\text{rel}} = k_{\text{cat}}/k_{\text{uncat}}$ ) vs the inverse of the  $\lambda_{\max}$  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 hydrogen bonding catalysts. In contrast, the  $\text{p}K_{\text{a}}$  values do not track well with the reactivity (Table 1,  $\text{p}K_{\text{a}}$  vs  $k_{\text{cat}}$ ).

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 hydrogen bonding. These preliminary results support the use of sensor **1** as a tool to gauge the relative reactivity of new hydrogen bonding catalysts and to further the understanding of why different hydrogen bonding catalysts are more effective

than others. Exploration of additional hydrogen bonding donors and Lewis acids with the pyrazinone sensor and with other reactions is underway.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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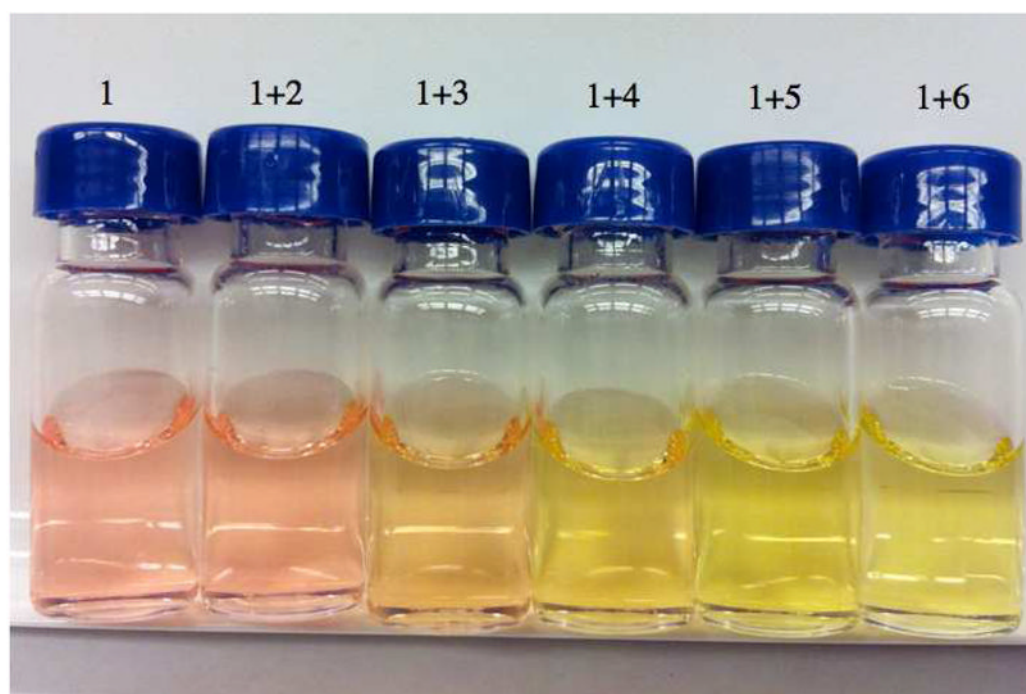
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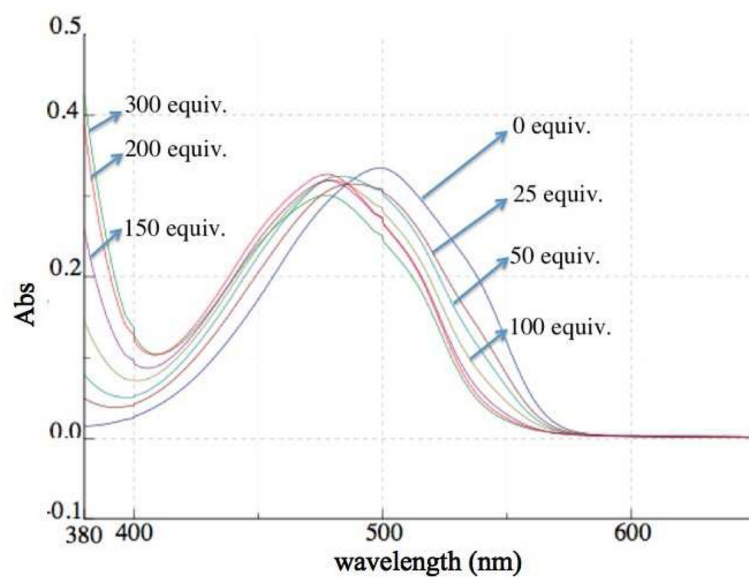
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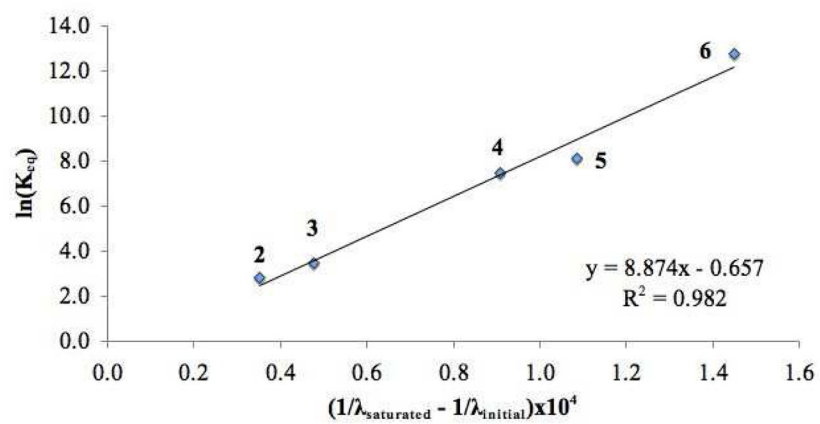
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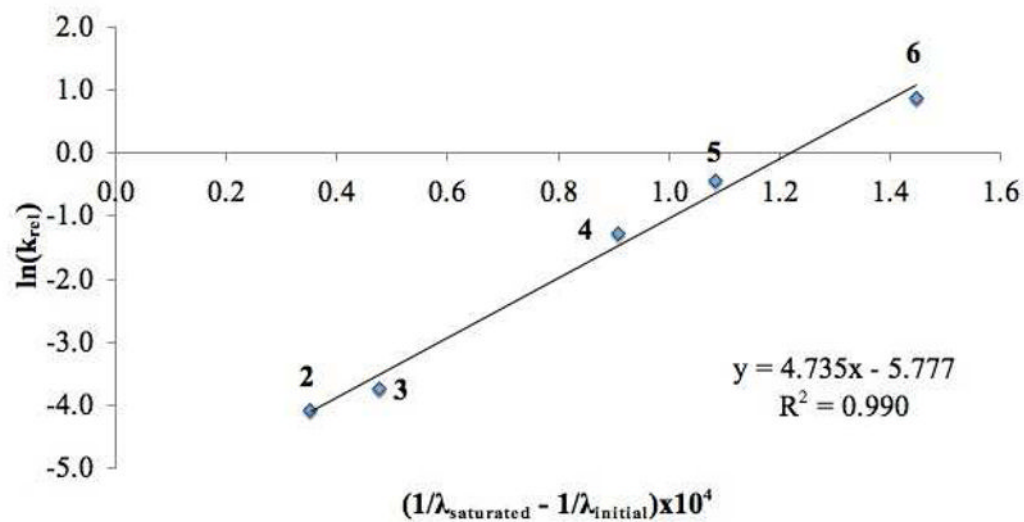
**Figure 1.** Change in color upon addition of hydrogen bonding catalysts (see Chart 1) to the pyrazinone sensor **1** in dichloromethane.



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

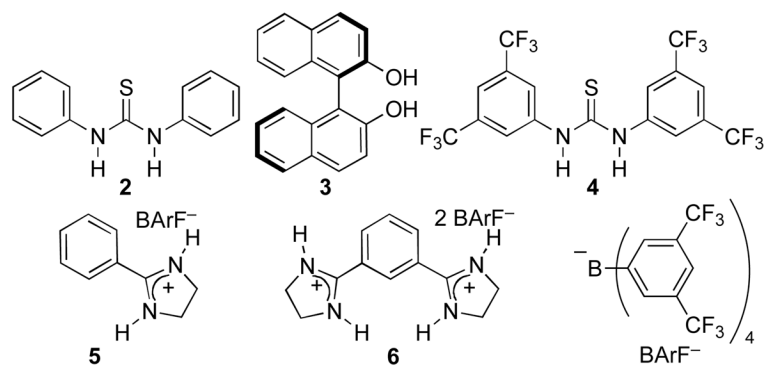


**Figure 3.**  
Correlation between wavelength shift and  $K_{eq}$ .



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





**Chart 1.**  
Hydrogen bonding catalysts.

**Table 1**

Hydrogen bonding catalyst saturated  $\lambda_{\max}$  values and  $K_{\text{eq}}$  values for binding to **1** along with  $k_{\text{cat}}$  values for the reaction in eq 2 at 1 mol% catalyst loading in benzene.

| Hydrogen bond donor | pK <sub>a</sub> (DMSO)                  | $\lambda_{\max}$ (nm) | $K_{\text{eq}}$ (M <sup>-1</sup> ) | $k_{\text{cat}}$ (s <sup>-1</sup> ) |
|---------------------|---|-----------------------|------------------------------------|-------------------------------------|
| None                |   | 499                   |                                    | <sup>a</sup>                        |
| <b>2</b>            | 13.4 <sup>vii</sup>                     | 490                   | $1.67 \times 10^3$                 | $1.26 \times 10^{-6}$               |
| <b>3</b>            | 17.1 <sup>xv</sup> , <sup>b</sup>       | 487                   | $3.23 \times 10^3$                 | $1.80 \times 10^{-6}$               |
| <b>4</b>            | 8.5 <sup>vii</sup>                      | 477                   | $1.77 \times 10^3$                 | $2.09 \times 10^{-5}$               |
| <b>5</b>            | 12.8–13.6 <sup>xvi</sup>                | 473                   | $3.34 \times 10^3$                 | $4.90 \times 10^{-5}$               |
| <b>6</b>            | 12.8–13.6 <sup>xvi</sup> , <sup>c</sup> | 465                   | $3.47 \times 10^5$                 | $1.79 \times 10^{-4}$               |

<sup>a</sup>  $k_{\text{uncat}} = 7.50 \times 10^{-5} \text{ s}^{-1}$ .

<sup>b</sup> For 2-naphthol.

<sup>c</sup> First pK<sub>a</sub> may be 1–2 units lower due to dicationic nature of **6**.