J|A|C|S
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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

Phuong N. H. Huynh, Ryan R. Walvoord, and Marisa C. Kozlowski*

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

*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 p$K_a$ 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 Δp$K_a$,[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 p$K_a$ 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 $\lambda_{max}$-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.

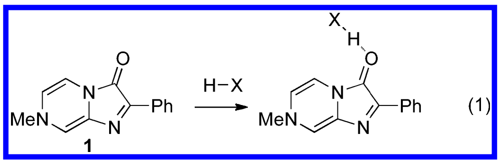
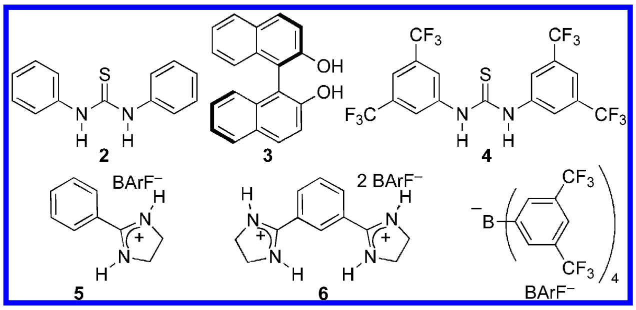


**Chart 1. Hydrogen-Bonding Catalysts**



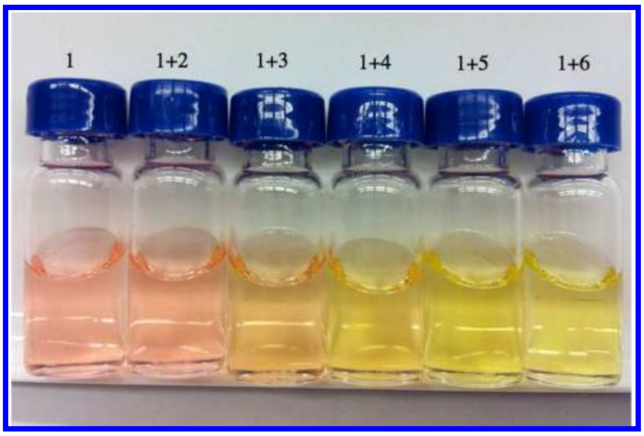


**Figure 1.** Change in color upon addition of hydrogen-bonding catalysts (see Chart 1) to the pyrazinone sensor **1** in dichloromethane.

**Received:** May 24, 2012

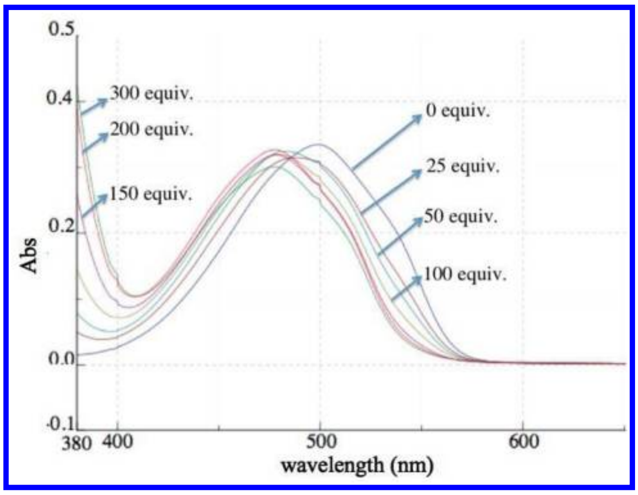


**Figure 2.** Response of sensor **1** at 2.22 × $10^{-5}$ M to increasing amounts of *N,N′*-di(3,5-bis(trifluoromethyl)phenyl)thiourea (**4**) in dichloromethane.

**Table 1. Hydrogen-Bonding Catalyst Saturated $\lambda_{max}$ 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 | p$K_a$ (in DMSO) | $\lambda_{max}$ (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 p$K_a$ may be 1–2 units lower due to dicationic nature of **6**.

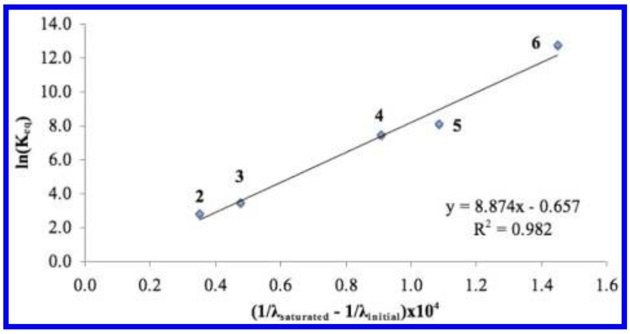
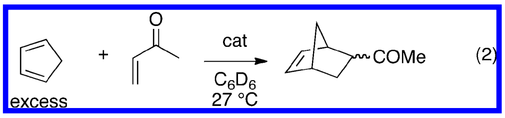


**Figure 3.** Correlation between wavelength-shift and $K_{eq}$.

Figure 2 further illustrates the blue-shift in the $\lambda_{max}$ 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 $\lambda_{max}$-shift obtained upon saturation with **2**–**6** showed a strong correlation with the $K_{eq}$ 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 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 $\lambda_{max}$ 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).



A plot of ln($k_{rel}$) ($k_{rel}$ = $k_{cat}/k_{uncat}$) 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 H-bonding catalysts. In contrast, the p$K_a$ values do not track well with the reactivity (Table 1, p$K_a$ vs $k_{cat}$).

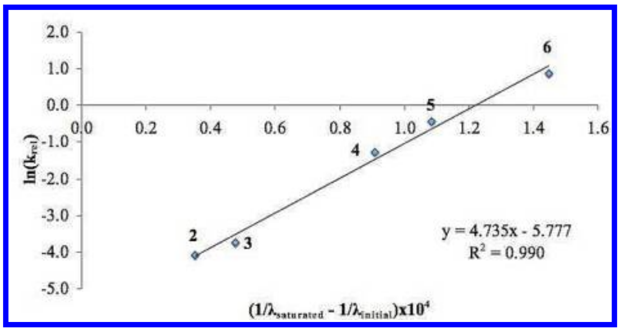


**Figure 4.** Correlation of Diels–Alder $k_{rel}$ values from different hydrogen-bonding catalysts with the wavelength-shifts of sensor **1**.

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.

## AUTHOR INFORMATION

### Corresponding Author

marisa@sas.upenn.edu

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

Financial support was provided by the NIH (RO1GM087605). Partial instrumentation support was provided by the NIH for NMR (1S10RR022442). P.N.H.H. gratefully acknowledges the Vietnam Education Foundation for a fellowship.

## REFERENCES

(1) For reviews, see: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−1543. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713−5743. (c) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418−5427. (d) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909−3912. (e) Connon, S. J. *Chem. Commun.* **2008**, 2499−2510. (f) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062−2064. (g) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797−5949. (h) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999−1010. (i) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744−5758. (j) Nagasawa, K.; Sohtome, Y. *Synlett* **2010**, 000A−000V. (k) Schenker, S.; Zamfir, A.; Freund, M.; Tsogoeva, S. B. *Eur. J. Org. Chem.* **2011**, 2209−2222. (l) Jensen, K. H.; Sigman, M. S. *J. Org. Chem.* **2010**, *75*, 7194−7201.

(2) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(3) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

(4) (a) Irving, H.; Williams, R. J. P. *Nature* **1948**, *162*, 746−747. (b) Irving, H.; Williams, R. J. P. *J. Chem. Soc.* **1953**, 3192−3210.

(5) Examples of applications of Irving−Williams order: (a) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407−1415. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.

(6) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48−76.

(7) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724−1727.

(8) Gilli, P.; Pretto, L.; Bertolasi, V.; Gilli, G. *Acc. Chem. Res.* **2009**, *42*, 33−44.

(9) Annamalai, V. R.; Linton, E. C.; Kozlowski, M. C. *Org. Lett.* **2009**, *11*, 621−624.

(10) Takamuki, Y; Maki, S.; Niwa, H.; Ikeda, H.; Hirano, T. *Tetrahedron* **2005**, *61*, 10073−10080.

(11) Fukuzumi, S.; Kei Ohkubo, K. *Chem.—Eur. J.* **2000**, *6*, 4532−4535.

(12) Fukuzumi, S.; Kei Ohkubo, K. *J. Am. Chem. Soc.* **2002**, *124*, 10270−10271.

(13) Protonation of the pyrazinone sensor with methanesulfonic acid in DMSO has been reported: Nakai, S.; Yasui, M.; Nakazato, M.; Iwasaki, F.; Maki, S.; Niwa, H.; Ohashi, M.; Hirano, T. *Bull. Chim. Soc. Jpn.* **2003**, *76*, 2361−2387. Based on the *K* value of protonation, the sensor can be determined to have a corresponding p*K* of −1.0 (DMSO). These data support interactions between the sensor and H-bond donors that do not involve proton transfer.

(14) See Supporting Information.

(15) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(16) Koppel, I.; Koppel, J.; Leito, I.; Grehn, L. *J. Phys. Org. Chem.* **1996**, *9*, 265−268.

(17) Corey, E. J.; Loh, T.-P; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945−6948.

(18) Goering, H. L.; Chang, C. *J. Org. Chem.* **1975**, *11*, 2565.

(19) Alston, P. V; Ottenbrite, R. M. *J. Org. Chem.* **1975**, *8*, 1111−1116.

(20) Williamson, K. L.; Hsu, Y. L. *J. Am. Chem. Soc.* **1970**, *92*, 7385−7389.

(21) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.

(22) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289−296.

(23) Wittkopp, A.; Schreiner, P. R. *Chem.—Eur. J.* **2003**, *9*, 407−414.