Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 9233–9237

Effect of a hydroxyl group in an anthracene-labelled pyridine amide receptor in molecular recognition of α-keto and hydroxy monocarboxylic acids

Kumaresh Ghosh* and Goutam Masanta

Department of Chemistry, University of Kalyani, Kalyani, Nadia 741235, India

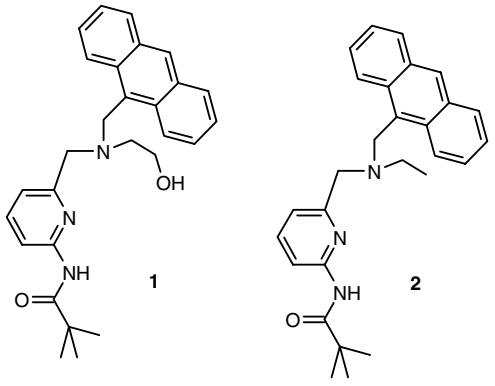
Received 12 July 2006; revised 16 October 2006; accepted 26 October 2006

Abstract—To ascertain the role of a hydroxyl group in carboxylic acid recognition, anthracene-labelled pyridine amide sensor **1** was designed and synthesized. The sensor functions as an 'off–on' fluorescence switch for α-keto and hydroxy acids. The binding properties were studied using ^{1}H NMR, fluorescence and UV–vis spectroscopic methods. Sensor **1** is selective for pyruvic acid.

The development of chemosensors for biologically important species has recently emerged as a key research area in supramolecular chemistry.[1] In this regard, the transduction of recognition events into a fluorescent signal is of great importance. Over the past few years, considerable effort has been focused on the development of photoinduced electron transfer (PET) sensory systems for various guest species.[2] In designing such systems, the use of amide N–H,[3] urea/thiourea,[4] sulfonamides,[5] etc. as binding groups along with particular fluorophores is well documented. In this respect, a hydroxyl group as binding motif has been less studied[6] although a steroidal skeleton bearing a hydroxyl group,[7] urethane N–Hs and hydroxyl groups[8] and amino-alcohols[6c] were found to be promising in recognition of substrates ranging in nature from charged to neutral.

During the course of our ongoing program to develop receptors for molecular recognition of neutral substrates,[9] we report here the synthesis and photophysical behaviour of anthracene-labelled receptor **1** to examine the cooperative hydrogen bonding effect of the hydroxyl group in recognition of α-keto and hydroxy acids.

Receptor **1**, in which one anthracene substituent and a pyridine amide subunit are appended through $-CH_2-$ spacers to the nitrogen atom of an ethanolamine, has been synthesized according to Scheme 1 and characterized by ^{1}H NMR, ^{13}C NMR, and mass analysis.[10]

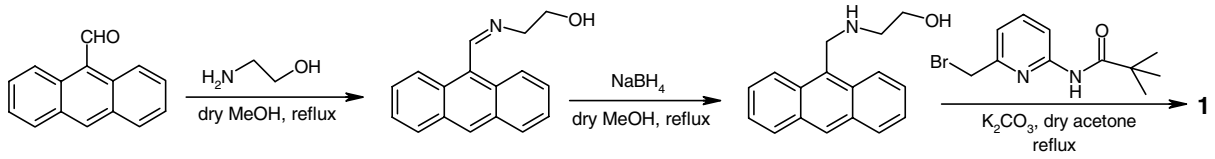


In receptor **1**, hydrogen bond donors (D) and acceptors (A) are arranged in a DAAD fashion and covalently linked to the 9-anthranilic position in order to generate the photoinduced electron transfer signal via the methylene ($-CH_2-$) bridge from the electron donor to electron acceptor (Fig. 1a). Molecular modelling[11a] revealed that receptor **1** (Fig. 1b; $E = 41.78$ kcal/mol) provides an open cavity into which the pyridine amide and alcoholic OH hydrogen bonding groups are well disposed for complexation.

The binding behaviour of **1** for benzoic, pyruvic, (*R*)-mandelic and 2-furoic acids was examined by ^{1}H

Keywords: Hydroxyl group; Off–on switch; Pyruvic acid; Mandelic acid; PET sensor.
* Corresponding author. Tel.: +91 33 25828282x306; fax: +91 33 25828282; e-mail: ghosh_k2003@yahoo.co.in

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.10.140



Scheme 1. Synthesis of receptor **1**.

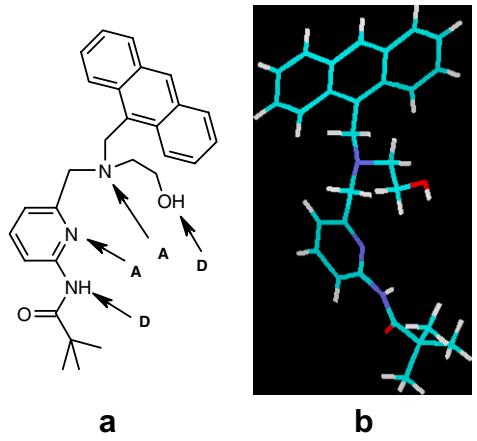


Figure 1. (a) Possible hydrogen bonding sites of **1** (A = hydrogen bond acceptor, D = hydrogen bond donor) and (b) energy minimized structure of **1**.

NMR titration, fluorescence and UV–vis methods. In dry $CDCl_3$ the signals of the OH and amide protons, which are D_2O exchangeable, appeared at 1.60 and 7.85 ppm, respectively (see Supplementary data). These two signals underwent significant downfield shifts upon addition of pyruvic, (*R*)-mandelic and 2-furoic acids suggesting that the hydroxyl group, along with the pyridine amide, serve as binding sites in complexation. The relatively smaller downfield shift of the amide proton compared to the hydroxyl proton is due to the steric nature of the pivaloyl group. As shown in Figures 2a and 2b, upon addition of pyruvic and (*R*)-mandelic acids, large changes in the chemical shift value of the OH protons ($\Delta\delta = 0.66$ ppm for pyruvic and 1.79 ppm for (*R*)-mandelic acids in their 1:1 complexes) were observed in the ^{1}H NMR spectra of **1**, while the signal of the amide proton shifted downfield by a smaller amount ($\Delta\delta = 0.36$ ppm for pyruvic and 0.49 ppm for (*R*)-mandelic acid in their 1:1 complexes). During complexation the $-CH_2-$ protons adjacent to the aliphatic nitrogen (a–d; see Fig. 3) also showed significant downfield shifts (Table 1) and suggest participation of the aliphatic nitrogen in complexation either in mode **A** or mode **B** as shown in Figure 3. Both forms **A** and **B** may exist in solution, in equilibrium, but we suggest that form **A** is more likely due to the six-centered hydrogen bonded structure as constituted by the carboxylic acid and alcoholic OH groups. The large downfield shift of the OH signal supports this proposition. During complexation in dry $CDCl_3$, the possibility of protonation of both the ring and aliphatic 3° nitrogens was neglected. This was proved by running ^{1}H NMR spectra in $CDCl_3$, but in the presence of the stronger acid HCl, which showed easy protonation by the appearance of a signal

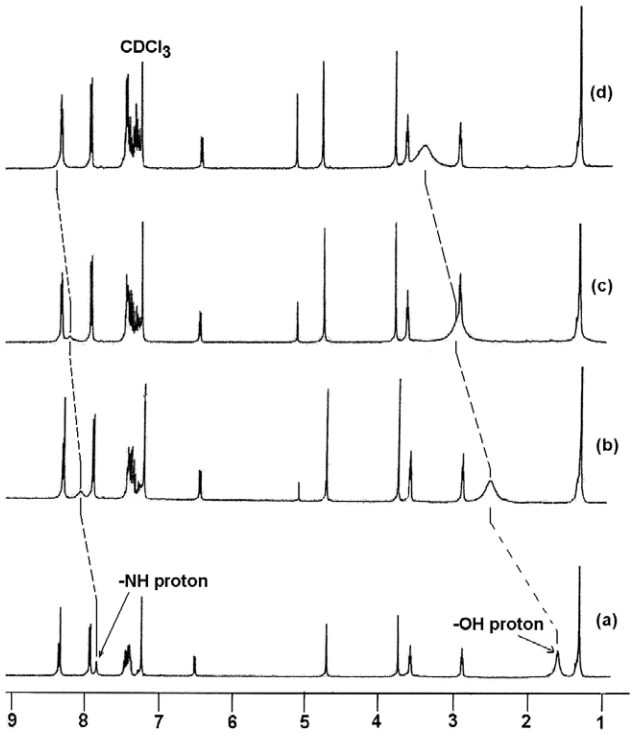


Figure 2a. ^{1}H NMR spectra on titration of **1** with (*R*)-mandelic acid in $CDCl_3$: (a) **1** ($c = 8.09 \times 10^{-3}$ M) only; (b) [G]/[H] = 0.29; (c) [G]/[H] = 0.57 and (d) [G]/[H] = 1.

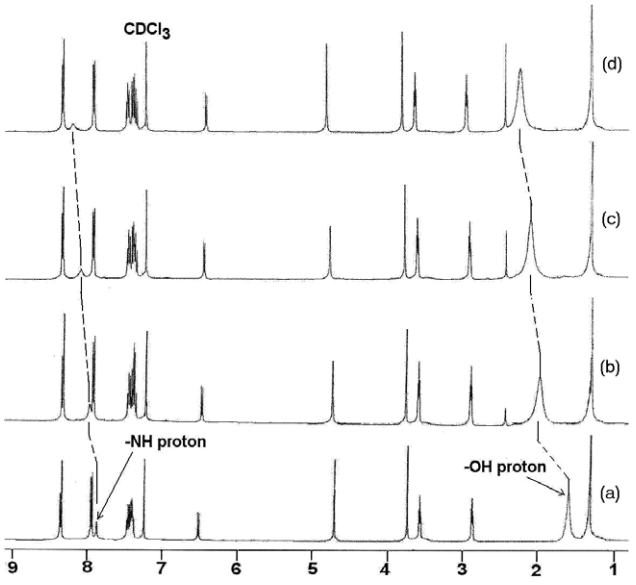


Figure 2b. ^{1}H NMR spectra on titration of **1** with pyruvic acid in $CDCl_3$: (a) **1** ($c = 7.77 \times 10^{-3}$ M) only; (b) [G]/[H] = 0.35; (c) [G]/[H] = 0.7 and (d) [G]/[H] = 1.

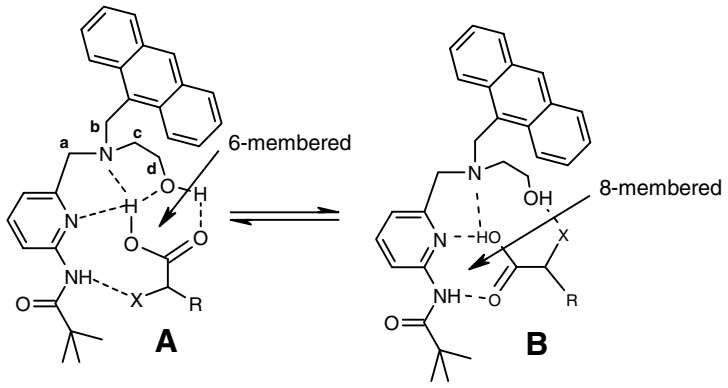


Figure 3. Possible structures of the hydrogen bonded complex.

Table 1. Change in chemical shift values in the 1:1 complexes

Guest acid	Δδ for 'a' Protons	Δδ for 'b' Protons	Δδ for 'c' Protons	Δδ for 'd' Protons
Pyruvic	0.13	0.09	0.09	0.08
(*R*)-Mandelic	0.05	0.04	0.03	0.04
2-Furoic	0.04	0.05	0.04	0.05
Benzoic	0.01	0.02	0.01	0.02

at 10.02 ppm for the protonated pyridinium group.[9c,d,11b] The ammonium proton was difficult to identify due to significant broadening of the signals in the aromatic region (7–9 ppm). The absence of a signal at 10.02 ppm for the acids studied thus ruled out the case of protonation. Quantitative assessments of the binding affinities[11c] of **1** towards benzoic, pyruvic, 2-furoic and (*R*)-mandelic acids in dry $CDCl_3$ (Table 2) revealed that **1** is selective and effective in forming 1:1 complexes with monocarboxylic acids having hetero atom substituents at the α-position. In this regard, **1** is selective for pyruvic acid among the other acids studied. The stoichiometries were determined from the break of the titration curves (Δδ vs [G]/[H]).

With the ability of the OH group as a donor of hydrogen bonds established, the fluorescence behaviour of **1** was examined in CH_3CN in the presence of the acids as mentioned in Table 2. In this context, it is of note that the fluorescence intensity of **1** was stable with time thereby neglecting the intermolecular photodimerisation of anthracene (see Supplementary data).[12c] Upon addition of pyruvic, 2-furoic and (*R*)-mandelic acids, the structured emission bands at 395, 412 and 440 nm assigned to anthracene monomer emission were significantly enhanced. As shown in Figure 4, **1** exhibits a large increase in emission intensity in the presence of pyruvic acid without producing any other spectral change (i.e. either exiplex or excimer formation). Benzoic acid did not induce any significant fluorescence change (Fig. 5). Concurrent study of the absorption spectra of **1** (peaks of the anthracene moiety) showed a very minor change (for example, see Fig. 4: inset) indicating the insulating role of the $-CH_2-$ spacer, which minimizes the ground state interactions between the fluorophore and carboxylic acid binding sites. This reveals that **1** behaves as an ideal PET sensor. The same experiments in $CHCl_3$ exhibited a similar behaviour. The fluorescence enhancement in the presence of the acids, therefore, is associated with cooperative hydrogen bonding interactions in forming the receptor—carboxylic acid complexes. The complexation inhibits the PET process either from the receptor sites to excited anthracene (described as 1° PET) or the reverse (2° PET) resulting in an increase in the fluorescence of **1**. In this regard, our previous report on sensor **2** is relevant where compromisation of 1° and 2° PET processes resulted in the 'on–off' switching behaviour[9d] of **2** in the presence of monocarboxylic acids. The present example, in contrast, shows the reverse switching mode. This could be attributed presumably to a hydrophobic and hydrophilic balance in receptor **1**, which has a role in regulating the PET process during complexation. Table 2 summarizes the 1:1 receptor-acid binding constants from fluorescence titrations,[12] which show a similar trend to that observed in the NMR titrations. Thus both the fluorescence and the NMR experiments undoubtedly demonstrate that the chemosensor **1** can discriminate the α-heteroatom substituted keto- and hydroxy-monocarboxylic acids

Table 2. Binding constants based on NMR and fluorescence analyses

Guest acid	Sensor **1** (K_a in M^{-1}) by ^1H NMR[a] in $CDCl_3$	Sensor **1** (log β) by fluorescence in CH_3CN	Sensor **1** (log β) by fluorescence in $CHCl_3$
Pyruvic	1.62×10^2	4.89	4.67
(*R*)-Mandelic	1.09×10^2	4.49	4.22
2-Furoic	0.79×10^2	3.27	3.24
Benzoic	0.44×10^2	2.98	2.20

[a] Binding constant values were determined by considering the shift of the –OH proton.

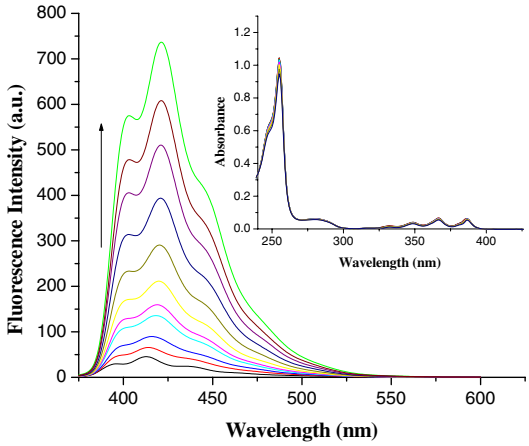


Figure 4. Fluorescence emission spectra of **1** (7.25×10^{-5} M) in CH_3CN with pyruvic acid and the change in the UV–vis spectra of **1** (6.34×10^{-6} M) (inset) upon addition of pyruvic acid.

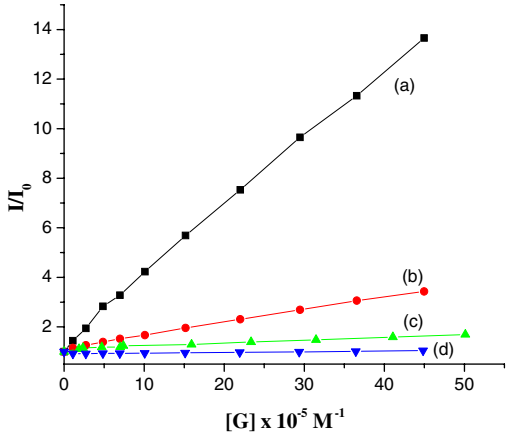


Figure 5. Change in fluorescence emission of **1** in CH_3CN with increasing guest (G) concentration: (a) pyruvic; (b) (*R*)- mandelic; (c) 2-furoic and (d) benzoic acids.

from monocarboxylic acids and selectively binds to pyruvic acid in the present case.

In conclusion, we have demonstrated that a simple sensor **1** bearing a hydroxyl group shows significant α-keto acid binding ability in both CH_3CN and $CHCl_3$. The hydroxyl group of the sensor acts as a hydrogen bond donor in cooperative hydrogen bonding to the carboxylic acid. This information will certainly help in building up chiral sensors from chiral amino alcohols for chiral recognition. Work along this direction is in progress in our laboratory.

Acknowledgements

We thank DST and CSIR, Government of India for financial support and DST-FIST for providing the facilities in the Department. G.M. thanks CSIR, Govt. of India for a fellowship.

Supplementary data

^{1}H NMR of receptor **1** in $CDCl_3$, in the presence of D_2O and in the presence of HCl and fluorescence spectra of **1** with time are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.140.

References and notes

1. (a) *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vogtle, F., Eds.; Elsevier: Exeter, 1996, and references cited therein; (b) Tellado, F. G.; Geib, S. J.; Goswami, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 9265–9269; For a general discussion of neutral molecule recognition see: (c) van Doorn, A. R.; Verboom, W.; Reinhoudt, D. N. In *Advances in Supramolecular Chemistry*; Gokel, G. W., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 3, pp 159–206.
2. (a) Rurack, K.; Resch-Genger, U. *Chem. Soc. Rev.* **2002**, *31*, 116–127; (b) Czarnik, A. W. *Acc. Chem. Res.* **1994**, *27*, 302–308; (c) Gunnlaugsson, T.; Davis, A. P.; O'Brien, J. E.; Glynn, M. *Org. Lett.* **2002**, *4*, 2449–2452; (d) Bu, J.-H.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2004**, *6*, 3301–3303; (e) De Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515–1566.
3. (a) Bisson, A. P.; Lynch, V. M.; Monahan, M.-K. C.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1997**, *36*, 2340–2342; (b) Kavallieratos, K.; Sachleben, R. A.; Berkel, G. J. V.; Moyer, B. A. *Chem. Commun.* **2000**, 187–188; (c) Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 2456–2457.
4. (a) Gomez, D.; Fabbrizzi, L.; Licchelli, M. *J. Org. Chem.* **2005**, *70*, 5717–5720; (b) Fan, E.; van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369–370; (c) Cho, E. J.; Ryu, B. J.; Lee, Y. J.; Nam, K. C. *Org. Lett.* **2005**, *7*, 2607–2609, and references cited therein; (d) Kondo, S.-I.; Hiroka, Y.; Kurumatani, N.; Yano, Y. *Chem. Commun.* **2005**, 1720–1722; (e) Lee, D. H.; Lee, H. Y.; Hong, J.-I. *Tetrahedron Lett.* **2002**, *43*, 7273–7276.
5. (a) Kavallierators, K.; Moyer, B. A. *Chem. Commun.* **2001**, 1620–1621; (b) Davis, A. P.; Perry, J. J.; Williams, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 1793–1794.
6. (a) Lee, D. H.; Lee, H. Y.; Lee, K. H.; Hong, J.-L. *Chem. Commun.* **2001**, 1188–1189; (b) Lee, K. H.; Lee, H. Y.; Lee, D. H.; Hong, J.-I. *Tetrahedron Lett.* **2001**, *42*, 8665–8668; (c) Cuevas, F.; Ballester, P.; Pericas, M. A. *Org. Lett.* **2005**, *7*, 5485–5487; (d) Zheng, Y.-S.; Zhang, C. *Org. Lett.* **2004**, *6*, 1189–1192.
7. (a) Davis, A. P.; Gilmer, J. F.; Perry, J. J. *Angew. Chem., Int. Ed.* **1996**, *35*, 1312–1315; (b) Davis, A. P.; Perry, J. J.; Wareham, R. S. *Tetrahedron Lett.* **1998**, *39*, 4569–4572.
8. Albert, J. S.; Hamilton, A. D. *Tetrahedron Lett.* **1993**, *34*, 7363–7366.
9. (a) Ghosh, K.; Masanta, G. *Tetrahedron Lett.* **2006**, *47*, 2365–2369; (b) Ghosh, K.; Adhikari, S. *Tetrahedron Lett.* **2006**, *47*, 3577–3581; (c) Ghosh, K.; Masanta, G. *Chem. Lett.* **2006**, *34*, 414–415; (d) Ghosh, K.; Masanta, G. *Supramol. Chem.* **2005**, *17*, 331–334.
10. Mp 84–86 °C; yield: 70%; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.37 (d, 2H, $J = 10$ Hz), 8.35 (s, 1H), 7.95 (d, 3H, $J = 10$ Hz), 7.85 (s, 1H, –NH–), 7.48–7.39 (m, 5H), 6.53 (d, 1H, $J = 10$ Hz), 4.73 (s, 2H), 3.76 (s, 2H), 3.58 (t, 2H, $J = 5$ Hz), 2.98 (t, 2H, $J = 5$ Hz), 1.59 (br s, 1H, –OH),

1.33 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): 177.4, 157.8, 151.2, 138.8, 131.8, 131.7, 129.7, 129.5, 128.3, 126.1, 125.2, 125.0, 119.1, 112.3, 59.5, 59.3, 56.6, 51.7, 40.2, 27.9; FTIR: ν cm^{-1}(KBr): 3328, 2927, 2868, 1688, 1604, 1577, 1453, 1148, 1072; UV (CH_3CN): ($c = 0.634 \times 10^{-5}$ M) λ_{max} (nm) 254, 283, 348, 366, 386. Mass (EI): 442.3 (M+1), 252.3, and 191.1.

11. (a) Energy minimization was carried out by MMX (PC Model Serena Software 1993). Molecular modelling was performed using standard constants, and the dielectric constant was maintained at 1.5; (b) Amendola, V.; Esteban-Gomiez, D.; Fabbrizzi, L.; Licchelli, M. *Acc. Chem. Res.* **2006**, *39*, 343–353; (c) Foster, R.; Fyfe, C. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1969**, *4*, 1–89.
12. Binding constants (log β) were determined using the equation $\log[(I_{max} - I_F)/(I_F - I_{min})] = \log$ [guest] $- \log \beta$. (a) Gunnlaugsson, T.; Davis, A. P.; O'Brien, J. E.; Glynn, M. *Org. Biomol. Chem.* **2005**, *3*, 48–56; (b) Cooper, C. R.; James, T. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 963–969; (c) Wallace, K. J.; Belcher, W. J.; Tumer, D. R.; Syed, K. F.; Steed, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 9699–9715, and references cited therein.