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Azocalix[4]arene Strapped Calix[4]pyrrole: A Confirmable Fluoride Sensor

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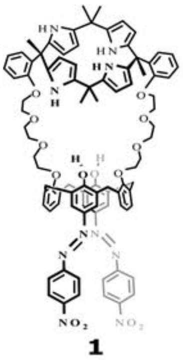
ABSTRACT



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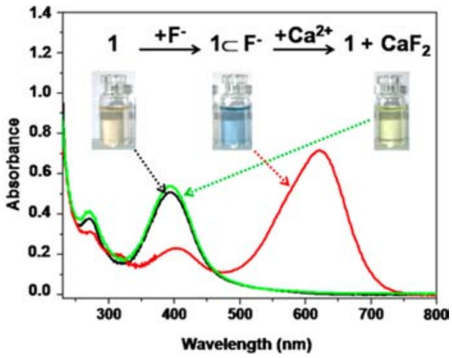

A new chromogenic fluoride sensor based on 1,3-di-*p*-nitrophenylazocalix[4]arene-calix[4]pyrrole (1) was designed and synthesized. The color of the solution of probe 1 changed upon the addition of any F^-, $CH_3CO_2^-$, $PhCO_2^-$, and $H_2PO_4^-$ ions. However, from these ions the highly specific sensing of F^- is achieved by the addition of Ca^{2+} which leads to a color change from light sky blue (of $1 \cdot F^-$) back to the original light orange color of 1.

Fluoride (F^-) plays an important role in human life, and the deficiency or overexposure of the amount of F^- causes osteoporosis and poor dental health.[1] Many design and syntheses of highly sensitive and selective chemosensors for F^- have been reported,[2] but there is still a need for further development. Presently, chromogenic anion sensors have received increasing attention and have become promising candidates for sensing probes, especially for F^-, because it allows detection of the species of interest with the naked eye.[3] Many frameworks have been developed,[3] such as porphyrin,[3a] calix[4]pyrrole,[4] and calix[4]arene,[5] but the chromogenic azo-calix[4]arene has become a preferred candidate for a sensing probe because of its particular preorganized framework that promptly accommodates ions or neutral molecules.[5a,6] Azo-calix[4]arene's selective sensing property can be monitored by a change in the UV–vis spectra and, more practically, by the visible change in their solution colors. Although many chromogenic sensors based on calix[4]arene have been developed for sensing specific cations and other molecules, calixarene-based chromogenic sensors for anions have rarely been

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(1) For example: (a) Gunnlaugsson, T.; Glynn, M.; Tocci (née Hussey), G. M.Kruger, P. E.; Pfeffer, F. M. *Coord. Chem. Rev.* **2006**, *250*, 3094. (b) Yeo, H. M.; Ryu, B. J.; Nam, K. C. *Org. Lett.* **2008**, *10*, 2931. (c) Upadhyay, K. K.; Mishra, R. K.; Kumar, V.; Chowdhury, P. K. R. *Talanta* **2010**, *82*, 312.

(2) For example: (a) Jung, H. S.; Kim, H. J.; Vincens, J.; Kim, J. S. *Tetrahedron Lett.* **2009**, *50*, 983. (b) Kwon, J. Y.; Jang, Y. J.; Kim, S. K.; Lee, H.-K.; Kim, J. S.; Yoon, J. *J. Org. Chem.* **2004**, *69*, 5155. (c) Lee, M. H.; Gabbaı, F. P. *Inorg. Chem.* **2007**, *46*, 8132. (d) Guha, S.; Saha, S. *J. Am. Chem. Soc.* **2010**, *132*, 17674. (e) He, X.-M.; Yam, V. W.-W *Org. Lett.* **2011**, *13*, 2172. (f) Zhang, J. F.; Lim, C. S.; Bhuniya, S.; Cho, B. R.; Kim, J. S. *Org. Lett.* **2011**, *13*, 1190.

(3) (a) Suksai, C.; Tuntulani, T. *Chem. Soc. Rev.* **2003**, *32*, 192. (b) Dix, J. P.; Vögtle, F. *Chem. Ber.* **1981**, *114*, 638. (c) Kim, J. Y.; Kim, G.; Kim, C. R.; Lee, S. H.; Lee, J. H.; Kim, J. S. *J. Org. Chem.* **2003**, *68*, 1933. (d) Chen, C. F.; Chen, Q. Y. *New J. Chem.* **2006**, *30*, 143. (e) Kaewtong, C.; Noiseephum, J.; Uppa, Y.; Wanno, B.; Morakot, N.; Morakot, N.; Tuntulani, T.; Pulpoka, B. *New J. Chem.* **2010**, *34*, 1104.

(4) For example: (a) Farinha, A. S. F.; Tomé, A. C.; Cavaleiro, J. A. S. *Tetrahedron* **2010**, *66*, 7595. (b) Yoo, J.; Kim, M.-S.; Hong, S.-J.; Sessler, J. L.; Lee, C.-H. *J. Org. Chem.* **2009**, *74*, 1065.

(5) For example: (a) Chang, K.-C.; Su, I.-H.; Wang, Y.-Y.; Chung, W.-S. *Eur. J. Org. Chem.* **2010**, 4700. (b) Quinlan, E.; Matthews, S. E.; Gunnlaugsson, T. *J. Org. Chem.* **2007**, *72*, 7497. (c) Kim, H. J.; Kim, S. K.; Lee, J. Y.; Kim, J. S. *J. Org. Chem.* **2006**, *71*, 6611.

(6) For example: (a) Menon, S. K.; Modi, N. R.; Patel, B.; Patel, M. B. *Talanta* **2011**, *83*, 1329. (b) Karakus, Ö. Ö.; Deligöz, H. *J. Macromol. Sci. A* **2010**, *47*, 1111.

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reported. More particularly, calix[4]arene strapped calix[4]pyrroles show a greater enhancement in terms of both anion binding affinities and modulating the inherent anion selectivity. Moreover, previous reports have shown that calix[4]-crown strapped calix[4]pyrroles display a highly specific ion-pair sensing property, such as that for CsF.[7] However, most anion receptors that bind F^- ions do so along with other anions, such as acetate, benzoate, or dihydrogen phosphate ions ($H_2PO_4^-$). Some of those receptors are chromogenic sensors, but their color changes upon binding of the F^- ion are quite similar to those upon binding of acetate, benzoate or $H_2PO_4^-$ ions. This led us to develop a chromogenic sensor for F^- ion detection based on calix[4]arene-calix[4]pyrrole.

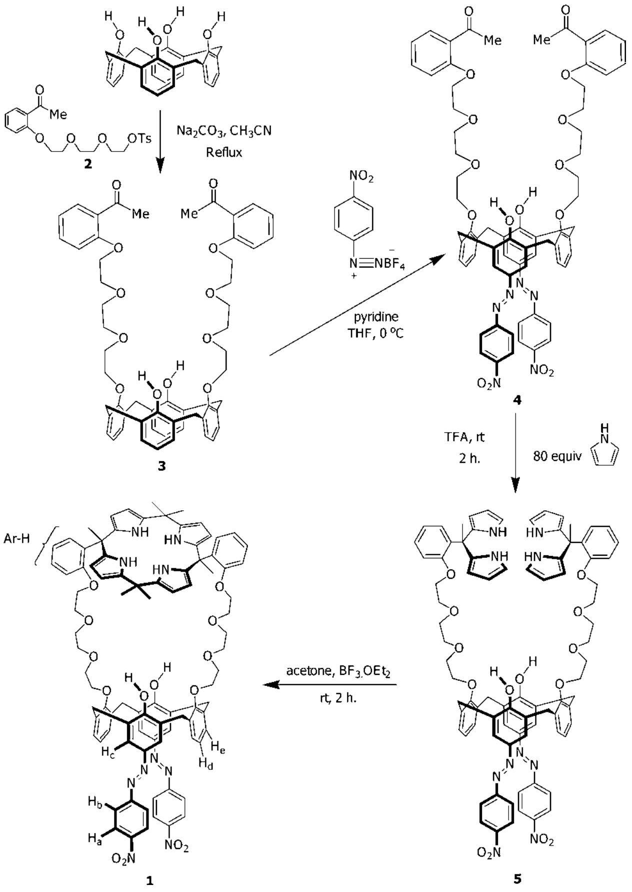
Here, we report the synthesis of a new design of chromogenic sensor, 1,3-di-*p*-nitrophenylazocalix[4]arene-calix[4]pyrrole (**1**), that serves as a confirmable and reversible F^- sensor. The molecule sensor **1** contains an azobenzene moiety serving as a sensing unit as well as enhancing the anion binding by increasing the H-bonding ability of the calix[4]arene platform, while the calix[4]pyrrole acts as an anion binding unit. The investigation of its affinity toward various anions was accomplished by UV–vis spectroscopy and its visible solution color changes.

The synthesis of **1** was carried out as shown in Scheme 1. The synthesis starts by the condensation of 2-(8-tosyltriethyleneglycol)acetophenone (**2**) with calix[4]arene using K_2CO_3 as a base in acetonitrile to provide 1,3-calix[4]diacetophenone (**3**) (85% yield). Subsequently, the diazocoupling reaction of **3** with *p*-nitrobenzene-diazoniumtetrafluoroborate in the presence of pyridine in tetrahydrofuran (THF) gave chromogenic 1,3-di-*p*-nitrophenylazocalix[4]-diacetophenone (**4**) (24% yield). According to the ^1H NMR spectra of **3** and **4**, the phenolic OH signal shifted from 7.26 to 8.70 ppm, which implies that the azo-*p*-nitrophenyl group not only can serve as a chromophore but also increases the H-bonding ability of the phenolic OH anion-binding site. Treating **4** with pyrrole in a presence of a catalytic amount of trifluoroacetic acid gave 1,3-calix[4]arene-bisdipyrroethane (**5**) in 39% yield. This key precursor (**5**) was then condensed with dry acetone in the presence of a catalytic amount of $BF_3 \cdot OEt_2$ at rt to provide the desired chromogenic sensor **1** in 13% yield.

The cone conformation of compounds **1**, **3**, **4**, and **5** was confirmed by the AB pattern of doublets at around 4.4 and 3.5 ppm ($J \cong 13$ Hz) for the methylenic protons (ArCH_2Ar) on the ^1H NMR spectra and a singlet at 31 ppm for methylene bridge carbons on the ^{13}C NMR spectra.

Upon allowing a dichloromethane/methanol solution of compound **4** to undergo slow evaporation at a temperature of 4 °C, single crystals suitable for X-ray analysis were obtained. The ORTEP drawing (Figure 1) confirms that **4** adopts a pinch cone conformation. The *p*-nitrophenylazo moiety aligned approximately planar to the phenolic unit of the calix[4]arene framework allowing electron transfer by resonance.

Scheme 1. Synthetic Pathway of Chromogenic Sensor **1**



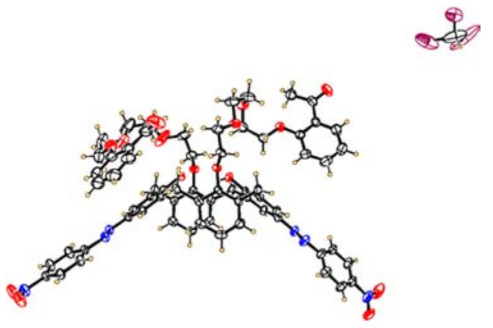


Figure 1. ORTEP drawing of **4**. Displacement ellipsoids are scaled to the 50% probability level.

The chromogenic behavior of **1** was revealed by UV–vis analysis (Figure 2). The UV–vis absorptions of **1** were investigated upon the addition of 6 equiv of tetra-*n*-butylammonium (TBA) salts of F^-, Cl^-, Br^-, I^-, $CH_3CO_2^-$, $PhCOO^-$, NO_3^-, PF_6^-, ClO_4^-, and $H_2PO_4^-$ into a solution of **1**. Free **1** exhibited one absorption band at 395 nm. The addition of the above anion based salts in the ligand solution gave a bathochromic shift, from 395 nm to around 600 nm, only with F^-, $CH_3CO_2^-$, $PhCO_2^-$, and $H_2PO_4^-$,

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(7) (a) Kim, S. K.; Sessler, J. L.; Gross, D. E.; Lee, C.-H.; Kim, J. S.; Lynch, V. M.; Delmau, L. H.; Hay, B. P. *J. Am. Chem. Soc.* **2010**, *132*, 5827. (b) Sessler, J. L.; Kim, S. K.; Gross, D. E.; Lee, C.-H.; Kim, J. S.; Lynch, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 13162.

while Cl^-, Br^-, I^-, NO_3^-, PF_6^-, and ClO_4^- did not effect ligand color. The magnitude of these bathochromic shifts is in the order $F^- > CH_3CO_2^- > PhCO_2^- > H_2PO_4^-$, with significant color changes from light orange to light sky blue, blue, light pink, and light yellow being observed, respectively (inset in Figure 2).

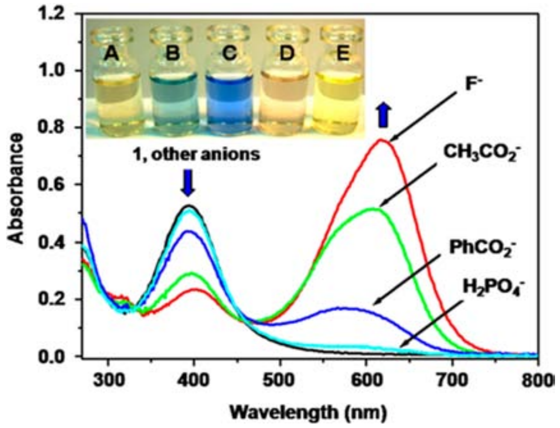

Figure 2. Wavelength changes of **1** upon the addition of various anions. Condition: **1** (0.02 mM)/CH_3CN; TBA salts (6 equiv)/CH_3CN; (inset) color change of **1** (A = Ligand **1**, B = **1** + F^-, C = **1** + $CH_3CO_2^-$, D = **1** + $PhCO_2^-$, E = **1** + $H_2PO_4^-$).

The spectroscopic changes can be explained by a charge transfer from the donor oxygen of the azophenol unit to the acceptor substituent ($-NO_2$) of the chromophore. After complexation of **1** with anions, the excited state would be more strongly stabilized by anion binding, resulting in a bathochromic shift of the absorption maxima as well as in color changes.[4] Thus, **1** could enable colorimetric differentiation of F^-, acetate, benzoate and $H_2PO_4^-$ anions possessing different sizes and shapes.[8]

In order to investigate the stoichiometry and stability constants between **1** and anions (as TBA salts), UV−vis titration was performed using 0.02 mM **1** in CH_3CN. The absorption peak at 600 nm increased with increasing concentrations of F^- added (Figure 3). The stoichiometry of the **1**·**F**complex was determined by the mole ratio plot (inset in Figure 3) and using the SIRKO program,[9] which clearly showed that at least two species of complexes (1:1 and 2:1 (anion/ligand) with log β = 3.07 and 11.09, respectively) existed. The association constants of 1:1 complexes of **1** with acetate, benzoate, and $H_2PO_4^-$ are summarized in Table 1. The specific order of the binding affinities is as follows: benzoate > acetate > F^- > $H_2PO_4^-$. The preference of **1** to bind benzoate over the other anions studied may be due to a preorganization of **1** to accommodate benzoate, which is confirmed by ^{1}H NMR titration study (Figures 5 and S19).

In order to understand the binding mode of **1** with F^- ions, ^{1}H NMR titrations were carried out. Figures 4 and S17 show the ^{1}H NMR spectra of **1** (3.58 mM) with different amounts of TBAF in acetonitrile-D_3 and revealed that the phenolic protons of the azocalix[4]arene moieties at 8.80 ppm disappeared when only 0.1 equiv of F^- was added into a solution of **1** along with displacement of the H_c proton signal from 7.82 to 7.72 ppm. This indicates that the phenolic protons of **1** were strongly reactive with F^-, as previously reported.[4] Moreover, protons H_a and H_b of the nitrobenzene units shifted upfield from 8.28 and 7.88 ppm to 8.26 and 7.80 ppm, respectively, which implies that the electron was pushed from the phenolic unit by the F^- ion.

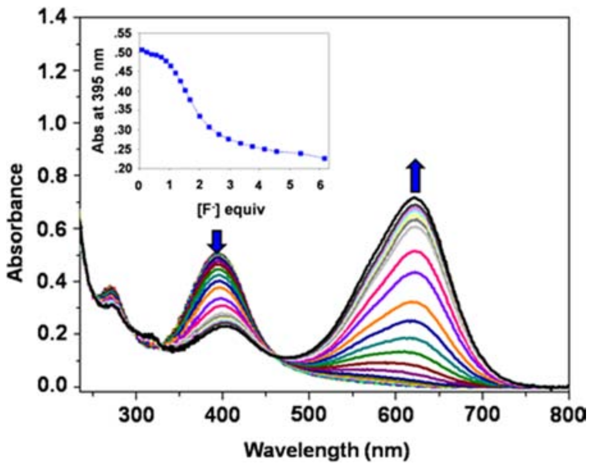

Figure 3. UV−vis titration of **1** (0.02 mM) in CH_3CN upon addition of F^- (0−6 equiv). (Inset) Plot of absorbance at 396 nm as a function of [F^-].

Table 1. Stability Constants (log β) of the 1:1 Complexes of **1** with the Indicated Anions in MeCN, as Evaluated by UV−vis Titration (t = 25 °C, I = 0.01 M Bu_4NPF_6)

anions	log β
F^-	3.07 (0.08), 11.09 (0.07)[a]
$H_2PO_4^-$	2.55 (0.02)
acetate	4.81 (0.06)
benzoate	5.64 (0.09)

[a] 2:1 complex (A_2L).

In addition, the H_d and H_e signals shifted upfield from around 6.86−6.72 and 7.02 ppm to 6.66 and 6.85 ppm, respectively, which indicated that the azocalix[4]arene platform rearranged to accommodate the F^- ion. The pyrrolic NH peak shifted downfield from 8.04 to 8.09 ppm at 0.1 equiv, and disappeared at 0.2 equiv, of added F^- anions, which was in contrast to the case of the β-pyrrolic protons. This suggests that the calix[4]pyrrole unit participated in F^- binding by H-bonding and also that the phenolic OH and the pyrrolic NH of probe **1** served as anion binding sites and enhanced the binding ability to detect anions.

However, ^{1}H NMR titration revealed a different manner of complexation of benzoate by probe **1** (Figure 5).

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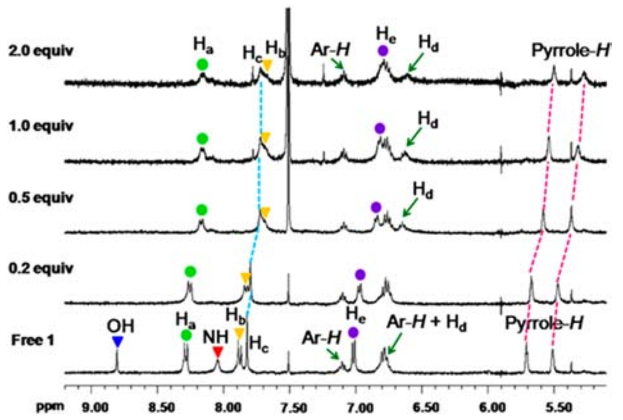

Figure 4. ^{1}H NMR spectra of compound **1** (3.58 mM) in MeCN in the presence of different amounts of TBAF.

The phenolic OH signal at 8.80 ppm became a broad peak and then dissapeared when only 0.1 and 0.2 equiv of benzoate were added into the solution of **1**, respectively, without displacement of the H_a and H_b signals. This implies that electron push did not occur. The NH peak gradually shifted downfield from 8.16 to 8.65 ppm while the pyrrolic signals were displaced upfield from 5.80 and 5.61 ppm to 5.75 and 5.57 ppm, respectively, upon the addition of the benzoate salt solution. This suggests that receptor **1** bound the benzoate ion by H-bonding from the −NH and −OH groups of the calix[4]pyrrole and azocalix[4]arene, respectively. Moreover, these ^{1}H NMR titration studies also showed that probe **1** preorganized prior to binding benzoate over F^-, since there were fewer peak shifts of **1**. The acetate−receptor **1** interaction was in between that for the F^- and benzoate complexes with **1**. The ^{1}H NMR titration studies also demonstrate that the complexation mode of receptor **1** with F^-, acetate, and benzoate was endocomplexation with different magnitudes of interactions with phenol and calix[4]pyrrole units.

The decomplexation of the **1**$\cdot$**F**$^-$ complex occurred upon the addition of Ca^{2+} (2 equiv) into the solution of **1** with F^- (6 equiv) in CH_3CN. The UV−vis spectrum and color change showed that the addition of Ca^{2+} to the solution of **1**$\cdot$**F**$^-$ results in a revival of the absorption spectra of free receptor **1** (Figure 6). This finding suggests that ion pair complexation did not occur but that the F^- ion was stripped out by Ca^{2+} to form the CaF_2 salt. Contrastingly, the ion pair complexes, $\mathbf{1\cdot CH_3CO_2^-\cdot Ca^{2+}}$ and $\mathbf{1\cdot PhCO_2^-\cdot Ca^{2+}}$, formed after addition of 2 equiv of $Ca(NO_3)_2$ into $\mathbf{1\cdot CH_3CO_2^-}$ and $\mathbf{1\cdot PhCO_2^-}$ complexes (Figures S23 and S24).

In summary, a chromogenic anion sensor **1** was successfully synthesized. The integration of an azobenzene unit onto the calix[4]arene framework enhanced the anion binding ability of the phenolic OH group of the calix[4]arene by the electron pull from the phenolic groups to the nitrobenzene units and provided naked-eye detection ability for anions. It was demonstrated spectroscopically and chromogenically that probe **1** could discriminate between F^-, acetate, benzoate and H_2PO_4, which possess different sizes and shapes, with binding affinities in the order benzoate > acetate > F^- > $H_2PO_4^-$. The detection of F^- can be confirmed by the addition of $CaNO_3$ solution into the solution of **1**$\cdot$**F**$^-$.

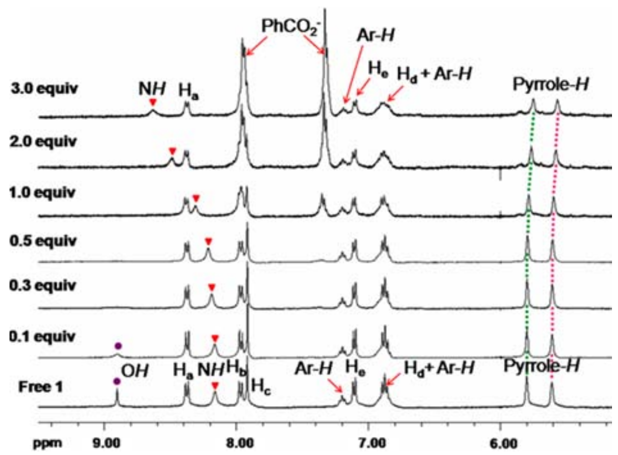

Figure 5. ^{1}H NMR spectra of compound **1** (3.58 mM) in CD_3CN in the presence of different amounts of benzoate ions.

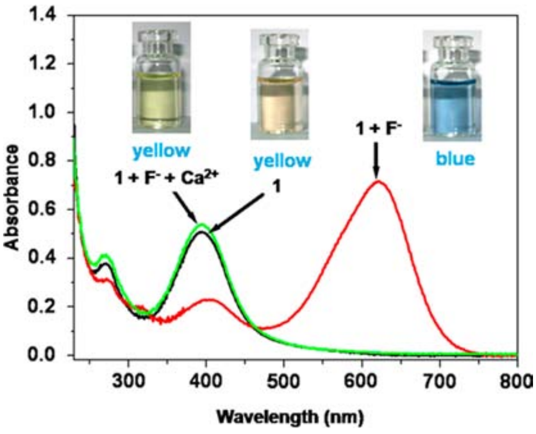

Figure 6. Reversibility of F^- coordination by **1** due to the addition of $Ca(NO_3)_2$ solution.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.