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A New Detection Mechanism involving Keto-Enol Tautomerization: Selective Fluorescence Detection of Al(III) by Dehydration of Secondary Alcohols in Mixed DMSO/Aqueous Media

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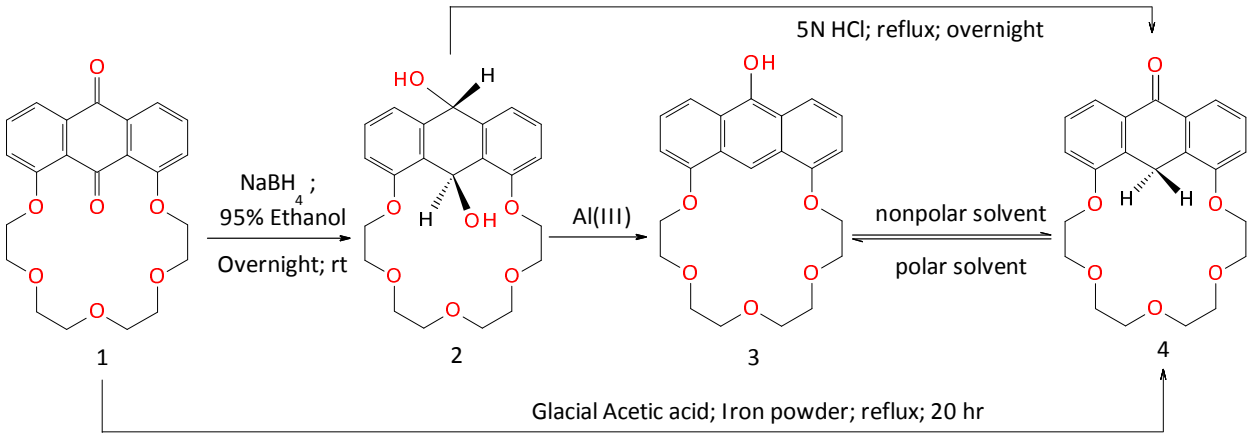
A new mechanism for the fluorescence detection of metal cations in solution is introduced involving a unique keto-enol tautomerization. Reduction of 1,8-anthraquinone-18-crown-5 yields the doubly reduced secondary alcohol, **2**. Compound **2** acts as a chemodosimeter for Al(III) ion producing a strong blue emission due to the formation of the anthracene fluorophore, **3**, via dehydration of the internal secondary alcohol in DMSO/aqueous solution. The enol form is not the most thermodynamically stable form under these conditions however and slowly converts to the keto form **4**. Reduction of **1** with Fe/AcOH or the reaction of **2** with HCl directly yields compound **4**, the keto tautomer of **3**, which also produces the same blue emission in more polar solvents. Competition studies reveal that compound **2** produces a blue emission exclusively in the presence of the strong Lewis acidic Al(III) ion and at relatively low pH.

Introduction

Aluminium is the third most abundant metallic element in the earth's crust found in ~8% by mass. Aluminium is produced/consumed in massive quantities in industrial settings and it also used in pharmaceuticals, food additives, cosmetics and other household products. Inhalation of aluminium is neurotoxic,[1] genotoxic,[2,3] and potentially carcinogenic,[4] and over the long term may lead to Alzheimer's[5,6] and Parkinson's[7,8] disease. Aluminium, as a pollutant, is also known to inhibit the growth of seeds and roots in plants.[9,10] Detection of Al(III) from biological and environmental systems is always challenging, and Electrothermal Atomic Absorption Spectrometry (ETAAS) and Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) are commonly employed methods for detection of aluminium; however these two techniques are expensive and generally time consuming. Thus, the development of easily accessible chemosensors/chemodosimeters for the detection of aluminium is essential. Fluorescent chemosensors[11-13] or chemodosimeters[14-16] for the detection of aluminium have previously been reported; although most of these are not employed in aqueous solution due to the high hydration energy of aluminium. In this study, we report a new, highly selective chemodosimetric mechanism for the detection of Al(III) in aqueous mixture, based on the dehydration of secondary alcohols to produce blue fluorescent anthracene fluorophores. We have previously reported Zn(II) mediated imine-enamine tautomerization,[17] and have used the Ritter amide synthesis to form molecule latches involving similar anthraquinone macrocycles containing mono secondary alcohols.[18] Here we report a different tautomerization reaction that leads to fluorescent products using related anthraquinone-based macrocycles and have followed the formation of luminescent products selective for Al(III) with time-dependent ^{1}H NMR spectroscopy, UV-Vis, and emission studies.

Scheme 1: Reaction scheme for compounds **2**-**4**



Results and Discussion

Compound **2** was synthesized by reducing both the carbonyl groups in compound **1** using $NaBH_4$ in 95% ethanol (Scheme 1), which produced a white-colored solid in ~80% yield. Compound **2** is well characterized by ^1H and ^{13}C NMR, 2D-COSY, ESI-MS, IR, and elemental analyses results, and is highly soluble in CH_3OH and CH_2Cl_2. The ^1H NMR signals at δ 6.42 (d, J=4.9 HZ, 1H, -CH-O anthranol (outer)); δ 6.13 (d, J=7.9 HZ, -OH anthranol (inner)); δ 5.68 (d, 1H, J=7.9 HZ, -CH-O anthranol (inner)); δ 4.75 (d, J=4.9 HZ, 1H, -OH anthranol (outer)) (Figure S1) confirm that both carbonyl groups in 1 have been reduced to secondary alcohols, and the 2D COSY spectrum reveals the correlation of inner vs. outer –OH and –CH protons positioned at the 9 and 10 positions (Figure S2). D_2O exchange for the OH protons and rerecording the COSY spectrum shows the missing singlets at δ 6.13 and 4.75 (Figure S3) which are due to the hydroxyl protons. The loss of ^{13}C NMR signals at ~180 ppm and the gain of signals at δ 55.5 and 66.4 (Figure S4) also confirm the formation of two secondary alcohols. In addition, the ESI-MS peak at 425.4 (**2**+Na^+) matches the doubly reduced parent ion (Figure S5), and the broad IR signal at 3427 cm^{-1} (Figure S6) shows the corresponding OH stretches for compound **2**.

Compound **1**, when reacted using acetic acid and iron powder (Method A), yields the anthrone (compound **4**) as opposed to the diol. ESI-MS, Elemental Analyses and IR data all indicate the presence of only one carbonyl group, where the inner carbonyl group has been reduced to a methylene group, observed as a singlet in the ^1H NMR spectrum at 4.19 ppm (Figure S7) and 22.6 ppm (CH_2) signal in the ^{13}C NMR spectrum (Figure S8). Compound **4** can also be made by dehydration of **2** using strong acid (Method B, Scheme 1).

Crystallography We successfully obtained X-ray quality crystals of compounds **2** and **4** after slowly diffusing diethyl ether into CH_2Cl_2/CH_3OH mixtures of **2** and **4** (Figure 1). The structure of **2** shows two hydroxyl groups present in the molecule, and the hydroxyl group within the polyether ring is located perpendicular to the anthraquinone plane, probably to minimize steric interactions with the neighboring oxygen atoms, while the hydroxyl group opposite the ring is found parallel to the macrocyclic plane, and *trans* to the inner OH group. The anthranol plane is bent in the middle, between the two aromatic rings, with a 39.4(1)° dihedral angle. The bond lengths for the two C-O single bonds equal C9-O1 1.428 (15) Å and C10-O2 1.4482 (14) Å. Two intermolecular hydrogen bonds form between OH and -OCH_2 groups: O(1)-H(99)…O(6) = 2.774(2) Å, 163(4)° and O(2)-H(100)…O(1) = 2.837(2) Å, 172(3)°. The structure of **4** clearly shows the presence of one external carbonyl group and the internal methylene group. The C=O distance measures 1.2302 (14) Å, typical for a C=O double bond.

Spectroscopic Studies Fluorescence studies were conducted using compound **2** upon addition of a variety of different metal cations in DMSO (90%)/pH = 7 Potassium Phosphate Buffer (10%) solution. A dramatic 32 fold increase in a bright blue emission was observed exclusively for the addition of Al(III) (Figure 2A). The blue emission manifold that is produced upon Al(III) addition is indicative of anthracene formation, where the three adjacent anthracenyl six-membered rings become conjugated. The excitation spectrum of the solution is a mirror of the emission spectrum also typical of anthracenes (Figure S9). The strongest evidence for anthracene formation comes from following the reaction *in situ* using proton NMR in DMSO-d_6. Approximately 20 minutes after the addition of excess Al(III) addition, a very clean NMR results where all the -CH and -OH protons due to the secondary alcohol groups disappear (between 6.42 to 4.75 ppm) and two new singlets at 10.02 (broad singlet, 1H, -OH anthracenol) and 8.71 ppm (s, 1H, anthracene) appear (Figure 3A & 3B). This suggests that the initial product of this reaction is the anthracenol derivative **3** (Scheme 1). The reaction is not stoichiometric however as a large excess of Al(III), approximately 25-30 equivalents, is required to cause saturation in luminescence intensity (Figure S10). Addition of strong acid (5N HCl) to a solution of **2** also directly converts **2** to **4** (Scheme 1, Method B).

A further investigation using different salts of Al(III) was also performed. For this study, aqueous solutions of 30 equivalents of added chloride, nitrate, sulphate, perchlorate salts of aluminium were compared (Figure S11). Fluorescence intensities generally parallel the basicity of these different anions. A competition study was also conducted between Al(III) (20 eq) with other cations present (20 eq), and only those cations that have a high oxidizing ability interfere with Al(III) (Figure 2B). We have previously demonstrated this chemistry where Hg(II), Cu(II) and Fe(III) oxidize secondary alcohols back to the starting quinone or anthrone.[19]

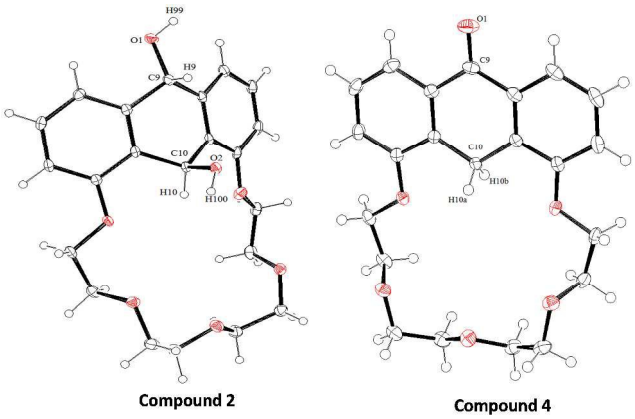


Figure 1: Thermal ellipsoid diagrams (30%) of **2** and **4**. (Selective atoms are labelled for clarity)

Specifically, in this case, **2** forms the oxidized bianthrone product, compound **11**, with addition of Hg(II). Product **11** was isolated and characterized by ^1H (Figures S24), ^{13}C NMR (Figures S25), ESI-MS (Figures S26), elemental analyses, and single crystal X-ray diffraction (Figure 7). Compound **11** is highly soluble in CH_3OH and CH_2Cl_2, and the crystal structure clearly shows the inner C-C bond, the methine hydrogen atoms, and the external carbonyl groups. Bianthrone formation from **2** using Hg(II) as oxidant was also confirmed by an ^1H NMR study in DMSO-d6 (Figures S27) showing the characteristic methine CH resonance at 5.63 ppm and is identical to the NMR spectrum of isolated **11**.

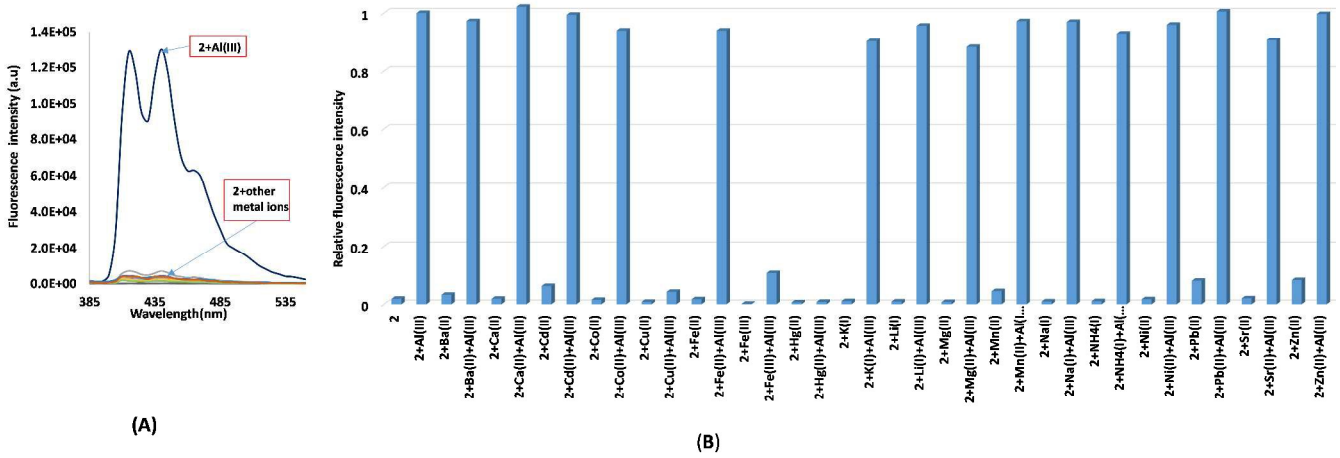


Figure 2: (A) Fluorescence spectrum of 10^{-4} M compound **2** in DMSO + pH = 7 buffer (10%) with added metal cations (20 eq). (B) Competition study: Relative fluorescence intensity at 410 nm of compound **2;** compound **2** + 20 equivs. of metal cations; and compound **2** + 20 equivs of metal cations + 20 equiv. of Al(III). λex = 365 nm.

pH Studies As Al(III) is the hardest Lewis acid of all the cations previously studied, the only harder Lewis acid is the proton itself. Consequently the effect of pH on compound **2** was investigated using different pH buffers ranging from pH = 1-9 (Figure 4). The bright blue emission depends significantly on the pH of the solution, as pH = 6-9 does not show any effect, while pH = 4-5 has a moderate effect, and pH = 1-3 produce the greatest fluorescence intensity. Formation of the anthracenol product **3** was also investigated under time-dependent ^{1}H NMR after adding pH = 1 buffer to DMSO-d_6 solution of $1x10^{-2}$ M compound **2**. After 5-10 minutes, the identical appearance of the anthracenol –OH and the aromatic –CH proton resonances dominate. For this reason, the addition of Al(III) in the previous studies was conducted with pH = 7 buffer to inhibit the effect of protonation. Monitoring the pH showed only a few tenths of a pH change upon Al(III) addition at pH = 7.

Keto-Enol Tautomerization Keto-enol tautomerization of the parent anthracene-9-ol and its tautomer 10*H*-anthr-9-one, without the polyether chains, were first observed by Meyer et. al.[20] Keto-enol tautomerization in this system is also observed, where compound **4** represents the keto tautomer of the enol **3** (Scheme 1). Over a period of several hours, the initial formation of **3** with added acid slowly converts to a third product, which we attribute to the keto tautomer **4**. The time-dependent UV/VIS spectroscopic study after adding pH = 1 buffer to compound **2**, shows the immediate growth of the anthracenol manifold from 350-400 nm, followed by its slow disappearance and conversion to a new peak at 320 nm with clean isosbestic points (Figure 5). Comparison of spectra shows that the final absorbance maximum at 320 nm of the reaction of **2** + acid after 3 hours, almost exactly matches the peak at 320 nm for synthesized **4** taken in the same solvent. The decrease in the anthracenol peaks and the growth of the 320 nm peak due to **4** indicates the anthrone tautomer is the more stable of the two, with an equilibrium constant roughly equal to <0.20 under these conditions (equilibrium expression as written in Figure 5). Evidence for this transformation is also found in the NMR spectrum of **2** + Al(III) ion in a DMSO/$CHCl_3$ mixture, where after eight hours, the presence of anthrone peaks are observed and are identical to an authentic sample of **4** (Figures 4C & 4D). In non-polar solvent, the anthrone tautomer **4** is preferred (Figure S12). We have found that the inner carbonyl group of 1,8-anthraquinone-18-crown-5,compound **1**, is always the most reactive, due to the presence of the neighboring electron-donating alkoxy groups, and this is the case here again with the internal secondary alcohol.[17,18] The inner OH group is complexed by acid or the oxophillic Al(III) Lewis cation with the subsequent loss of water or Al-OH species to generate the carbocation. Loss of the outer proton and aromatization of the central ring yields the anthracenol which slowly equilibrates with the anthrone over time (Scheme 2). Recent synthetic and computational studies have confirmed the formation of anthracenone keto isomers with identical substitution patterns.[21,22]

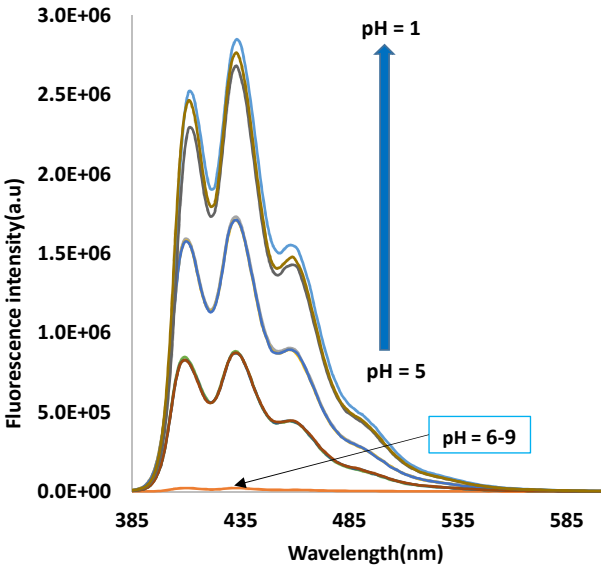


Figure 3: Fluorescence spectrum of 10^{-4} M compound **2** in DMSO with 10% added buffers. λex = 365 nm.

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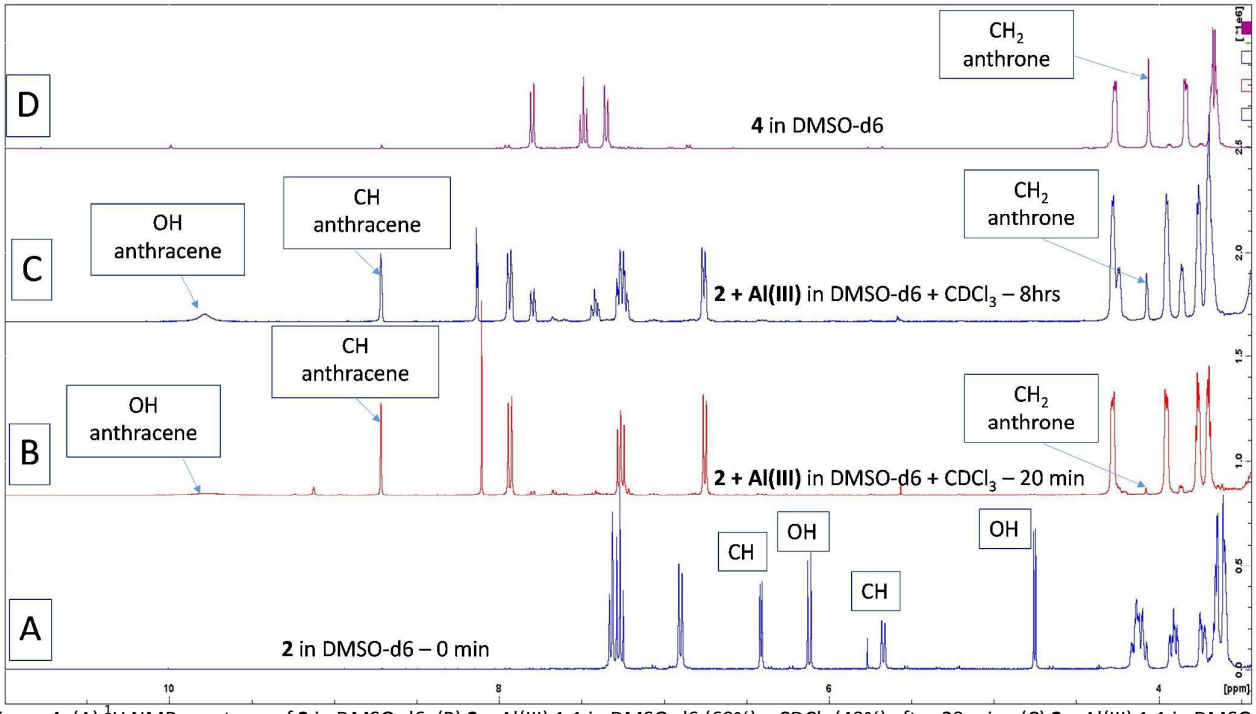

Figure 4: (A) ^{1}H NMR spectrum of **2** in DMSO-d6. (B) **2** + Al(III) 1:1 in DMSO-d6 (60%) + $CDCl_3$ (40%) after 20 min. (C) **2** + Al(III) 1:1 in DMSO-d6 (60%) + $CDCl_3$ (40%) after 8 hours. (D) **4** in DMSO-d6.

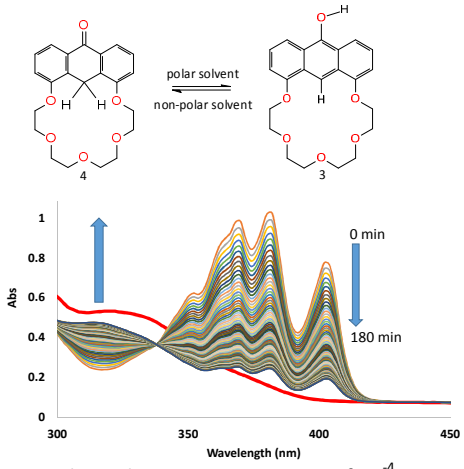

Figure 5: Time dependent UV-VIS spectrum of 10^{-4} M **2** in DMSO + pH = 7 buffer (10%) after adding 50µL of pH = 1 buffer (total time of analysis 3.0 hours) and **4** in DMSO + pH = 7 buffer (10%) (Red line).

To show that this phenomenon in more general, we have observed formation of anthracenes from secondary alcohols involving two other related anthranol macrocycles (Figure 6). Compound 5 has previously been reported as a Pb(II) detector.[19] This molecule contains an inner amide group linked to a dansyl fluorophore and an outer secondary alcohol that when exposed to Al(III) or acid produces the same blue anthracene emission as observed here (Figure S13). Lastly, compound 7, an anthranol macrocycle which contains an amide macrocyclic ring and a linked rhodamine fluorophore has been synthesized. Compound 7 similarly forms an intense blue emission upon the addition of Al(III) (Figure S14). Of additional interest, in the presence of Hg(II), only the opening of the spirolactam ring was observed for 7, demonstrating this macrocycle can act as a multichannel sensor for both Al(III) and Hg(II). The synthesis of 7 and supporting characterization data including a crystal structure of compound 6 are provided in the supporting material (Figures S15- S23).

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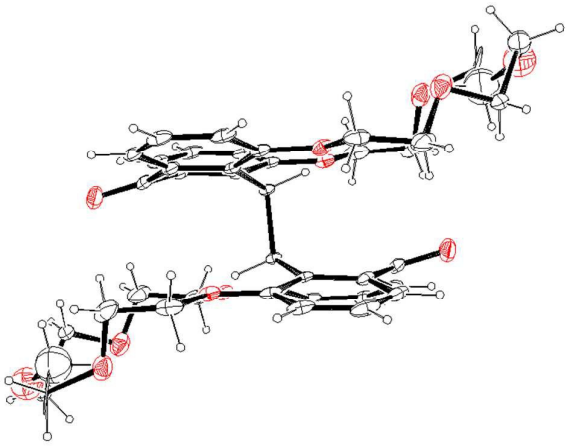
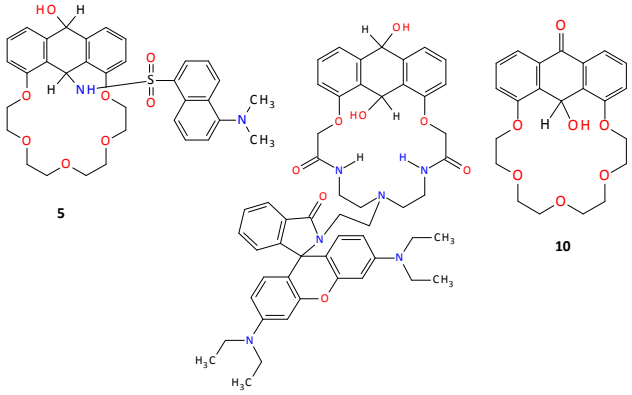


Figure 6: Thermal ellipsoid diagram of the compound **11** (bianthrone). The bottom of the macrocyclic ring is disordered and is modelled over two positions in 50:50 occupancy. Only one of the disordered chains is shown.

Conclusion

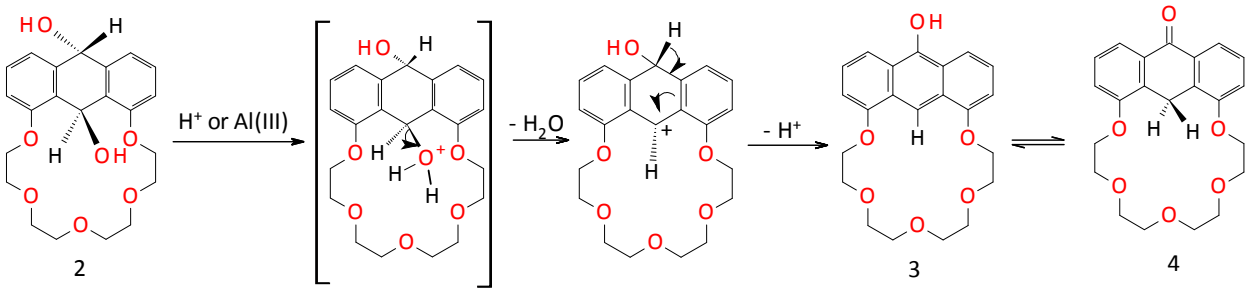
We have demonstrated that strong Lewis acids can dehydrate secondary alcohols and produce fluorescent anthracenol macrocycles in aqueous solution. The anthracenol formed is the enol tautomeric form of the corresponding keto anthrone and is dependent on solvent polarity. Only the isomer where the keto group is located on the outside of the macrocycle is produced. The hydrolysis of secondary alcohols by Lewis acids represents a new mechanism for the fluorescence detection of Al(III) cation of biological and environmental concern. To our knowledge generation of keto-enol tautomers in this manner has not been used as a detection strategy previously.



5 7 10

Figure 7: Structures of compounds **5**, **7** and **10**

Scheme 2: Proposed mechanism of compound **2** with Lewis acid.



2 3 4

Experimental

1,8-oxybis(ethyleneoxyethyleneoxy)-9,10-anthraquinone (**1**)[23], compound **8**,[24] compound **9**[25], and compound **10**[29] were synthesized by previously reported procedures. $NaBH_4$, Aluminum(III) perchlorate nonahydrate were purchased from Sigma Aldrich and used without further purification. Eighteen metal salts of NH_4(I), Ba(II), Ca(II), Cd(II), Co(II), Cu(II), Fe(II), Fe(III), Hg(II), Li(I), Mg(II), Mn(II), Na(I), Ni(II), Pb(II), Sr(II), Zn(II) as perchlorates were purchased from Sigma-Aldrich and used for emission and absorbance studies after drying using an Abderhalden drying apparatus at 100 C. Buffers pH = 1-3 (potassium chloride /HCl buffer), pH = 4-5 (potassium biphthalate buffer), pH = 6-8 (potassium monophosphate buffer), pH = 9 (boric acid/potassium chloride) were purchased from Fisher Scientific. 400 MHz Bruker Alpha spectrophotometer was used for NMR studies. Absorbance data was collected using a HP 8452A diode array spectrophotometer or a Varian Cary 50. Emission studies were conducted using a SPEX Fluoromax 4 fluorimeter. ESI-MS was recorded on the Varian 500-MS IT ESI mass spectrometer. Melting points were determined using open capillaries and are uncorrected. Elemental analyses (CHN) were conducted using an Exeter CE-440 Elemental Analyzer. Lab glassware were dried at 100 C prior to use. X-ray crystals were grown from samples dissolved

in CH_2Cl_2 (80%) + MeOH (20%) and diffused with diethyl ether. Crystallographic data was collected at 100 K using MoKα radiation on a Bruker APEXII diffractometer for **2**, **4** and **6**. Cell constants were determined after integration from typically more than 9,000 reflections. Structures were solved by direct methods using SIR97 and refined using SHELXL-97.[26] Data reduction and refinement was done with the help of WinGX software suite,[27] and hydrogen atoms were placed in ideal positions and were refined as riding atoms with relative isotopic displacement parameters, with the exception of hydrogen-bonded protons which were found from the difference map.[28] Two macrocycles were found in the asymmetric unit of compound **4**, each with different ring conformations. Part of the polyether ring in one macrocycle was found disordered over two positions in a 3:1 ratio. Crystallographic and refinement data are provided in Table S1.

Synthesis of 1,8-oxybis(ethyleneoxyethyleneoxy)-9,10-dihydroxyanthranol (2): 0.0475 g $NaBH_4$ (1.255 mmol) was added to a solution of 0.500 g **1**, (1.255 mmol) dissolved in 30 mL of 95% ethanol. The solution was stirred overnight and mixed with 100 mL of distilled water and extracted with 50 mL of methylene chloride. Methylene chloride solution was dried with anhydrous sodium sulfate, filtered and most of the solvent evaporated under reduced pressure which yielded a white-colored solid. Compound **2** was purified by diffusing diethyl ether into methylene chloride solution. Yield: 0.404 g (80%). Melting point is 147-150°C. Elemental analyses calculated for $C_{22}H_{26}O_7$: C, 65.69; H, 6.46 %. Found: C, 65.26; H, 6.57 %. ESI - MS Calculated for $C_{22}H_{26}O_7Na^+$: 425.22; found: 425.4 (**2**+Na^+). ^{1}H NMR (DMSO-d6 at 25 °C); δ 7.33 (d, J = 7.7 HZ, 2H, ArH); 7.27 (t, J = 7.2 HZ, 2H, ArH); 6.90 (d, J = 7.9 HZ, 2H, ArH); 6.42 (d, J = 4.9 HZ, 1H, -CH-O anthranol (outer)); 6.13 (d, J = 7.9 HZ, 1H, -OH anthranol (inner)); 5.67 (d, J= 7.9 HZ, 1H, -CH-O anthranol (inner)); 4.75 (d, J = 4.9 HZ, 1H, -OH anthranol (outer); 4.13 (m, 4H, CH_2-O in polyether chain); 3.91 (m, 2H, CH_2-O in polyether chain); 3.75-3.61 (m, 10H, CH_2-O in polyether chain). ^{13}C, NMR (DMSO-d_6 at 25 °C): δ 55.6; 66.4; 69.12; 6.19; 70.1; 70.5; 110.0; 116.8; 126.0; 128.2; 145.6; 155.8. IR: Broad-OH band at 3427 cm^{-1}.

Synthesis of 1,8-oxybis(ethylenoxyethyleneoxy)-9(10H)-anthrone (4): *Method (a):* 0.500 g (1.255 mmol) of **1** was dissolved in 35 mL of glacial acetic acid. The solution was stirred for 15 min and 1.123 g iron powder (20.10 mmol) was added to the solution. The mixture was refluxed for 20 hours. After cooling to room temperature the solution was filtered to remove the iron power and was washed with 25 mL methylene chloride. 25 mL of water was then added and the solution neutralized with $NaHCO_3$, extracted with methylene chloride, and dried over with Na_2SO_4. After removing solvent under reduced pressure a cream-colored solid was obtained. The compound was purified on a silica gel column using a 98:2 methylene chloride/ methanol mixture. Yield: 0.338 g (70%).

Method (b): 0.250 g (0.622 mmol) of **2** was dissolved in 25 mL of 5M HCl and the mixture was refluxed overnight. After cooling to room temperature the solution was extracted with 25 mL methylene chloride, washed with water, and dried over Na_2SO_4. After removing solvent under reduced pressure the product was purified by column chromatography using silica gel and methylene chloride: ethyl acetate mixture to obtain a light brown colored solid. Yield: 0.070 g (30%). Melting point 194-196°C. Elemental analyses calculated for $C_{22}H_{24}O_6$: C, 68.77; H, 6.25 %. Found: C, 68.29; H, 6.16 %. ESI MS: Calculated for $C_{22}H_{24}O_6$: 384.22; found: 385.4 (**4**+H^+) and 407.4 (**4**+ Na^+). ^{1}H NMR (CDCl3 at 25 °C); δ 8.00 (dd, J = 8.0 HZ, 2H, ArH); 7.43 (t, J = 8.4 HZ, 1H, ArH); 7.10 (d, J= 8.1 HZ, 2H, ArH), 4.27 (m, 4H, CH2-O in polyether chain); 4.19 (S, 2H, -CH2-); 3.98 (m, 4H, CH2-O in polyether chain); 3.83 (m, 8H, CH2-O in polyether chain). ^{13}C, NMR (CDCl3 at 25 °C): δ 22.6 (CH2); 68.3; 69.1; 70.1; 71.1; 114.0; 119.3; 127.1; 130.4; 132.7; 156.0; 184.4. IR: C=O 1686 cm^{-1}.

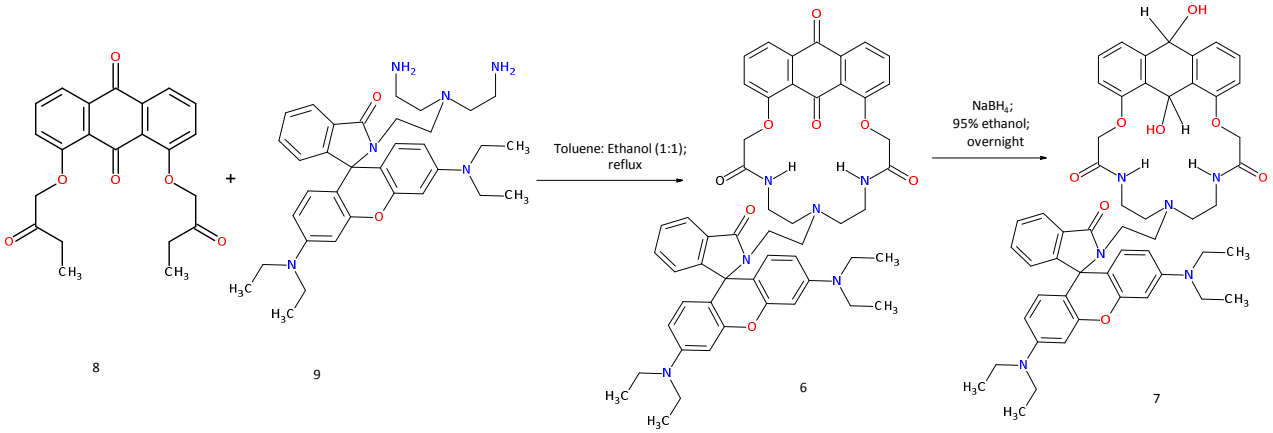
Synthesis of 12-[2-[3',6'-bis(diethylamino)-3-oxo-2,3-dihydro-spiro [isoindole-1,9'-xanthene]-2-yl]ethyl]-6,18-dioxa-9,12,15-tri-azatetra-cyclo [21.3.1.05, 26, 019, 24] heptacosa-1,3,5(26), 19,21,23-hexaene-8,16,25,27-tetrone (6): 1.932 g (1.5 eq, 3.38 mmol) of **8** was dissolved in 25 mL of a 1:1 mixture (v/v) of dry toluene and absolute EtOH. 9 drops of diisopropylethylamine and drying spheres were added to the solution. With stirring, 0.9308g (1 eq, 2.26 mmol) of **9** was added at once. The resulting solution was refluxed for 48 hours under argon protection with minimal exposure to light. Solvent was removed under reduced pressure. The red semisolid was redissolved in CH_2Cl_2, and the solvent was removed under reduced pressure to remove all traces of the toluene-ethanol mixture. The resulting semisolid was again dissolved in a minimal amount of CH_2Cl_2 and gently heated. Ether was added gradually until precipitation was first observed, and then the solution was slowly cooled. The red crystalline precipitate was filtered, rinsed with small portions of ether, and then crushed to remove traces of ether. Yield: 1.1458g (57.0%). Elemental analyses calculated for $C_{52}H_{54}N_6O_8.1.5H_2O$: C, 68.06; H, 6.21 %, N, 9.16 %. Found: C, 68.12; H, 6.58 %, N, 9.10 %. Water is found in both the NMR and X-ray crystal structure of this compound. The thermal ellipsoid diagram of compound **6** is shown in Figure S23). ESI MS: Calculated for $C_{52}H_{54}N_6O_8$: 890.52; found: 891.4 (**6**+H^+) and 913.4 (**6**+Na^+). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ 1.12-1.22 (m, 12H, -CH_3); 2.43 (bs, 2H, (R2N)-CH_2); 2.59 (bs, 4H, ((C=O)-R_2N)-H_2C-(CR_2); 3.25 (bs,8H, ((NR_2)-H_2C-(CR_2), ((CH_3)-CH_2); 3.39 (bs, 4H, (C=O)NR-CH_2); 3.46-3.50 (m, 2H, (-CH_2- CH_3); 4.48 (s, 4H, O-CH_2); 6.07 (bs, 2H, Rh-H); 6.21 (bs, 2H, Rh-H); 6.32 (bs, 2H, Rh-H); 6.96 (bs, 1H, Rh-H); 7.19 (bs, 2H, Aq-H); 7.36 (bs, 2H, Rh-H); 7.69-7.71(m, 3H, Aq-H); δ 7.91-7.93 (bs, 2H, Rh-H); 8.25 (bs, 2H, (C=O)NH_2). ^{13}C (400 MHz, $CDCl_3$, 25°C): δ 12.6; 38.1; 38.8; 44.3; 53.7; 56.4; 67.7; 97.9; 105.7; 107.8; 118.8; 120.1; 122.5; 123.5; 127.9; 128.5; 130.9; 132.1; 134.5; 134.7; 148.4; 153.3; 157.2; 167.1; 167.9; 182.0; 182.9.

Synthesis of 12-[2-[3',6'-bis(diethylamino)-3-oxo-2,3-dihydro-spiro [isoindole-1,9'-xanthene]-2-yl]ethyl]-25,27-dihydroxy-6,18 -dioxa-9,12, 15-triazatetracyclo [21.3.1.05,26.019 .24] heptacosa-1(26),2,4,19,21,23-hexaene-8,16-dione (7): 0.2003 g (1 eq, 0.225 mmol) of **6** was added to 10 mL 95% EtOH. While stirring, 0.1g (11.75eq, 2.64 mmol) of $NaBH_4$ was added to the solution. The mixture was stirred for 3.5 hours at room temperature. All glassware used in the purification procedure were rinsed with dilute NaOH and then dried (as appropriate). The reaction was quenched with water, and the organic product was extracted in methylene chloride. The organic layer was dried over anhydrous sodium sulfate, and then the solvent was removed under reduced pressure leaving a light tan solid. Yield: 0.0830g (41.3%) Elemental analyses calculated for ($C_{52}H_{58}N_6O_8$+1.0 H_2O+0.5CH_2Cl_2): C, 66.03; H, 6.40; N, 8.80% Found: C, 66.02; H, 6.66; N, 8.56%. Water and CH_2Cl_2 were both found in the NMR spectrum (Figure S15). ESI MS: Calculated for $C_{52}H_{58}N_6O_8Na^+$: 917.52; found: 917.4 (**7**+Na^+). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ 1.12-1.21 (3/9*, 12H, -CH_3); 1.99-2.02 (t, J = 8.4 HZ, 2H, (-N-CH_2); 2.20-2.23 (m, 2H, R2N-CH_2); 2.32-2.36 (m, 2H, (-N-CH_2); 2.49-2.52 (d, J = 9.5 HZ, 1H,-OH); 3.00-3.04 (t, J = 8.3 HZ, 2H, CH_2-(N)); 3.29-3.35(t, J = 7.7 HZ, 10H, (C=O)NH-CH_2, CH_2-(CH_3)); 3.45-3.50 (q, J = 7.0 HZ, 2H, CH_2 (CH_3); 4.56-4.68 (q, J = 17.8 HZ, 4H, O-CH_2); 5.96-5.98 (s, 2H, CH and -OH); 6.07-6.09 (d, J = 8.9 HZ, 2H, Rh-H); 6.16-6.19(dd, J = 9.1 HZ, 2H, Rh-H); 6.33-6.41 (d, J = 2.5 HZ, 2H, Rh-H); 6.49-6.51 (d, J = 7.2 HZ, 1H, (-OH)-CH); 6.86-6.88 (d, J = 8.1 HZ, 2H, Aq-H); 6.97-6.99 (d, J = 6.9 HZ, 1H, Rh-H); 7.34-7.41 (m, 4H, Rh-H Aq-H); 7.51-7.55 (m, 3H, Aq-H Rh-H); 8.77 (s, 2H, (C=O)NH). ^{13}C (400 MHz, $CDCl_3$, 25°C): δ 12.5; 18.3; 36.7; 39.6; 44.3; 52.0; 55.7; 57.9; 58.2; 65.5; 66.8; 67.3; 97.9; 104.8; 108.0; 110.2; 119.3; 122.6; 123.7; 124.7; 128.1; 128.3; 129.0; 130.6; 132.6; 142.2; 148.8; 153.0; 153.3; 155.5; 168.2; 168.7.

Synthesis of Bis (1,8-oxybis(ethylenoxyethyleneoxy)-9(10H)-anthrone) (11): 1.0 g of (0.622 mmol) of **10** was dissolved in 10 mL of 95% ethanol and 20 mL of 12M HCl in 20 mL of water,[29] and refluxed overnight. After cooling to room temperature, 100 mL of water was added and the solution was extracted with 3 x 50 mL methylene chloride, washed with water, and the product was dried over Na_2SO_4. After removing solvent under reduced pressure, the product was purified by column chromatography using silica gel and methylene chloride:methanol mixture (95:5) to obtain a light brown colored solid. Yield:

0.68 g (35.47%). Melting point 280 °C. Elemental analyses calculated for $C_{44}H_{46}O_{12}$: C, 68.92; H, 6.05 %. Found: C, 68.95; H, 6.16 %. ESI MS: Calculated for $C_{44}H_{46}O_{12}$: 766.83; found: 767.43 (M+1). ^{1}H NMR (CDCl3 at 25 °C); δ 7.44 – 7.46 (dd, J = 7.9 HZ, 4H, ArH); 7.21 - 7.26 (t, J = 8.7 HZ, 4H, ArH); 6.70 - 6.72 (dd, J = 8.3 HZ, 4H, ArH); 5.63 (s, 2H, CH-methine); 3.96-3.98 (m, 4H, -CH_2-O in polyether chain); 3.88 - 3.90 (m, 4H, CH2-O in polyether chain); 3.61 – 3.72 (m, 24H, CH2-O in polyether chain). ^{13}C, NMR (CDCl3 at 25 °C): δ 39.2 (CH-methine); 67.9; 68.9 ; 70.3; 71.4; 13.0; 118.0; 127.6; 130.9; 136.4; 156.0; 183.8.

Scheme 3: Reaction scheme for compounds **6-9.**



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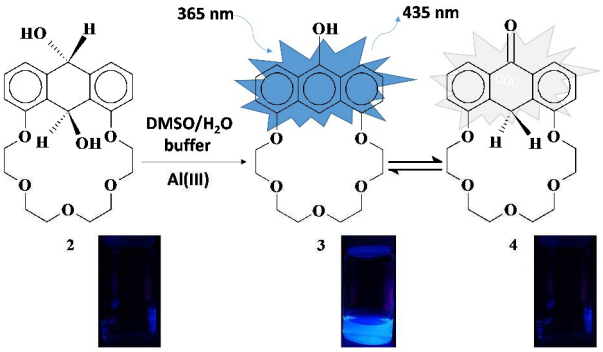
References

1. Nayak, P. *Environ. Res.* **2002**, *89*, 101-115.
2. Achary, V. M. M.; Panda, B. B. *Mutagenesis* **2009**, 1-9.
3. Geyikoglu, F.; Turkez, H.; Bakir, T. O.; Cicek, M. *Toxicol Ind Health* **2012**, 1-12.
4. Darbre, P. D.; Mannello, F.; Exley, C. *J. Inorg. Biochem.* **2013**, *128*, 257-261.
5. Exley, C. *Mol. Med. Today* **1998**, *4*, 107-109.
6. Flaten, T. P. *Brain Res. Bull.* **2001**, *55*, 187-196.
7. Good, P. F.; Olanow, C.; Perl, D. P. *Brain Res.* **1992**, *593*, 343-346.
8. Hirsch, E.; Brandel, J. P.; Galle, P.; Javoy-Agid, F.; Agid, Y. *J. Neurochem.* **1991**, *56*, 446-451.
9. Delhaize, E.; Craig, S.; Beaton, C. D.; Bennet, R. J.; Jagadish, V. C.; Randall, P. J. *Plant Phys.* **1993**, *103*, 685-693.
10. Shen, Z.; Wang, J.; Guan, H. *J. Plant Nut.* **1993**, *16*, 2135-2148.
11. Jang, Y. K.; Nam, U. C.; Kwon, H. L.; Hwang, I. H.; Kim, C. *Dyes Pigm.* **2013**, *99*, 6-13.
12. Maity, S. B.; Bharadwaj, P. K. *Inorg. Chem.* **2013**, *52*, 1161-1163.
13. Park, H. M.; Oh, B. N.; Kim, J. H.; Qiong, W.; Hwang, I. H.; Jung, K.-D.; Kim, C.; Kim, J. *Tetrahedron Lett.* **2011**, *52*, 5581-5584.
14. Cheng, X.-Y.; Wang, M.-F.; Yang, Z.-Y.; Li, Y.; Li, T.-R.; Liu, C.-J.; Zhou, Q.-X. *J. Coord. Chem.* **2013**, *66*, 1847-1853.
15. Dhara, A.; Jana, A.; Konar, S.; Ghatak, S. K.; Ray, S.; Das, K.; Bandyopadhyay, A.; Guchhait, N.; Kar, S. K. *Tetrahedron Lett.* **2013**, *54*, 3630-3634.
16. Vallejos, S.; Muñoz, A.; Ibeas, S.; Serna, F.; García, F. C.; García, J. M. *J. Hazard. Mater.* **2014**, *276*, 52-57.
17. Basa, P. N.; Bhowmick, A.; Horn, L. M.; Sykes, A. G. *Org. Lett.* **2012**, *14*, 2698-2701.
18. Kadarkaraisamy, M.; Caple, G.; Gorden, A.R.; Squire, M.A.; Sykes, A.G. *Inorg. Chem*. **2008**, *47*, 11644-11655.
19. Alaparthi, M.; Sykes, A. G. *J. Incl. Phenom. Macrocycl. Chem.* **2015**, *83*, 149-157.
20. Meyer, K. *Annalen* **1911**, *379*, 37-73.
21. Opitz, A.; Wei-Opitz, D.; Gebhardt, P.; Koch, R. *J. Org. Chem.* **2006**, *71*, 1074-79.
22. Lovell, J.M.; Joule, J.A. *Synth. Commun*. **1997**, *27*, 1209-1215.
23. Delgado, M.; Gustowski, D. A.; Yoo, H. K.; Gatto, V. J.; Gokel, G. W.; Echegoyen, L. *J. Am. Chem. Soc.* **1988**, *110*, 119-124.
24. Park, D. H., Kang, S. O., Lee, H. J., Nam, K. C., Jeon, S. *Bull. Korean Chem. Soc.* **2001**, *22*(6), 638-640.
25. Lee, M. H., Lee, S. J., Jung, J. H., Lim, H., Kim, J. S. *Tetrahedron* **2007**, *63*(48), 12087-12092.
26. Sheldrick, G. M.., SHELX97 - Programs for Crystal Structure Analysis (Release 97-2) 1998.
27. Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837-838.
28. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.***1999**, *32*, 115-119.
29. Kadarkaraisamy, M.; Caple, G.; Gorden, A.R.; Squire, M.A.; Sykes, A.G. *Inorg. Chem*. **2008**, *47*, 11644-11655.



Selective chemodosimetric detection of Al(III) via hydrolysis of secondary alcohols involving a unique keto-enol tautomerization reaction.