Tetrahedron Letters 49 (2008) 4697–4700

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Salicylaldehyde fluorescein hydrazone: a colorimetric logic chemosensor for pH and Cu(II)

Xiaotong Chen, Zifan Li, Yu Xiang, Aijun Tong *

Department of Chemistry, Tsinghua University, Beijing 100084, China

ARTICLE INFO

Article history:
Received 25 February 2008
Revised 10 May 2008
Accepted 30 May 2008
Available online 4 June 2008

Keywords:
Colorimetric
Logic chemosensor
pH
Cu(II)

ABSTRACT

In this work, salicylaldehyde fluorescein hydrazone (**1**) was synthesized and characterized. Exhibiting reversible color changes responding to different pH in the presence of Cu(II) in buffered media, **1** could be applied as a colorimetric chemosensor for the detection of pH and Cu(II) bi-functionally. It presented a tunable system integrated with a Cu(II)-driven YES logic gate as well as an INHIBIT logic gate, with pH and Cu(II) as its chemical inputs based on encoding binary digits of logical conventions.

Electronic device miniaturization technology maintains its urgent requirement for rapid progress in information processing, communicating, and storing in digital binary form.[1] Especially for chemists, one relevant research field is focused on molecular-leveled logic system modulation.[2–4] Logic systems consist of input elements, output states, and the truth table illustrating the relationship between them.[5–9] Since de Silva and his co-workers reported an AND logic gate, investigations about logic systems acting as logic binary operations have flourished extensively.[10–18] Notably, to meet the needs of high density information processing technology, multifunction logic systems which integrate several functions within a single molecule have been prestigious in both basic research and applications[19–25] because monomolecular logic circuits could eliminate the possibility of mutual interferences rooting from molecular interactions.[26–28] On the other hand, studies on colorimetric logic gate have drawn a great deal of attention.[29,30] However, many of the reported colorimetric logic gates worked only in organic solvents.[31,32] There are few reports which are applicable in aqueous[33] or other environmental friendly media such as ethanol although these systems would be more attractive.

In our previous report, salicylaldehyde rhodamine hydrazone was synthesized and displayed selective Cu(II)-amplified absorbance and fluorescence emission in neutral buffer media.[34] Altering the rhodamine backbone into fluorescein, salicylaldehyde fluorescein hydrazone (**1**) (Fig. 1) was synthesized, of which the hydroxyl group was sensitive to pH and the salicylaldehyde hydrazone moiety could complex with Cu(II), accompanied by ring opening of the spirolactam of fluorescein backbone. In 50% water/ethanol buffer media, **1** exhibited absorbance enhancement with maximal absorption peaks at two separate wavelengths in the presence of Cu(II) under different pH conditions. Consequently, the addition of proton and Cu(II) could be introduced as chemical inputs of this system, with obvious absorption spectral changes at two wavelengths as output signals. Moreover, this logic system can be applied as a 'naked-eye' logic chemosensor for pH and Cu(II) undergoing reversible protonation and complexation reactions.

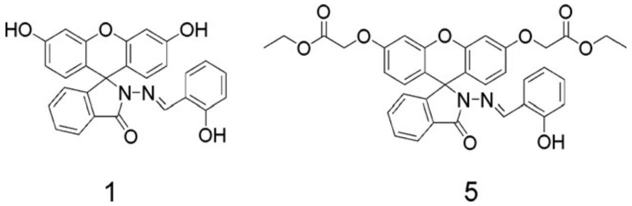


Figure 1. The chemical structures of **1** and control compound **5**.

The absorption spectra of **1** and **5** in the absence and presence of Cu(II) at different pH are shown in Figure 2. When dissolved in 50% water/ethanol (10 mM Tris–HCl) solution, **1** was colorless and exhibited no absorption band above 350 nm regardless of pH (spectrum a in Fig. 2A). Upon the addition of Cu(II), the spirolactam moiety of **1** was opened by the formation of **1**–Cu(II) complex and new absorption peaks appeared at around 420 nm and 502 nm (spectra c and d in Fig. 2A) according to different pH values. In the range of pH 2.5–5.0, the absorption band appeared at 420 nm for **1**–Cu(II) complex, which increased as the pH was increased

---

* Corresponding author. Tel./fax: +86 10 62787682.
E-mail address: tongaj@mail.tsinghua.edu.cn (A. Tong).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.137

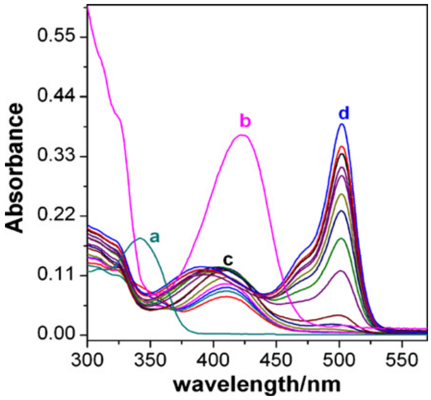


Figure 2A. Absorption spectra in 50% water/ethanol (10 mM Tris–HCl) (a) 20 μM **1**; (b) 20 μM **5** and 100 μM Cu (II); (c) 20 μM **1** and 100 μM Cu (II) at pH 2.5–5.0 from bottom to top; and (d) 20 μM **1** and 100 μM Cu (II) at pH 2.5–8.0 from bottom to top.

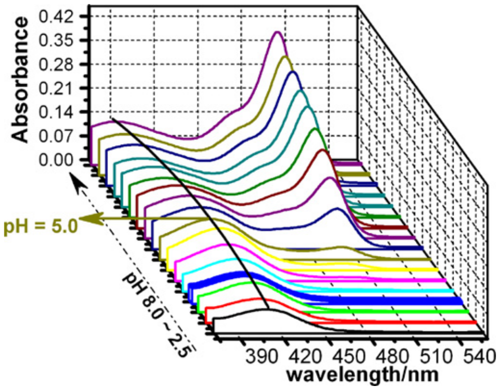


Figure 2B. Detailed spectra of spectra c and d in Figure 2A.

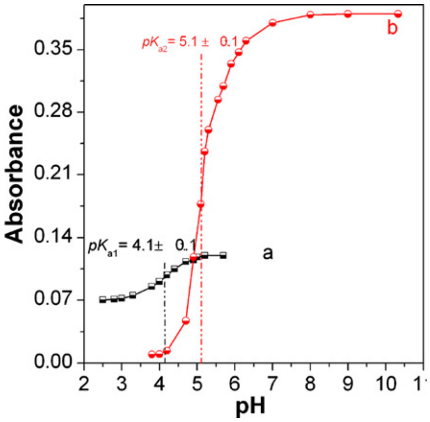


Figure 4. Absorption titration against pH at 420 nm (a) and 502 nm (b) in 50% water/ethanol (10 mM Tris–HCl).

(spectrum c in Fig. 2A, more details are shown in Fig. 2B). In the pH range of 5.0–8.0, another absorption band at 502 nm emerged for **1**–Cu(II) complex and the peak increased with increase of the pH value (spectrum d in Fig. 2A, more details are shown in Fig. 2B). The solution turned from yellow to orange as the peak at 420 nm shifted to 502 nm. All the above absorption spectra responses were reversible, which was confirmed by the reversible titration using EDTA/Cu(II) and NaOH/HCl (Fig. 3). To be brief, pH 5.0 and 8.0 were selected to be two typical circumstances in the following discussion.

Besides, the absorption at 502 nm ascribed to **1**–Cu(II) complex for pH > 5.0 was much stronger than that at 420 nm for pH ⩽ 5.0. The absorbance at 502 nm of pH 8.0 was nearly 6 times larger than that at 420 nm of pH 5.0, which was probably due to (1) the difference in molecular absorptivity of protonized and deprotonized states of ring-opened **1**–Cu(II) complex; and (2) the difference in binding affinity of protonized and deprotonized **1** to Cu(II). The two acid dissociation constants pK_a were thus obtained from the absorption titration against pH as 4.1 ± 0.1 and 5.1 ± 0.1, respectively (Fig. 4). The corresponding proton dissociation process is shown in Scheme 1.

To get an insight into the spectroscopic properties of **1** versus pH, a reference compound **5** (Fig. 1) was synthesized. With substitution of the two protons on hydroxyl groups of **1**, absorption spectra of **5**-Cu(II) complex only presented an absorption peak at 420 nm (spectrum b in Fig. 2A) independent of pH, which indicated the key role of two hydroxyl groups for **1** responding to pH.

To investigate the binding mode of **1** to Cu(II), Job's method, absorption titration, and ESI-MS studies were carried out. A 1:1 stoichiometry was assumed by Job's plot[35] under both pH 5.0 and 8.0 (Fig. 5). The nonlinear fitting of two titration curves at these two pH conditions yielded association constants K_a of 8.6 × 10^3 and 7.8 × 10^4, respectively (Fig. 6).

The binding stoichiometry was also confirmed by ESI-MS. As shown in S-Figure 3, a unique peak at m/z = 451.2 (calcd = 451.1)

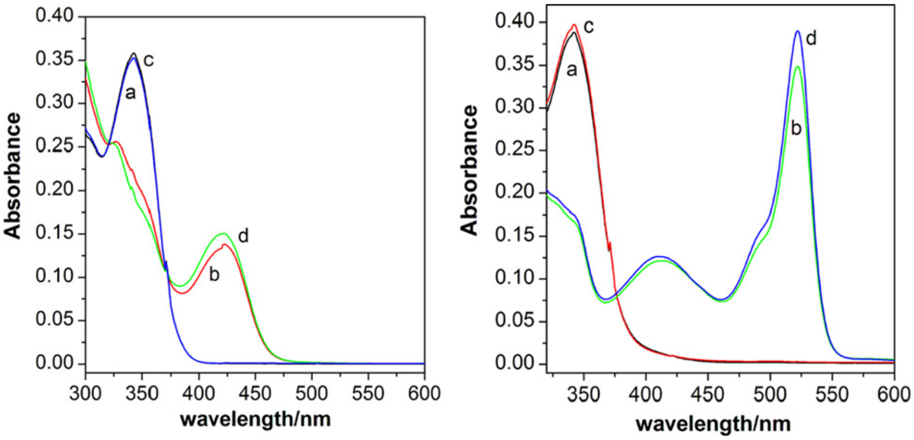
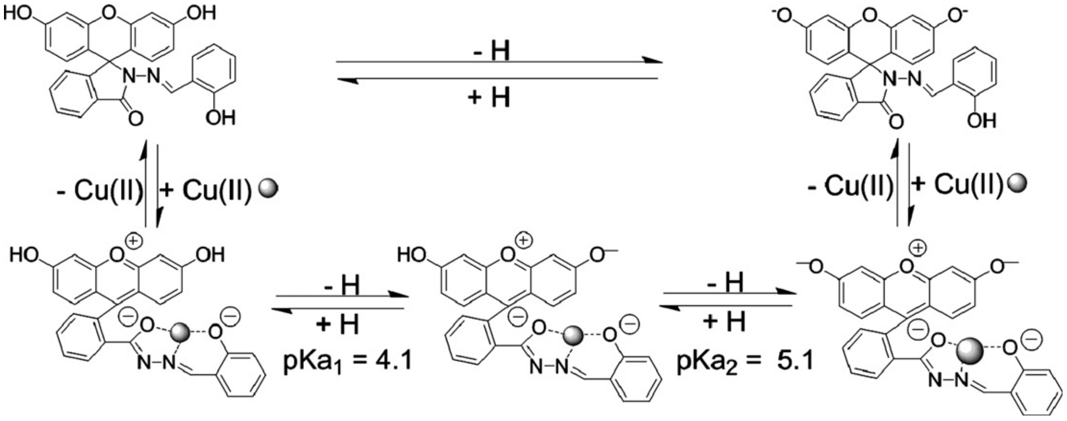


Figure 3. Reversible titration response of **1** to Cu(II) in Tris–HCl (10 mM) buffer containing 50% (v/v) water/ethanol. Left: pH 5.0; right: pH 8.0. (a) 40 μM **1**; (b) 40 μM **1** with 20 μM Cu(II); (c) 40 μM **1** with 20 μM Cu(II) and then addition of 20 μM EDTA (sodium salt); (d) 40 μM **1** with 20 μM Cu(II), 20 μM EDTA and then addition of 22 μM Cu(II).



Scheme 1. Proton dissociation of **1**–Cu(II).

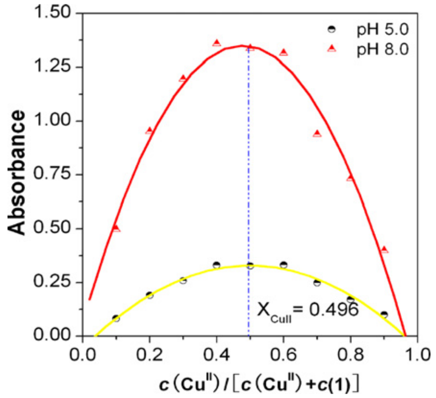


Figure 5. Absorbance at 410 nm and 502 nm of **1** and Cu(II) with a total concentration of 100 μM in Tris–HCl buffer (10 mM, pH 5.0 and 8.0, respectively) containing 50% (v/v) water/ethanol, both indicating a 1:1 metal–ligand ratio.

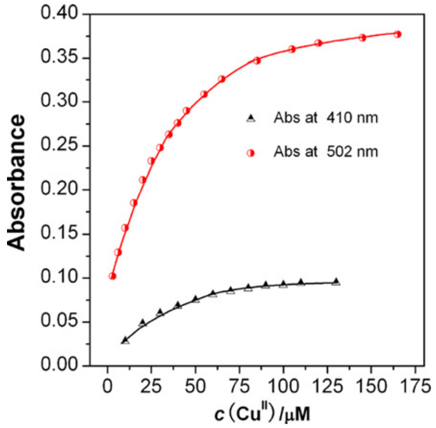


Figure 6. Absorbance at 410 nm (triangle) and 502 nm (dot) of **1** (10 μM) in Tris–HCl (10 mM, pH 5.0 and 8.0, respectively) buffers containing 50% (v/v) water/ethanol upon the addition of different amounts of Cu(II). The association constants (K_a) of **1**–Cu(II) were calculated to be 8.6×10^3 and 7.8×10^4, respectively.

was observed for **1** in the absence of Cu(II), while **1**–Cu(II) complex exhibited a peak of $[\mathbf{1} + \mathrm{Cu{-}H} + H_2O]^+$ at $m/z = 530.1$, (calcd = 530.0). Moreover, the isotopic patterns of the peak ascribed to **1**–Cu(II) complex corresponded well with the calculated data. ^{1}H NMR spectra of **1**–Cu(II) and **5**-Cu(II) compared to that of **1** and **5** showed broadening of the phenol proton on salicylaldehyde moiety and the vinyl proton near the imino group of hydrazone moiety, indicating the coordination of Cu(II) to **1** and **5**.

The selectivity for Cu(II) against other metal ions is shown in Figure 7. Under pH 5.0 and pH 8.0, transition metal ions such as

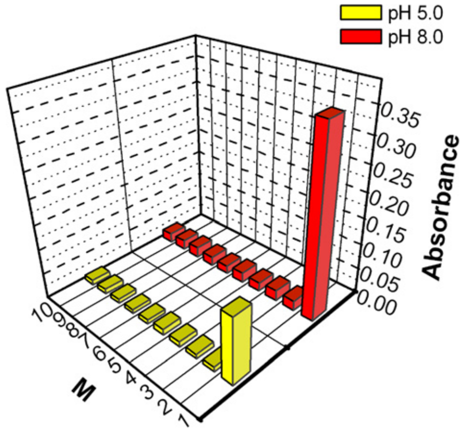


Figure 7. Absorbance at 410 nm, pH 5.0 (yellow column) and at 502 nm, pH 8.0 (orange column) of **1** (10 μM) upon the addition of 10 μM different metal ions in 10 mM Tris–HCl buffer containing 50% (v/v) water/ethanol. 1: Cu(II), 2: Cr(III), 3: Pb(II), 4:Cd(II), 5: Zn(II), 6: Hg(II), 7: Co(II), 8: Mn(II), 9: alkali/alkaline earth metal ions, 10: Blank.

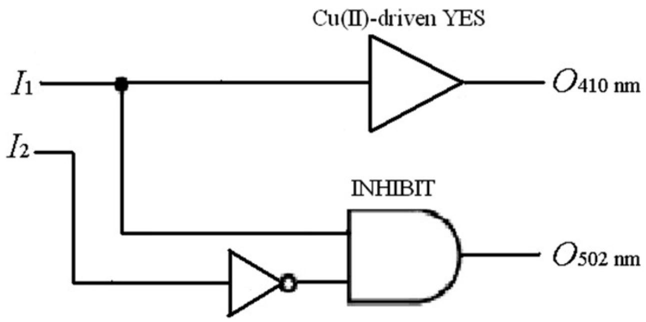


Figure 8. Illustration of the principles of operation of a tunable Cu-driven YES ($O_{410\ nm}$) and INHIBIT ($O_{502\ nm}$) integrated logic gate. I_1 and I_2 are input elements of addition of Cu(II) and pH, respectively. I_1: state '0': [Cu(II)] < 1 μM; state '1': [Cu(II)] ⩾ 1 μM; I_2: state '0': pH > 5.0; state '1', pH < 5.0; $O_{410\ nm}$ is the output with 'on' state of $Abs_{410\ nm} > 0.05$ and $O_{502\ nm}$ with $Abs_{502\ nm} > 0.1$, respectively.

Table 1
Truth table for **1**-Cu integrated logic system

Input$_1$ Cu^{2+}	Input$_2$ H$^+$	Output$_{410\ \mathrm{nm}}$	Output$_{502\ \mathrm{nm}}$
0	0	0	0
0	1	0	0
1	0	1	1
1	1	1	0

Cr(III), Pb(II), Cd(II), Zn(II), Hg(II), Co(II), Mn(II), and alkali/alkaline earth metal ions displayed almost no response compared to equivalent Cu(II), suggesting the high selectivity of **1** to Cu (II).

Based on the absorption response discussed above, **1** was capable of acting as a colorimetric logic gate as summarized in Figure 8 and Table 1. Input$_1$ and Input$_2$ represented the presence of Cu(II) and H$^+$, respectively. Without the addition of Cu(II) (I_1 state '0'), the solution was colorless and there was no absorption at the wavelength range of 350–600 nm; only if the concentration of Cu(II) was sufficiently high($\geqslant$1 μM) (I_1 state '1'), the system would response to the environmental pH colorimetrically. In the presence of Cu (II), when pH $\leqslant$ 5.0 (I_2 state '1'), the system generated a Cu(II)-driven YES logic gate giving the output signal $O_{410\ \mathrm{nm}}$ with the 'on' state of Abs$_{410\ \mathrm{nm}}$ > 0.05; when pH was increased further to > 5.0(I_2 state '0'), the system turned to an INHIBIT logic gate giving the output signal $O_{502\ \mathrm{nm}}$ with the 'on' state of Abs$_{502\ \mathrm{nm}}$ > 0.1. Since our eyes response more sensitively to orange than to yellow color, this system would apparently display orange color when $O_{410\ \mathrm{nm}}$ and $O_{502\ \mathrm{nm}}$ were at 'on' state simultaneously.

In conclusion, we have synthesized a molecular probe, salicylaldehyde fluorescein hydrazone, which could serve as a bi-functional colorimetric logic gate integrating a Cu(II)-driven YES and an INHIBIT logic gate on basis of its own chemical and optical properties responding to Cu(II) and pH. This contribution suggested its potential application in monomolecular logic system, presenting a possible alternative in filing, carrying, processing, and expressing information electronically.

Acknowledgment

The authors thank the National Natural Science Foundation of China for financial support (NSFC, No. 20675043).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.137.

References and notes

1. Kalinnikov, V. A. *Instrum. Exp. Technol.* **2006**, *49*, 743.
2. Zhou, Y. C.; Wu, H.; Qu, L.; Zhang, D. Q.; Zhu, D. B. *J. Phys. Chem. B* **2006**, *110*, 15676.
3. Raymo, F. M. *Adv. Mater.* **2002**, *14*, 401.
4. Uchiyama, S. G.; McClean, D.; Iwai, K.; de Silva, A. P. *J. Am. Chem. Soc.* **2005**, *127*, 8920.
5. de Silva, A. P.; McClenaghan, N. D. *Chem.-Eur. J.* **2004**, *10*, 574.
6. de Silva, A. P.; Fox, D. B.; Huxley, A. J. M.; Moody, T. S. *Coordin. Chem. Rev.* **2000**, *205*, 41.
7. de Silva, A. P.; Leydet, Y.; Lincheneau, C.; McClenaghan, N. D. *J. Phys.-Condes. Mat.* **2006**, *18*, S1847.
8. de Silva, A. P.; Uchiyama, S.; Vance, T. P.; Wannalerse, B. *Coordin. Chem. Rev.* **2007**, *251*, 1623.
9. de Silva, A. P.; Uchiyama, S. *Nat. Nanotechnol.* **2007**, *2*, 399.
10. Xu, H.; Xu, X. H.; Dabestani, R.; Brown, G. M.; Fan, L.; Patton, S.; Ji, H. F. *J. Chem. Soc., Perkin Trans. 2* **2002**, 636.
11. de Sousa, M.; de Castro, B.; Abad, S.; Mirandab, M. A.; Pischel, U. *Chem. Commun.* **2006**, 2051.
12. Fang, C. J.; Zhu, Z.; Sun, W.; Xu, C. H.; Yan, C. H. *New J. Chem.* **2007**, *31*, 580.
13. Nath, S.; Maitra, U. *Org. Lett.* **2006**, *8*, 3239.
14. Bergamini, G.; Saudan, C.; Ceroni, P.; Maestri, M.; Balzani, V.; Gorka, M.; Lee, S. K.; Heyst, J. V.; Vogtle, F. *J. Am. Chem. Soc.* **2004**, *126*, 16466.
15. Zhou, Y.; Zhang, D.; Zhang, Y.; Tang, Y.; Zhu, D. *J. Org. Chem.* **2005**, *70*, 6164.
16. de Silva, A. P.; McClenaghan, N. D. *Chem.-Eur. J.* **2002**, *8*, 4935.
17. Zhan, W.; Crooks, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 9934.
18. Singh, P.; Kumar, S. *New J. Chem.* **2006**, *30*, 1553.
19. Guo, Z. Q.; Zhu, W. H.; Shen, L. J.; Tian, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5549.
20. Guo, X. F.; Zhang, D. Q.; Zhu, D. B. *Adv. Mater.* **2004**, *16*, 125.
21. Guo, X. F.; Zhang, D. Q.; Tao, H. R.; Zhu, D. B. *Org. Lett.* **2004**, *6*, 2491.
22. Callan, J. F.; de Silva, A. P.; McClenaghan, N. D. *Chem. Commun.* **2004**, 2048.
23. Shiraishi, Y.; Tokitoh, Y.; Hirai, T. *Chem. Commun.* **2005**, 5316.
24. Tian, H.; Wang, S. *Chem. Commun.* **2007**, 781.
25. Montenegro, J. M.; Perez-Inestrosa, E.; Collado, D.; Vida, Y.; Suau, R. *Org. Lett.* **2004**, *6*, 2353.
26. Guo, X.; Zhang, D.; Zhang, G.; Zhu, D. *J. Phys. Chem. B* **2004**, *108*, 11942.
27. Roque, A.; Pina, F.; Alves, S.; Ballardini, R.; Maestri, M.; Balzani, V. *J. Mater. Chem.* **1999**, *9*, 2265.
28. Sortino, S.; Petralia, S.; Bella, S. D. *J. Am. Chem. Soc.* **2003**, *125*, 5610.
29. Brown, G. J.; de Silva, A. P.; Pagliari, S. *Chem. Commun.* **2002**, 2461.
30. Wang, Z. X.; Zheng, G. R.; Lu, P. *Org. Lett.* **2005**, *7*, 3669.
31. Lee, J. W.; Park, S. Y.; Cho, B. K.; Kim, J. S. *Tetrahedron Lett.* **2007**, *48*, 2541.
32. Liu, J. W.; Lu, Y. *Adv. Mater.* **2006**, *18*, 1667.
33. Qu, D. H.; Ji, F. Y.; Wang, Q. C.; Tian, H. *Adv. Mater.* **2006**, *18*, 2035.
34. Xiang, Y.; Tong, A. J.; Jin, P. Y.; Ju, Y. *Org. Lett.* **2006**, *8*, 2863.
35. Vosburgh, W. C.; Cooper, G. R. *J. Am. Chem. Soc.* **1941**, *63*, 437.