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SYNTHESIS OF A NOVEL HEXADENTATE CHELATING AGENT BASED ON 8-HYDROXYQUINOLINE

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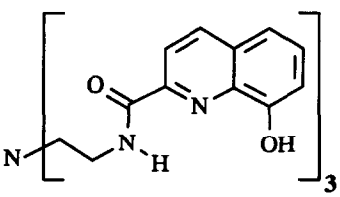
Abstract: A new hexadentate chelator was synthesized by the functionalization of 8-hydroxyquinoline to its 2-carboxy-N-hydroxysuccinimidyl ester and subsequent condensation with tris(2-aminoethyl)amine to give tris-N-(2-aminoethyl-[8-hydroxyquinoline-2-carboxamido])amine. This molecule is a siderophore analog with a non-naturally occurring binding unit comprising a combination of both oxygen and nitrogen donor atoms.

A continuing objective in chelation chemistry has been the development of biomimetic chelating agents which mirror the naturally occurring iron binding compounds, termed siderophores, that are produced by many microorganisms.[1-3] Siderophores such as enterobactin and desferrioxamine bind iron via three identical bidentate units suspended from a framework possessing appropriate sterochemistry for chelation of a single metal atom by all three units. The bidentate units employed in nature are either catacholate or hydroxamate moieties and siderophore analogs reported to date have been based on linking together three or more such moieties through a synthetic framework.[4-12] Inasmuch as the siderophores and their biomimetic analogs bind to metals through six oxygen atoms, they must be classified as hard ligands. We set out to synthesize hexadentate siderophore analogs which contain a mixture of both hard and soft donor atoms and this report describes the first such compound, obtained by linking together three 8-hydroxyquinoline units to provide a chelating agent that presents three hard oxygen donor sites and three soft nitrogen donor sites.

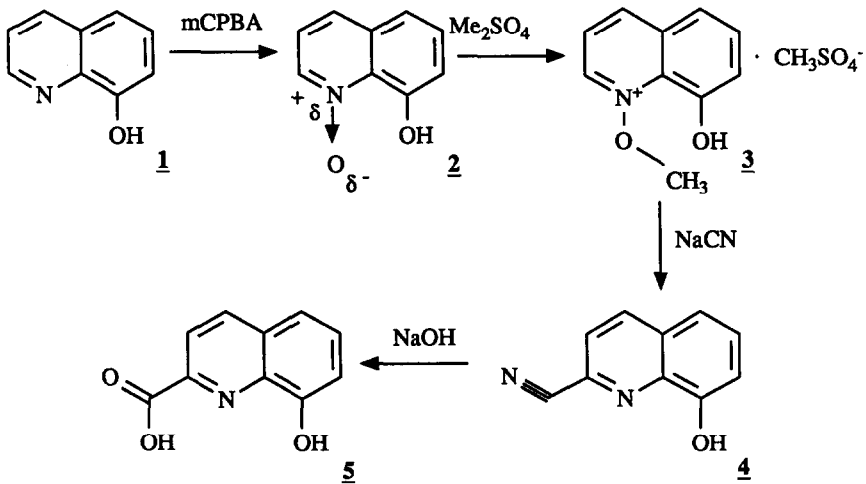
This agent, tris-N-(2-aminoethyl-(8-hydroxyquinoline-2-carboxamido)amine, was obtained by functionalization of 8-hydroxyquinoline **1** to 2-carboxy-8-hydroxyquinoline **5**, Scheme **I**, followed by condensation of the corresponding N-hydroxysuccinimidyl ester with tris(2-aminoethyl)amine, Scheme **II**.



Tris-N-(2-aminoethyl-[8-hydroxyquinoline-2-carboxamido])amine

The synthetic route employed in Scheme **I** is essentially that of Krasavin *et al.*[15], modified as described below. In Scheme **I**, **1** was oxidized to the corresponding N-oxide **2** cleanly with 3-chloroperoxybenzoic acid in $CHCl_3$ at 0° C. The precipitated 3- chlorobenzoic acid was removed by filtration, the filtrate was evaporated to dryness, triturated with 2% NH_4OH and recrystallized from 10:1 hexane:acetone followed by sublimation to give **2** as bright yellow needles, mp 138-39 °C, (77% yield).[13,15] **2** was alkylated with dimethyl sulfate in CCl_4, during a 10 hour reflux under Ar. As the reaction progressed, **3** separated from solution and formed a film on top of the CCl_4. The CCl_4 phase was decanted off, leaving the film adhering to the reaction flask. This material was washed with diethyl ether and vacuum dried for three days to yield **3** as a dark orange semicrystalline solid. This material is extremely hygroscopic, and so additional purification was not attempted beyond vacuum drying, mp 143-45 °C, (95% yield).[13,15] Treatment of **3** with aqueous NaCN (3:1 molar ratio NaCN:**3**) at 0° C for 3 hours yielded **4**. The pH of the solution was adjusted to 4.5 with HOAc and the resultant precipitate was isolated on a frit. The crude product was washed well with H_2O and dried *in vacuo*, and the material was recrystallized from 10:1 hexane:acetone followed by sublimation to give **4** as pale yellow crystals, mp 134.5-35 °C, (72% yield).[13] Compound **4** was refluxed in 3N NaOH for 4 hours, until base was no longer detectable at the top of the condenser by pH paper. The pH was then reduced to pH 4.5 with aqueous 5N HCl and the reaction mixture was extracted with ethyl acetate. The organic phase was separated and evaporated to dryness to give crude **5**, which was dissolved in CH_3OH and applied to a Sephadex LH-20 column (100:1, bed weight:sample weight), and eluted with CH_3OH. Evaporation of the eluate to dryness and recrystallization of the resulting residue from water gave pure **5** in the form of bright yellow needles, mp 216-217 °C, (70% yield).[14]

Scheme I

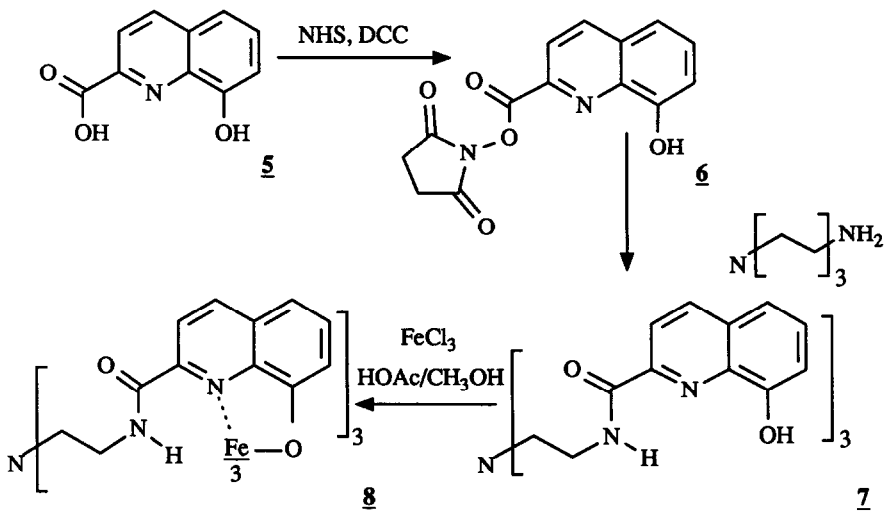


In Scheme **II**, esterification of **5** with 1,3-dicyclohexylcarbodiimide and N-hydroxysuccinimide in THF at ambient temperature for 24 hours gave the N- hydroxysuccinimidyl ester **6** as a light yellow solid (95% yield). Without further purification, the crude **6** was condensed with tris(2-aminoethyl)amine in THF at ambient temperature for 24 hours. After solvent removal, the resulting solid was dissolved in ethyl acetate, washed with water and concentrated to dryness *in vacuo*. The residue was dissolved in CH_3OH and applied to a Sephadex

LH- 20 column (500 : 1, bed weight : sample weight). Elution of the column with CH_3OH afforded the desired tris-N-(2-aminoethyl-[8-hydroxyquinoline-2-carboxamido])amine, 7 as fibrous white needles which crystallized spontaneously from the eluate and were filtered off and dried, mp 222-23 °C, (65% yield).

Preliminary metal binding studies have shown that 7 is capable of forming a 1:1 complex with iron (III). The complex was prepared by dissolving 7 (25.0 mg, .038 mmole) in a minimum volume of CH_3OH to form a saturated solution. Anhydrous $FeCl_3$ (6.5 mg, .040 mmole) was dissolved in 6.5 ml of glacial acetic acid and the pH was adjusted to 2.5 with 6N HCl. These two solutions were then mixed and stirred for six hours at room temperature followed by solvent removal to yield a dark green/yellow solid. The mass spectrum of this crude material showed it to contain the complex, 8, which appeared as a parent molecular ion at *m/e* 713 (positive fast atom bombardment, nitrobenzyl alcohol matrix, 5 KeV Xe, $C_{36}H_{30}N_7O_6Fe$ = 712.52 g/mole).

SCHEME II



5 6 7 8

References and Notes

1. Tait, G. H. *Biochem. J.* **1975**, *146*, 191.
2. Peterson, T.; Neilands, J. B. *Tetrahedron Lett.* **1979**, *50*, 4805.
3. Bergeron, R. J.; Garlich, J. R.; McManis, J. S. *Tetrahedron* **1985**, *41*, 507.
4. Bergeron, R. J.; Kline, S. J.; Stolowich, N. J.; McGovern, K. A.; Burton, P.S. *J. Org. Chem.* **1981**, *46*, 4524.
5. Bergeron, R. J.; Kline, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 4489.
6. Wong, G. B.; Kappel, M. J.; Raymond, K. N.; Matzanke, B.; Winkelmann, G. *J. Am. Chem. Soc.* **1983**, *105*, 810.
7. Bergeron, R. J.; Stolowich, N. J.; Kline, S. J. *J. Org. Chem.* **1983**, *48*, 3432.
8. Bergeron, R. J.; Garlich, J. R.; Stolowich N. J. *J. Org. Chem.* **1984**, *49*, 2997.
9. Bergeron, R. J.; Kline, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 3089.
10. Barclay, S. J.; Huynh, B. H.; Raymond, K. N. *Inorg. Chem.* **1984**, *23*, 2011.

11. Barclay, S. J.; Riley, P. E.; Raymond, K. N. *Inorg. Chem.* **1984,** *23*, 2005.
12. Rodgers, S. J., Lee, C. W.; Ng, C. Y.; Raymond, K. N. *Inorg. Chem.* **1987**, *26*, 1622.
13. Clark, C. R.; Hay, R. W. *J. C. S. Dalton*, **1974**, 2148-2152.
14. Hay, R. W.; Clark, C. R. *J. C. S. Dalton*, **1976**, 1866-1874.
15. Krasavin, I. A.; Dziomko, V. M.; Radin, Y. P. *Metody Policheniya Khim, Reactivov i Preparatov*, **1965**, *13*, 68, 94.
16. NMR data for compounds. 2, ^{1}H NMR ($CDCl_3$, TMS internal standard, 300 MHz) δ 7.04 (double doublet, J = 8.08 Hz, J = 1.10 Hz, 1H), 7.22 (d, J = 8.82 Hz, 1H), 7.23 (apparent triplet, J = 8.45, J = 8.08, 1H), 7.29 (s, phenol proton, <1H), 7.47 (t, J = 8.09 Hz, 1H), 7.78 (double doublet, J = .91 Hz, J = 8.64 Hz, 1H), 8.23 (double doublet, J = 1.11 Hz, J = 6.25 Hz, 1H). ^{13}C NMR ($CDCl_3$, TMS internal standard, 75MHz) δ 114.67, 116.65, 120.26, 129.54, 130.40, 132.08, 134.34, 153.79. 3, ^{1}H NMR (d_6-DMSO, TMS internal standard, 300 MHz)δ 3.45 (s, 3H), 4.46 (s, 3H), 7.67 (d, J = 9 Hz, 1H), 7.89 (t, J = 9 Hz, 1H), 7.94 (d, J = 6 Hz, 1H), 8.14 (t, J = 6 Hz, 1H), 9.24 (d, J = 9 Hz, 1H), 9.76 (d, J = 6 Hz, 1H). 4, ^{1}H NMR ($CDCl_3$, TMS internal standard), δ 7.30 (double doublet, J = 1.1 Hz, J = 7.72 Hz, 1H), 7.42 (double doublet, J = 1.1 Hz, J = 8.45 Hz), 7.64 (apparent triplet, J = 8.1 Hz, J = 7.7 Hz, 1H), 7.73 (doublet, J = 8.5 Hz, 1H), 7.89 (singlet, 1H), 8.32 (doublet, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, TMS internal standard), δ 112.07, 117.29, 118.01, 123.94, 129.12, 130.90, 131.25, 137.63, 138.44, 152.36. 5 ^{1}H NMR (d_6-DMSO, TMS internal standard, 300 MHz), δ 7.25 (d, J = 9.0 Hz, 1H), 7.54 (d, J = 7.50 Hz, 1H), 7.65 (t, J = 7.4 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H), 8.58 (d, J = 9.0 Hz, 1H), 10.23 (broad s, 1H). ^{13}C NMR (d_6-DMSO, TMS internal standard, 75MHz) δ 111.98, 117.56, 119.92, 129.89, 130.42, 136.43, 138.29, 144.23, 153.80, 165.10. 7 ^{1}H NMR (d_6-DMSO, TMS internal standard, 300 MHz) δ 2.96 (t, J = 6.62 Hz, 6H), 3.62 (q, J = 6.98 Hz, 6H), 7.19 (d, J = 7.72 Hz, 3H), 7.46 (d, J = 8.09 Hz, 3H), 7.57 (t, J = 7.72 Hz, 3H), 8.15 (d, J = 8.82, 3H), 8.45 (d, J = 8.45 Hz, 3H), 9.68 (t, J = 5.88 Hz, 3H). ^{13}C NMR (d_6-DMSO, TMS internal standard, 75 MHz) δ 37.49, 53.69, 111.37, 117.40, 118.65, 129.16, 129.30, 136.31, 137.46, 147.42, 153.45, 163.74.
17. Selected Mass Spectra. 2, $C_9H_7NO_2$ = 161.16 g/mol, direct chemical ionizaton (NH_3) *m/e* 161 (M^+, base peak), 116, 89, 63. 3, $C_{10}H_{10}O_2N^+SO_4CH_3^-$ = 287.28 g / mol, positive fast atom bombardment, *m/e* 176 (M^+, base peak parent cation), 176, 190, 226, 256, 270, 289. 4, $C_{10}H_6NO_2$ = 170.17 g/mol, direct chemical ionization (NH_3); *m/e* 171 ($(M+H)^+$, base peak), 162, 146, 188 (M^++ NH_3). 5, $C_{10}H_7N0_3$ = 189.17 g / mol, positive fast atom bombardment; *m/e* 190 ($(M+H)^+$, base peak), 172, 162, 143, 116, 104, 89. 7, $C_{36}H_{33}N_7O_6$ = 659.17 g / mol, direct chemical ionization; *m/e* 660 ($(M+H)^+$ base peak) 458, 244, 215, 171, 144, 93.

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