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Structure of a Terbium(III)–Quinizarine Complex: The First Crystallographic Model for Metalloanthracyclines

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The crystal structure of a complex of terbium(III) with quinizarine 2-sulfonate has been solved by single-crystal X-ray diffraction methods. The metal cation is coordinated by two adjacent phenolate and quinone oxygens of the anthraquinone moiety of a quinizarine sulfonate anion and by six water molecules. To our knowledge, this is the first structure of a metal complex of the 1,4-dihydroxy anthraquinone ligand. On the basis of strict similarities in the spectroscopic features of the terbium adducts with either doxorubicin or quinizarine 2-sulfonate, the present structure is proposed as a model for the metal complexes of anthracyclines.

The anthracycline antibiotics doxorubicin and daunorubicin, the most frequently prescribed anticancer drugs, are used in the treatment of various malignancies including leukemia, non-Hodgkin's lymphoma, and breast cancer.[1-4] Interactions of anthracyclines with metal ions have been the subject of several studies for their important biological and pharmacological implications.[5-19]

Specifically, anthracycline complexes with iron(III),[5-11] copper(II),[12] palladium(II),[13] platinum(II),[14] aluminum(III),[15] tin(IV),[16] and various lanthanides(III)[17-19] have been extensively characterized by various spectroscopic methods and by potentiometric measurements. Particular attention has been devoted to the complexes that doxorubicin forms with iron(III) since these species are believed to be responsible for free radical production in vivo and for the cardiotoxic effects.[20-22]

It is postulated that anthracyclines form relatively tight complexes with tripositive "hard" cations, in which the metal ion is coordinated to the adjacent phenolate and quinone oxygens of the anthraquinone moiety.[23] In contrast, "soft" cations such as platinum(II) and palladium(II) form weaker complexes by coordinating to the nitrogen atom of the aminosugar.

Structural information on metal−anthracycline complexes is still lacking due to the inherent difficulties in obtaining suitable crystals for X-ray diffraction studies. Only the crystal structures of a few free anthracyclines are available.[24-26]

To overcome these difficulties and obtain some reliable structural information on this important system, simpler ligands have been selected that might reproduce the main features of the metal−anthracycline interactions. In particular, quinizarine and its 2-sulfonic acid derivative, both bearing

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(1) Arcamone, F.; Penco, S. *Anthracycline and Anthracenedione-based Anticancer Agents*; Elsevier: Amsterdam, 1988.
(2) Young, R. C.; Ozols, R. F.; Myers, C. E. *N. Engl. J. Med.* **1981**, *305*, 139.
(3) Keizer, H. G.; Pinedo, H. M.; Schuurhuis, G. J.; Joenje, H. *Pharmacol. Ther*. **1990**, *47*, 219.
(4) Olson, R. D.; Mushlin, P. S. *FASEB J.* **1990**, *4*, 3076.
(5) Gosalvez, M.; Blanco, M. F.; Vivero, C.; Valles, F. *Eur. J. Cancer* **1978**, *14*, 1185.
(6) Fiallo, M. M.; Drechsel, H.; Garnier-Suillerot, A.; Matzanke, B. F.; Kozlowski, H. *J. Med. Chem.* **1999**, *42*, 2844.
(7) Fiallo, M. M.; Garnier-Suillerot, A.; Matzanke, B. F.; Kozlowski, H. *J. Inorg. Biochem*. **1999**, *75*, 105.
(8) Drechsel, H.; Fiallo, M. M.; Garnier-Suillerot, A.; Matzanke, B. F.; Schunemann, V. *Inorg. Chem.* **2001**, *40* (21), 5324.
(9) Beraldo, H.; Garnier-Suillerot, A.; Tosi, L.; Lavelle, F. *Biochemistry* **1985**, *24*, 284.
(10) Matzanke, B. F.; Bill, E.; Butzlaff, C.; Trautwein, A. X.; Winkler, H.; Hermes, C.; Nolting, H. F.; Barbieri, R.; Russo, U. *Eur. J. Biochem.* **1992**, *207*, 747.
(11) Capolongo, F.; Giomini, M.; Giuliani, A. M.; Matzanke, B.; Russo, U.; Silvestri, A.; Trautwein, A.; Barbieri, R. *J. Inorg. Biochem.* **1997**, *65*, 115.
(12) Beraldo, H.; Garnier-Suillerot, A.; Tosi, L. *Inorg. Chem.* **1983**, *22*, 4117.
(13) Fiallo, M. M.; Garnier-Suillerot, A. *Biochemistry* **1986**, *25*, 924.
(14) Pasini, A. *Gazz. Chim. Ital.* **1987**, *117*, 763.
(15) Pereira, E.; Fiallo, M. M.; Garnier-Suillerot, A.; Kiss, T.; Kozlowski, H. *J. Chem. Soc., Dalton Trans.* **1993**, 455.
(16) Balestrieri, E.; Bellugi, L.; Boicelli, A.; Giovini, M.; Giuliani, A. M.; Giustizi, M.; Marciani, L.; Sadler, P. *J. Chem. Soc. Trans.* **1997**, 4099.
(17) Bel Haj-Tayeb, H.; Fiallo, M. M.; Garnier-Suillerot, A.; Kiss, T.; Kozlowski, H. *J. Chem. Soc., Dalton Trans.* **1994**, 3689.
(18) McLennan, I. J.; Lenkiski, R. E. *J. Am. Chem. Soc.* **1984**, *106*, 6905.
(19) Wei, X.; Ming, L. J. *Inorg. Chem.* **1998**, *37*, 2255.
(20) Muindi, J. R. F.; Sinha, B. K.; Gianni, L.; Myers, C. E. *FEBS Lett.* **1984**, *172*, 226.
(21) Myers, C. *Semin. Oncol.* **1998**, *25* (4 Suppl 10), 10.
(22) Minotti, G.; Ronchi, R.; Salvatorelli, E.; Menna, P.; Cairo, G. *Cancer Res.* **2001**, *61* (23), 8422.
(23) Koch, T. S.; Rava, R. P. *Biophys. Chem.* **1990**, *36*, 187.
(24) Arcamone, F.; Cassinelli, G.; Di Matteo, F.; Forenza, S.; Ripamonti, M. C.; Rivola, G.; Vigevani, A.; Clardy, J.; McCabe, T. *J. Am. Chem. Soc*. **1980**, *102*, 1462.
(25) Arora, S. K. *J. Biomol. Struct. Dyn.* **1985**, *3*, 377.
(26) Berkowitz, D. A.; Danishefski, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1992**, *114*, 4518.

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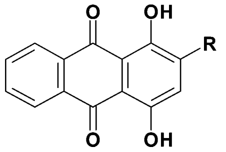
Chart 1. Quinizarine (Qz, R = H) and Quinizarine 2-Sulfonic Acid (QzSH, R = SO_3H)



a 1,4-dihydroxy anthraquinone moiety (Chart 1), are well suited for this purpose and were already employed as models for anthracyclines.[27] Notably, quinizarine forms tight complexes with tripositive metal cations, exhibiting coordination preferences similar to those of doxorubicin.[28] The crystal structure of a peculiar ternary complex of iron(III) with quinizarine and the salen ligand was reported a few years ago by Maroney et al.;[28] in that dinuclear iron(III) complex, quinizarine is simultaneously coordinated to two iron(III)–salen fragments, acting, on both sides, as a bidentate ligand toward the iron(III) centers, through its phenolic and quinone oxygens.

We report here on the interaction of quinizarine 2-sulfonate (QzS$^-$ hereafter) with terbium(III) that is analyzed in comparison to the terbium(III)/doxorubicin system. The reaction of QzS$^-$ with terbium ions was investigated spectrophotometrically, at pH 7.4. Notably, the addition of increasing amounts of terbium(III) ions to QzS$^-$ solutions produces spectral changes that are characteristic of metal complexation by the anthraquinone moiety, accompanied by deprotonation of the phenolic group. In particular, the main visible band of QzS$^-$, at 460 nm, with shoulders at 450 and 480 nm, is progressively replaced by a new band centered at 550 nm, with shoulders at 520 and 560 nm (Figure 1A). Such spectral changes reach completion for a Tb to QzS$^-$ 1:1 stoichiometry, being indicative of the formation of a tight 1:1 Tb/QzS complex. A similar spectrophotometric pattern is observed when adding the stoichiometric amount of terbium ions to doxorubicin at pH 7.4 (Figure 1B). This suggests that quinizarine 2-sulfonate and doxorubicin produce a nearly identical interaction pattern with terbium(III) ions, in agreement with previous spectroscopic reports of lanthanide–anthracycline systems[17–19] and with a recent investigation of the ytterbium/MEN 10755 complex.[29]

Remarkably, in the course of the present investigation, we succeeded in crystallizing a complex of terbium(III) with quinizarine 2-sulfonate and solving its structure by X-ray diffraction. Single crystals of the compound were obtained by slow evaporation of aqueous solutions of terbium nitrate in the presence of a 4:1 excess of QzS$^-$, at pH = 5.5. The light violet crystals were in the form of very thin and fragile plates with limited diffracting power.[30] To the best of our knowledge, this is the first crystal structure of a mononuclear metal complex of quinizarine. Since crystals formed at pH 5.5, we checked the spectrophotometric behavior of QzS$^-$ with terbium at this pH and obtained results nearly superimposable to those at pH 7.4 shown in Figure 1A.

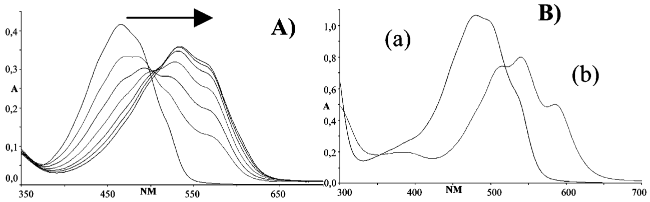


Figure 1. (A) Visible spectra obtained upon titration of QzS$^-$ with increasing amounts of Tb(NO$_3$)$_3$. Spectra corresponding to metal/QzS$^-$ ratios of 0, 0.25, 0.5, 0.75, 1.0, 1.25, and 1.5 are shown. Titration was carried out at pH 7.4. QzS$^-$ concentration is 1.0×10^{-4} M. (B) Visible spectrum of a 1×10^{-4} M doxorubicin sample at pH 7.4 before (a) and after (b) addition of 1.5 equiv of Tb(NO$_3$)$_3$.

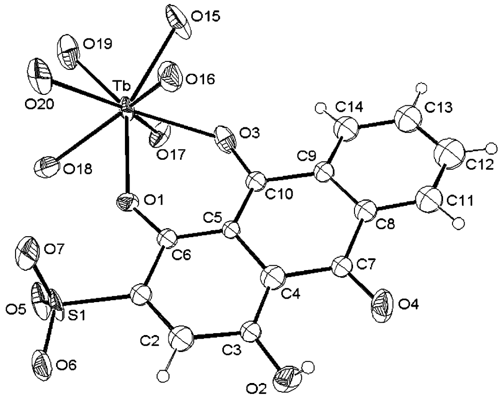


Figure 2. ORTEP diagram of the [Tb(H$_2$O)$_6$(QzS)]$^+$ cation showing 50% probability thermal ellipsoids. Selected interatomic distances (Å) are Tb–O(1) 2.27(1), Tb–O(3) 2.29(1), Tb–O(15) 2.33(1), Tb–O(16) 2.44(2), Tb–O(17) 2.36(2), Tb–O(18) 2.44(2), Tb–O(19) 2.38(2).

The structure consists of [Tb(H$_2$O)$_6$(QzS)]$^+$ cations, QzS$^-$ anions, and solvate water molecules. The QzS moiety in the complex cation is dianionic, due to deprotonation of the coordinating phenol oxygen. The structure of the cation is shown in Figure 2.

The terbium(III) center is eight-coordinated by six water molecules and two oxygen atoms of the bidentate ligand forming a slightly distorted dodecahedron. The best plane through the chelating quinizarine molecule and that of the QzS$^-$ counterion form a 20° angle. There is a complex network of hydrogen bonds between the coordinating water molecules, the oxygen atoms of the sulfonate groups, and the water solvate molecule. These interactions, combined with those due to the stacking of the quinizarine groups (Figure 3), probably represent a key feature for the crystal assembly mechanism.

The present structure provides definitive evidence that the anthraquinone moiety binds the terbium(III) ion in a bidentate fashion through the adjacent phenolate and quinone groups, according to previous suggestions.[17–19] In our opinion, the structural features of the present compound are of general relevance to model the interactions of the anthraquinone

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(27) Kiraly, R.; Martin, B. *Inorg. Chim. Acta* **1982**, *67*, 13.

(28) Maroney, M. J.; Day, R. O.; Psyris, T.; Fleury, L. M.; Whitehead, J. P. *Inorg. Chem.* **1989**, *28*, 173.

(29) Di Bari, L.; Pintacuda, G.; Ripoli, S.; Salvatori, P. *Magn. Res. Chem.* **2002**, *40*, 396.

(30) Diffraction data (3202 independent reflections) were collected on a Bruker-AXS CCD platform mounted on a rotating anode generator, using Cu Kα radiation. Crystal data for [Tb(H$_2$O)$_6$(QzS)]QzS·H$_2$O: triclinic, space group $P\bar{1}$, $a = 8.658(1)$ Å, $b = 10.527(1)$ Å, $c = 17.763(1)$ Å, $\alpha = 97.47(1)°$, $\beta = 90.64(1)°$, $\gamma = 94.65(1)°$, $Z = 2$. The structure was solved by direct methods and refined on F^2 with anisotropic Tb, S, and O and isotropic C and H (water hydrogens not included) atoms; R1 = 0.097, R2 = 0.231 for $I > 2\sigma N$.

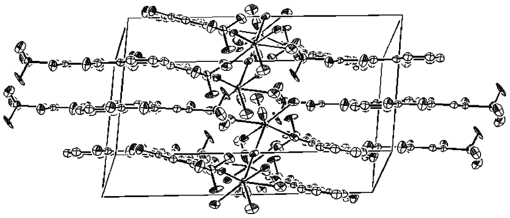

Figure 3. Packing diagram of $[Tb(H_2O)_6(QzS)]QzS \cdot H_2O$.

moiety with tripositive and bipositive “hard” metal ions. It is very likely that such a binding model holds substantially unmodified for the coordination of anthracyclines to “hard” cations. Remarkably, this is the first structure of a metal complex of the 1,4-dihydroxyanthraquinone ligand.[31]

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Supporting Information Available: Crystallographic information in a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) The crystal structures of the parent system ruthenium(III) alizarine have been recently reported, exhibiting related structural features. Churchill, M. R.; Keil, K. M.; Bright, F. V.; Pandey, S.; Baker, G. A.; Keister, J. B. *Inorg. Chem.* **2000**, *39* (25), 5807. Churchill, M. R.; Keil, K. M.; Gilmartin, B. P.; Schuster, J. J.; Keister, J. B.; Janik, T. S. *Inorg. Chem.* **2001**, *40* (17), 4361.