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Barbituric acid as a new locking fragment in macrocyclization: synthesis and structural characterization of [aqua(perchlorato)(2′,4′,6′-trioxohexahydropyrimidine-5′-spiro-6-1,4,8,11-tetraazacyclotetradecane)copper(II)] perchlorate hydrate

Yaroslaw D. Lampeka,[*,a] **Alexander I. Prikhod'ko,**[a] **Alexander Y. Nazarenko**[b] **and Edward B. Rusanov**[c]

[a] *L. V. Pisarzhevsky Institute of Physical Chemistry, National Academy of Sciences of Ukraine, Prospekt Nauki 31, Kiev 252039, Ukraine*
[b] *Analytical Chemistry Department, Taras Shevchenko University, Kiev 252601, Ukraine*
[c] *Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev 253660, Ukraine*

The reaction of $[Cu(danda)]^{2+}$ (danda = 3,7-diazanonane-1,9-diamine) with formaldehyde and barbituric acid resulted in a new macrocyclic compound, bearing barbituric acid as a spiro substituent which was characterized by spectral and potentiometric methods, cyclic voltammetry and single-crystal X-ray diffraction.

Template condensation of nickel(II) and copper(II) acyclic tetraamine complexes with formaldehyde and nucleophiles is a convenient way to prepare functionalized macrocyclic complexes.[1] The use of primary amines as nucleophiles in these reactions results in the formation of complexes of azacyclam ligands (cyclam = 1,4,8,11-tetraazacyclotetradecane) possessing non-co-ordinated nitrogen atom(s) in the macrocyclic backbone.[2–4] Such molecules are unstable in the free (non-co-ordinated) state owing to the hydrolytic instability of the diaminomethylene fragments[5] and this feature restricts their applicability for the preparation of complexes with metals other than nickel or copper. From this point of view, the employment of C–H acids, which form C–C bonds upon interaction with formaldehyde, as nucleophiles seems more preferable, but their assortment is rather limited. To date only nitroalkanes and malonic acid esters have been used as locking fragments in the preparation of macrocycles.[1,6,7] Reactions with the latter reagent usually result in low yields of the desired products.[7]

In our search for polytopic macrocyclic compounds we intended to prepare complexes bearing fragments of barbituric acid by the reaction of urea with 6,6,13,13-tetraethoxycarbonyl-substituted cyclamcopper(II).[8] Unfortunately, only the decarboxylated product was obtained.

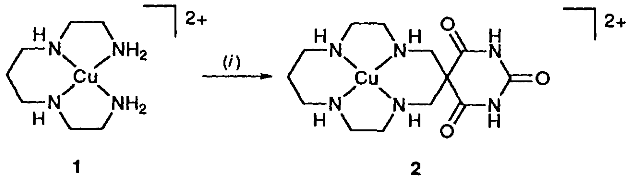
Having implied that barbituric acid itself can behave as a nucleophile, we tried to use it in a formaldehyde–amine condensation and succeeded in the preparation of complex **2** in good yield, starting from **1** (Scheme 1).† Interestingly, the reactions of the analogous open-chain tetraamine nickel(II) complex or $[Cu(en)_2]^{2+}$ (en = ethane-1,2-diamine) under similar conditions do not result in macrocyclic compounds and only the acyclic condensation products are formed.[9]

The IR spectrum of complex **2**† is fully consistent with the structure proposed; the UV/VIS characteristics are typical of copper(II) complexes having 14-membered tetraaza ligands,[10] with a single band in the visible region attributable to d–d transitions. The intense UV absorption can be considered as a superposition of the metal-to-ligand charge transfer band (*ca.* 210 nm) and the intramolecular band of the barbituric moiety (254 nm). As for the latter, its intensity is *ca.* half that of barbituric acid (λ = 258 nm, ε = 9300 dm^3 mol^{-1} cm^{-1}).

The solution properties of the new complex are determined to a great extent by the barbituric fragment of the macrocycle. Thus, the complex is sparingly soluble in acidic aqueous solutions but has high solubility in alkaline media. This fact is undoubtedly connected with the acid–base equilibria affecting the substituent. Potentiometric investigations revealed a pK_a value of 6.78 ± 0.03 (0.1 mol dm^{-3}, $NaClO_4$, 290 K) which is lower than for 5,5-diethylbarbituric acid (pK_a = 7.79),[11] indicating the strong influence of a neighbouring metal centre on the proton equilibrium. It follows also from the spectrophotometric titration that there is a second acid–base equilibrium with $pK_a > 10.5$.

The mutual influence of the substituent and the metal centre is also clearly evident from electrochemical data.‡ Thus, the $E_{\frac{1}{2}}$ value of the Cu^{III}–Cu^{II} couple for **2** in 10 mol dm^{-3} $HClO_4$ is *ca.* 1.1 V *vs.* saturated calomel electrode, *i.e.* 0.1 V higher than for Cu^{III}–Cu^{II}(cyclam) under the same conditions. This feature indicates a substantial electron-withdrawing effect of the barbituric acid fragment, similar to that produced by the nitro group in copper–amide macrocyclic complexes.[13]

The molecular structure of complex **2** determined by X-ray



Scheme 1 (*i*) Barbituric acid, HCHO, MeOH–water (6:1, v/v), reflux 4 h. Axial H_2O and ClO_4 in **2** are omitted

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† Complex **1** (2.1 g, 5 mmol) was dissolved in methanol (100 cm^3) under reflux and concentrated perchloric acid (0.1 cm^3) and 37% aqueous formaldehyde (1.0 cm^3, 13 mmol) were added. Barbituric acid (0.8 g, 6 mmol) dissolved in aqueous methanol (1:1, v/v; 40 cm^3) was added dropwise during 1 h. Boiling was continued for 3 h and then the mixture was cooled and filtered. The solution was evaporated and the dry residue dissolved with heating in water (10 cm^3) and acidified to pH 3 with $HClO_4$. After cooling in a refrigerator, the precipitate was filtered off, washed with methanol and recrystallized from acidic aqueous solution. Yield 1.2 g (41%). IR $\tilde{\nu}$/cm^{-1} (KBr): 3592m, 3507m (ν_{OH}); 3253m (ν_{NH}); 1756s, 1725s, 1693s (ν_{CO}); *ca.* 1100vs, 619s (ν_{ClO_4}). UV/VIS λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}) (H_2O): 515 (76), 254 (4500), *ca.* 210 (*ca.* 6800) (Found: C, 23.35; H, 4.30; N, 12.65. $C_{13}H_{28}Cl_2CuN_6O_{13}$ requires C, 23.25; H, 4.15; N, 12.50%).

‡ Glassy carbon working electrode, sweep rate 100 mV s^{-1}; strongly acidic medium was used to attain the reversibility of the redox couple.[12]

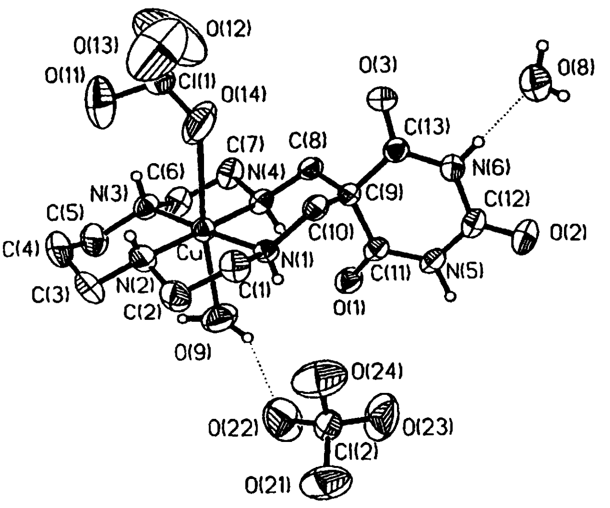

Fig. 1 Molecular structure of complex **2**, C–H protons have been omitted for clarity. Selected interatomic distances (Å) and angles (°): Cu–N(1) 2.025(4), Cu–N(2) 1.995(5), Cu–N(3) 2.007(4), Cu–N(4) 2.008(4), Cu–O(9) 2.52(1), Cu–O(14) 2.69(1); N(1)–Cu–N(2) 85.9(2), N(2)–Cu–N(3) 95.4(2), N(3)–Cu–N(4) 86.2(2), N(4)–Cu–N(1) 92.4(2). Hydrogen bonds: O(9)–H···O(22) 2.88, O(9)–H···O(22) $(1 - x, -y, -z)$ 2.92, N(6)–H···O(8) 2.88, O(8)–H···O(23) $(-x, 0.5 + y, -0.5 - z)$ 2.95, O(8)–H···O(12) $(-1 - x, 1 - y, -z)$ 2.97, N(5)–H···O(11) $(x, 0.5 - y, -0.5 + z)$ 3.03

crystallography is shown in Fig. 1.* The copper ion has a distorted tetragonal-bipyramidal co-ordination with equatorial Cu–N distances [average 2.009 Å] typical of 14-membered tetraazamacrocyclic copper complexes.[10,15] The axial *d*(Cu–O) values [Cu–O(H_2O) 2.52 and Cu–O(ClO_4) 2.69 Å] are slightly longer than usually observed in copper complexes (2.28–2.52 and 2.49–2.57 Å, respectively[16]). Nevertheless, **2** can be formulated as $[CuL(H_2O)(ClO_4)]ClO_4 \cdot H_2O$ because such elongation of axial bonds is a common feature of six-co-ordinate tetragonal azamacrocyclic copper complexes.[17]

The average interatomic distances and angles in the macrocyclic backbone are also typical for those of known complexes.[10,15] The torsion angles of the C–C bonds correspond to a *gauche* and those of the C–N bonds to a *trans* conformation. Both six-membered rings of the macrocycle have a chair conformation, while both five-membered rings have a twist one. The overall macrocycle symmetry is distorted C_{2h} with a mirror plane through C(4)–Cu–C(9), which is a common motif for the cyclam molecule.[15] The barbituric acid fragment is disposed nearly perpendicular to a macrocycle plane (85°); its geometry is very similar to other known barbiturate derivatives.[18] In addition, there is a network of hydrogen bonds to water molecules and perchlorate anions.

Thus, our investigation offers a convenient route to new functionalized macrocyclic complexes. The synthetic approach proposed possesses the following advantages: mild reaction conditions, short reaction times and relatively high yields. The applicability of this method to the syntheses of copper(II) macrocyclic complexes bearing N-substituted barbituric acids is currently under investigation in our laboratory. Metal complexes such as **2** are prone to form a network of hydrogen bonds, similar to those found in barbiturates, as well as to co-ordinate additional ligands. This ability to display ditopic properties may be of special interest in the study of the biological activity of such complexes.

Acknowledgements

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* Crystal data: $C_{13}H_{28}Cl_2CuN_6O_{13}$, $M = 670.85$, monoclinic, space group $P2_1/c$, $a = 8.188(2)$, $b = 13.758(3)$, $c = 20.922(4)$ Å, $\beta = 94.73(3)°$, $U = 2348.8(9)$ Å^3, $Z = 4$, $D_c = 1.727$ g cm^{-3}, $\mu = 4.11$ mm^{-1}, $F(000) = 1260$, $0.28 \times 0.35 \times 0.21$ mm. 3460 ($R_{int} = 0.0406$) Independent reflections were measured at 295 K on Enraf-Nonius CAD-4 diffractometer using Cu-Kα radiation ($\lambda = 1.541\,78$ Å) with ω–2θ scans ($3 < \theta < 60°$). The structure was solved by the heavy-atom method,[14] refinement was by full-matrix least squares on F^2 for all data with anisotropic displacement parameters for non-hydrogen atoms and isotropic for hydrogen atoms {goodness-of-fit = 1.039, final *R* indices $[I > 2\sigma(I)]$ $R1 = 0.0574$, $wR2 = 0.1506$, $w = 1/[\sigma^2(F_o)^2 + (0.1065P)^2 + 4.70P]$, $P = [\max(F_o, O)^2 + 2F_c{}^2]/3$}. Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 186/33.