

Communications

"Colloidal Bismuth Subcitrate" (CBS): Isolation and Structural Characterization of the Active Substance against *Helicobacter pylori*, a Causal Factor of Gastric Diseases

The stomach bacterium *Helicobacter pylori*, discovered as late as 1983,¹ has been assigned a pathogenic factor in the etiology of chronic gastritis and of the peptic ulcer.^{1,2} This microorganism is typical of patients who suffer from type B gastritis or duodenal ulcers and is resistant against all pharmaceuticals for the treatment of ulcer *except* certain bismuth salts and complexes. Beyond that, *H. pylori* may present problems in terms of epidemiology because of the possible direct infection from person to person.^{2c} Again, the traditional "bismuth therapy" seems again preferred over the treatment of ulcers with acid-suppressing H₂-antagonists (e.g., cimetidin, ranitidin), since the rates of recidivs are generally lower and side effects are less frequent.³ It seems that the so-called "colloidal bismuth subcitrate" present in the medicines Telen and De-Nol is specifically active against *H. pylori*.⁴ However, nothing is known about the mechanisms, e.g. bactericidal effect vs formation of coating films in a bismuth-specific hydrolysis chemistry. Eradication rates of up to 75% have been achieved by means of combined treatment with bismuth salts and antibiotics.³

In order to provide the basis of the pharmacokinetics and -dynamics of bismuth compounds, we have isolated the "colloidal bismuth subcitrate" (CBS) and have determined the three-dimensional structure of this important compound. This is the first report on the coordination chemistry and stereochemistry of any bismuth compound that has been successfully applied (for many decades) in medicinal therapies. We show here that high coordination numbers of bismuth resulting from citrate and water coordination as well as from channel-forming aggregation of the subunits [Bi(C₆H₄O₇)]⁻ result in the unusually high solubility of this particular bismuth compound in water.

CBS of analytical composition K₃Bi(C₆H₅O₇)₂ is practically the only bismuth salt of very high solubility in water. If such solutions stand for some time at ca. 8 °C, the colorless hydrated double salt KBi(C₆H₄O₇)·3H₂O (1) crystallizes. The content of water was determined by quantitative differential thermogravimetry (DTG). Exactly the same compound is obtained upon neutralization of an equimolar suspension of bismuth citrate and

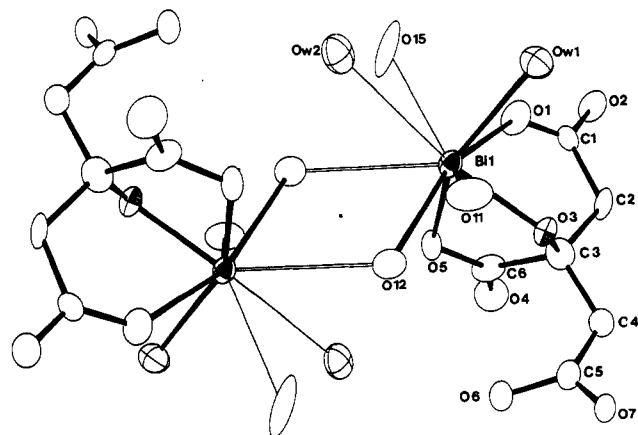


Figure 1. Representative section of the three-dimensional network in the crystal structure of potassium bismuth citrate $\text{KBi}(\text{C}_6\text{H}_4\text{O}_7) \cdot 3\text{H}_2\text{O}$. Important bond distances (pm) and angles (deg): Bi(1)–O(3) = 213.2 (6)/212.7 (7); Bi(1)–O(3)–C(3) = 114.2 (6)/113.9 (6). The center of symmetry is indicated by an asterisk.

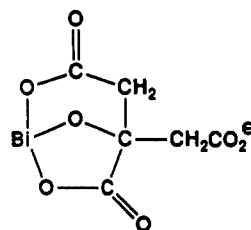


Figure 2. Constitution of the complex anion $[\text{Bi}(\text{C}_6\text{H}_4\text{O}_7)]^-$ in the crystalline aggregate (intermolecular contacts and solvating water molecules omitted for clarity).

the potassium citrate $\text{K}_3[\text{C}_6\text{H}_5\text{O}_7]$ by means of ammonia in water at 60 °C. Compound 1 crystallizes in the monoclinic space group $P2_1/n$ with two crystallographically independent molecules A/B.⁵ The compound exhibits a very unusual molecular and crystal structure that is based on the polyfunctionality of the citrate ion and its ability of coordinating to potassium and bismuth ions as well as to water molecules in the crystal lattice.

As an ion that has a sterically active "free" electron pair, the bismuth ion (Bi^{3+}) forms an irregular coordination polyhedron. The angles and Bi–O distances [213.2 (6)–252.8 (8)/212.7 (7)–249.3 (7) pm] are in a first approximation compatible with an unusual distorted pentagonal bipyramid, with the free electron

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- (2) (a) O'Connor, H. J.; Wyatt, J. L.; Dixon, M. F.; Axon, A. T. R. *J. Clin. Pathol.* 1986, *35*, 531. (b) Langenberg, M. L.; Tygat, G. N. J.; Schipper, M. E. I.; Rietra, P. J. G. M.; Zanen, H. C. *Lancet* 1984, *I*, 1348. (c) Berkowicz, J.; Lee, A. *Ibid.* 1987, *II*, 680.
- (3) For state-of-the-art reviews on uses of bismuth drugs in medicine, cf.: (a) Kreusel, U. Diploma Thesis, Technische Universität München, 1990 (copy available upon request from correspondence author). (b) Börsch, G. *Med. Monatsschr. Pharm.* 1988, *11*, 301.
- (4) CBS is present as the effective drug in Telen (Byk Gulden) and in De-Nol (Gist Brocades). We thank Dr. Krüger (Konstanz) and Dr. Klempner (Kronberg) for many discussions and useful hints concerning medicinal effects of bismuth and other metals.

- (5) The crystallographically independent molecules A and B differ only marginally in the details of their coordination to bismuth. Corresponding distances and angles are given for both molecules in the order A/B. Figure 1 and the discussion of the structure, however, are only given for molecule A and can be applied to molecule B as well.

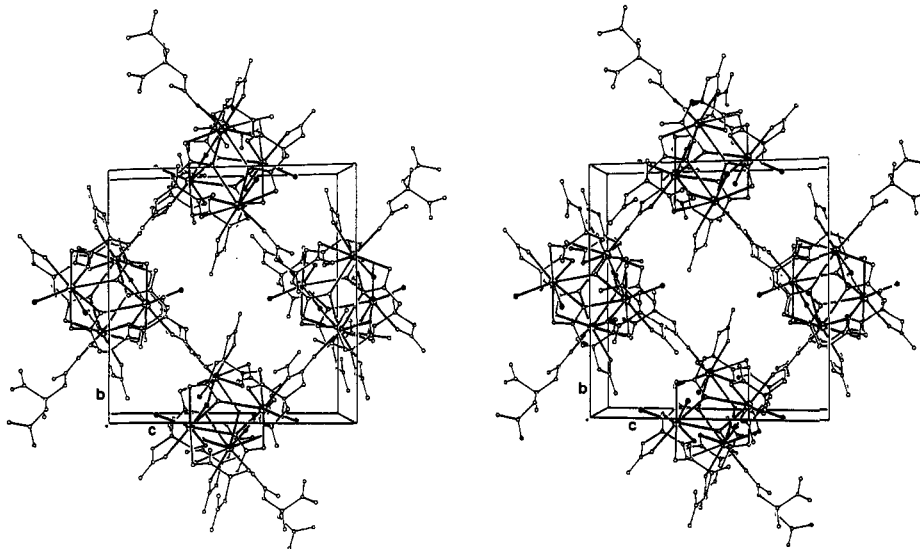


Figure 3. Stereoscopic representation of the anionic framework $[\text{Bi}-\text{O}-\text{C}_6\text{H}_4\text{O}_6]_n^-$, as viewed parallel to the a axis. Arbitrary radii are assigned to the atoms.

pair and the hydroxy oxygen O(3) adopting the apical positions.⁶ The corresponding distances are emphasized in Figure 1 by means of thick bond lines.

The formal interpretation does not consider, however, that the Bi(1)–O(12*) distances of 298.4 (7) and 305.4 (8) pm (molecules A and B, respectively) still meet the requirements for ionic interactions.^{7a,b} They in fact lead to loosely connected dimeric units, the basic structure of which is characterized by a planar Bi_2O_2 (four-membered) ring system. Further away but still closer than van der Waals distances (360 pm)^{7c} are located the atoms O(15) and Ow(2): 311.6 (8)/323.5 (8) and 339.1 (7)/332.6 (8) pm, respectively (Figure 1).

From a coordination chemistry point of view, the short Bi(1)–O(3) distance concerning the hydroxy oxygen atom of the citrate ligand is surprising (<216 pm). As a matter of fact, this distance is compatible with a covalent, strong single bond.^{7a,b} In addition, two of the three free carboxylate groups are engaged in the bismuth coordination via an oxygen atom each (Figures 1 and 2). The third carboxylate group of the citrate ligand is used to connect molecules A and B to form a three-dimensional, negatively charged network.⁹ Formally the complex anion $\{[\text{Bi}(\text{C}_6\text{H}_4\text{O}_7)]\}^-$ is thus formed, with the four-basic citrate ligand acting as both a chelating and a bridging ligand. A unique channel structure parallel to [100], [010], and [001] in the crystal lattice results from this unprecedented type of aggregation. The proper number of potassium ions (K^+) necessary for charge equilibration is embedded in the cages of these channels (Figure 3). Finally, extensive hydrogen bridging between water molecules coordinated to bismuth as well as to potassium and free crystal water on the

one hand and the oxygen atoms of the citrate ligands on the other hand stabilizes the architecture of the crystal lattice.¹⁰

Only the quantity of the crystal water and the finer details of the space network structure are changed upon replacement of ammonium for the potassium ions. Primary and secondary structures around the bactericidal bismuth are otherwise unchanged, and again the hydroxy groups of the citric acid are present in the deprotonated form.¹¹ This seems to be a general feature of hydroxy carboxylic acids coordinated to bismuth.

The ionic architecture of citrate complexes of bismuth as shown in this paper explains the high water solubility, in which terms CBS principally differs from all other common bismuth medicals of therapeutical use.

The outstanding, versatile chelate properties of the body-specific (physiological) citrate anion as well as the apparently very stable covalent bonds between bismuth ions (Bi^{3+}) and alkoxy groups (RO^- of citrate) guarantee the strikingly high chemical resistance of CBS in gastric juice, just in contrast to the "basic bismuth salicylate" (BBS), which is rather sensitive to hydrolysis and

- (6) Similar arguments for $\text{ClSb}[\text{C}(\text{NSiMe}_3)_2\text{C}_6\text{H}_5]_2$; Patt-Siebel, U.; Müller, U.; Ergenzinger, Ch.; Borgsen, B.; Dehnicke, K.; Fenske, D.; Baum, G. *Z. Anorg. Allg. Chem.* **1990**, *30*, 582.
- (7) (a) Covalent bond distance ca. 216 pm: March, F. C.; Ferguson, G. J. *Chem. Soc., Dalton Trans.* **1975**, 1291. (b) The sum of ionic radii amounts to 235 pm for Bi^{3+} (CN 6) and O^{2-} (CN 2); cf.: Shannon, R. D.; Prewitt, C. T. *Acta Crystallogr.* **1969**, *25B*, 925. (c) Estimated from distances in the metal; cf.: Wells, A. F. *Structural Inorganic Chemistry*; Clarendon Press: Oxford, England, 1984; p 876. Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
- (8) Barton, H. R.; Charpiot, B.; Tran Huu Dau, E.; Motherwell, W. B.; Pascard, C.; Pichon, C. *Helv. Chim. Acta* **1984**, *67*, 586.
- (9) Three out of 14 oxygen atoms are involved in bismuth coordination; the others act as bridging links between bismuth and potassium ions. There are seven (!) different types of water molecules in the unit cell (two are located in general positions with occupancy factors $1/2$ but are disordered). Two H_2O molecules are attached to bismuth, and five, to potassium. Only one H_2O molecule does neither interact with Bi^{3+} nor interact with K^+ . If one considers $\text{K}-\text{O}$ distances up to 350 pm, then the K^+ ions are of coordination number (CN) 9. The hydrogen bridges are between 270 and 300 pm in distance.

- (10) Tiny colorless crystals of dimensions $0.01 \times 0.01 \times 0.07$ mm were obtained from aqueous solution. *Crystal data*: systematic absences $h0l$ ($h+l=2n+1$) and $0k0$ ($k=2n+1$); space group $P2_1/n$ (No. 14); unit cell constants by least-squares refinement from 25 reflections at high angles ($2\theta \geq 51.5^\circ$) $a = 1092.4$ (2) pm, $b = 1528.0$ (1) pm, $c = 1496.7$ (3) pm, $\beta = 105.48$ (1)°; $V = 2408 \times 10^6$ pm³; $Z = 8$; empirical formula $\text{C}_6\text{H}_4\text{BiKO}_7 \cdot 3\text{H}_2\text{O}$ (490.2 amu); $F(000) = 1824$; $\rho(\text{calc}) = 2.705$ g·cm⁻³. *Data collection*: Enraf-Nonius CAD-4; Cu $K\alpha$ irradiation ($\lambda = 154.184$ pm); graphite monochromator; $T = 23 \pm 1$ °C; recording range $2.0^\circ \leq \theta \leq 65.0^\circ$; $\theta/2\theta$ scan; scan width $(1.20 + 0.25 \tan \theta)^\circ \pm 25\%$ before and after each reflection for background determination; $t(\text{max}) = 90$ s. *Solution and refinement of structure*: 4532 recorded reflections ($+h, +k, \pm l$); 3745 independent reflections, of which 464 with $I > 2.0\sigma(I)$ were classified as not observed; 35 reflections with $(\sin \theta)/\lambda \leq 0.120$ were discarded; 3247 (NO) independent reflections and 329 (NV) parameters subjected to full-matrix least-squares refinement; 36 of the 37 heavy atoms refined with anisotropic temperature factors. The structure solution was achieved by means of Patterson methods and difference Fourier techniques; Lorentz polarization correction was applied but no absorption correction ($\mu = 323.5$ cm⁻¹). Anisotropic correction for decomposition was considered (-48.7% within 108 h). The positions of the citrate hydrogen atoms were calculated in idealized geometry ($d(\text{C}-\text{H}) = 95$ pm) and were included in the structure factors but not refined. Anomalous dispersion was considered. Shift/error < 0.001 in the last cycle of refinement; residual electron densities $+2.26$ e/Å³ and -2.31 e/Å³ next to the Bi atom. $R = \sum |F_o| - |F_c| / \sum |F_o| = 0.053$; $R_w = \{ \sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2 \}^{1/2} = 0.049$; $\text{GOF} = [\sum w(|F_o| - |F_c|)^2 / (\text{NO} - \text{NV})]^{1/2} = 2.934$ ($\rho = 0.00$) with $w = 1/\sigma^2(F_o)$. Further details on the crystal structure determination can be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-7514 Eggenstein-Leopoldshafen 2, Germany, quoting the depository number CSD 54652, the names of the authors, and the journal citation.
- (11) Herdtweck, E.; Herrmann, W. A.; Pajdla, L. Unpublished results, 1990.

decomposes in hydrochloric acid with liberation of salicylic acid (ca. 75% within a period of 60 min at pH 2). For these reasons, CBS unlike any other bismuth-containing drug seems to arrive in the ulcer regions chemically mostly intact and is finally attached via sulfhydryl (-SH) groups. Chemical model experiments addressing this latter question are presently being performed in our laboratories.

Supplementary Material Available: Tables of atomic coordinates and thermal parameters for non-hydrogen atoms, bond distances, bond angles, and root-mean-square amplitudes of thermal vibration (14 pages); a table of calculated and observed structure factors (21 pages). Ordering information is given on any current masthead page. These data, including additional drawings, have also been deposited at the Fachinformati-onszentrum Energie Mathematik Physik (FIZ), Eggenstein-Leopoldshafen, Germany, under the registry number CSD 54652.

Anorganisch-chemisches Institut der
Technischen Universität München
Lichtenbergstrasse 4
D-8046 Garching bei München,
Germany

Wolfgang A. Herrmann*
Eberhard Herdtweck
Liba Pajdla

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Remarkable Solvent Effect on the Shape-Selective Oxidation of Olefins Catalyzed by Iron(III) Porphyrins

Metalloporphyrin-catalyzed oxidations have been extensively studied, and higher valent oxo-metalloporphyrin intermediates are considered as reactive intermediates in many reactions.¹ In fact, the solid evidence for the formation of oxo-ferryl porphyrin cation radicals (1) was shown in the reaction of Fe^{III}TMP and *m*-CPBA in CH₂Cl₂.^{2,3} Meanwhile, we have reported that the same reaction in an aromatic solvent such as toluene gave the *N*-oxide of Fe^{III}TMP (2) due to the homolytic O-O bond cleavage of a peracid-iron complex (3) (Scheme I).⁴ We herein describe competitive epoxidation of norbornylene and α -methylstyrene by *m*-CPBA in the presence of a catalytic amount of iron porphyrins in CH₂Cl₂ and toluene. The results indicate possible participation of 3 in the epoxidation of olefins when the formation of 1 is a less favorable process.

Scheme I

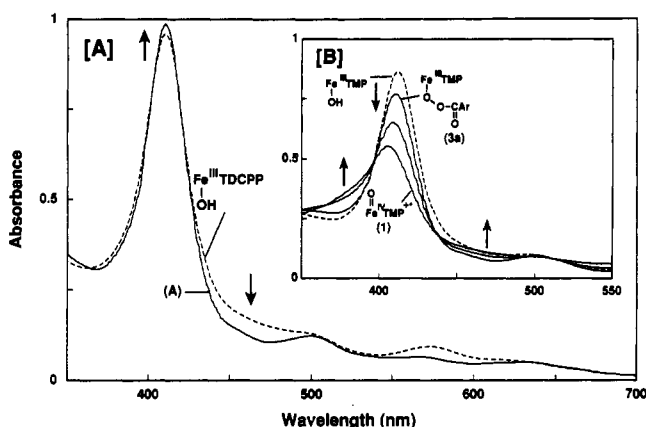
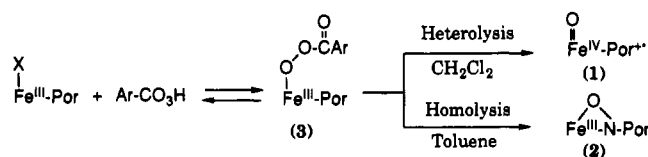


Figure 1. (A) Spectral change in the reaction of 1.0×10^{-5} M of Fe^{III}TDCPP(OH) (---) and *m*-CPBA in CH₂Cl₂ at -78 °C. (B) Time-dependent spectral changes of 0.85×10^{-5} M Fe^{III}TMP(OH) (---) upon the addition of *m*-CPBA in CH₂Cl₂ at -78 °C. Scan interval: 2 min.

In a typical reaction, oxidation of a mixture of norbornylene and α -methylstyrene (1:1, 300 equiv with respect to the catalyst) took place in CH₂Cl₂ (0.5 mL) at -78 °C for 3 h by employing a catalytic amount of Fe^{III}TMP(Cl) (1 mM). The reaction was initiated by adding *m*-CPBA (30 equiv), and preferable epoxidation of norbornylene over α -methylstyrene was observed in 63% yield (norbornylene oxide: α -methylstyrene oxide⁶ = 100:9; Table I, run 3). Change of the axial ligand from chloride to hydroxide did not cause any appreciable changes in the catalytic activity and selectivity (run 4). A similar result was also obtained in the oxidation catalyzed by Fe^{III}TDMPP(Cl) (run 6).² In these reactions, a rapid color change from brown to green by the addition of *m*-CPBA was observed. These color changes are indicative of oxo-ferryl porphyrin cation radical formation as shown in Figure 1B.^{3a,b}

Mechanistic studies on the iron porphyrin catalyzed epoxidations by Groves and his co-workers indicated that the side-on approach of olefins to the iron-bound oxo oxygen in 1 results in the preferable *cis*-olefin epoxidation over *trans*-olefins.⁷ More recently, they have examined the crystal structure of an adduct of styrene oxide and Ru^{II}TDCPP(CO).^{2,8} The structure clearly shows the coordination of the epoxide ring at 49° with respect to the porphyrin plane and the two oxirane protons protrude toward the pyrrole ring of the porphyrin with vertical distances of ca. 2.8 Å from the plane. Thus, it will be difficult for α -methylstyrene to have a position suitable for the epoxidation, consistent with our results.

When the same reactions were carried out in toluene, remarkable changes in the shape selectivity of the olefins were observed; i.e., comparable amounts of α -methylstyrene to norbornylene were oxidized (Table I, runs 5 and 7). As reported before, the formation of 2 is predominant if olefins are absent.⁴ Further, the oxidation of the olefins under the same condition without catalysts gave less than 5% epoxides (based on the Fe^{III}TMP-catalyzed epoxide formation). Therefore, these very different shape selectivities in toluene and CH₂Cl₂ would be at-

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- (2) Abbreviations used are: Fe^{III}TMP, (tetramesitylporphyrinato)iron(III); Fe^{III}TDMPP, (tetrakis(2,6-dimethoxyphenyl)porphyrinato)iron(III); Fe^{III}TDCPP, (tetrakis(2,6-dichlorophenyl)porphyrinato)iron(III); Fe^{III}TPFPP, (tetrakis(pentafluorophenyl)porphyrinato)iron(III); *m*-CPBA, *m*-chloroperbenzoic acid, *o*-CPBA, *o*-chloroperbenzoic acid.
- (3) (a) Groves, J. T.; Haushalter, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1981**, *103*, 2884-2886. (b) Groves, J. T.; Watanabe, Y. *Ibid.* **1986**, *108*, 7834-7836. (c) Penner-Hahn, J. E.; Eble, K. S.; McMurry, T. J.; Renner, M.; Balch, A. L.; Groves, J. T.; Dawson, J. H.; Hodgson, K. O. *Ibid.* **1986**, *108*, 7819-7825. (d) Hashimoto, S.; Tastsuno, Y.; Kitagawa, T. *Ibid.* **1987**, *109*, 8096-8097.
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- (5) A small amount of endo epoxide was observed in the iron porphyrin catalyzed oxidations.
- (6) α -Methylstyrene oxide gives two peaks in the GLC analysis due to its thermal rearrangement to phenylpropionaldehyde. The ratio of two species was not constant even when a purified oxide was analyzed. Thus, the yields of the oxide represent a total amount of two products.
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