# Synthesis and Properties of Boranocarbonate: A Convenient in Situ CO Source for the Aqueous Preparation of $[^{99m}Tc(OH_2)_3(CO)_3]^+$

Roger Alberto,[*,†] Kirstin Ortner,[†] Nigel Wheatley,[†]
Roger Schibli,[‡] and August P. Schubiger[‡]

*Contribution from the Institute of Inorganic Chemistry, University of Zürich, CH-8057 Zürich, Switzerland, and Center for Radiopharmacy, Paul Scherrer Institute, CH-5232 Villigen, Switzerland*

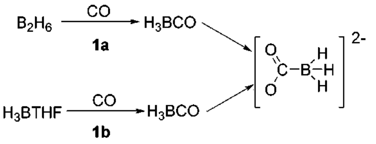
*Received November 13, 2000*

The recently described technetium(I) complex $[^{99m}Tc(OH_2)_3(CO)_3]^+$ **1** has attracted much interest as a precursor for technetium-99m radiopharmaceuticals.[1] A number of biomolecules, for example, peptides, scFv, and CNS receptor ligands, have already been labeled with technetium by this approach, demonstrating the potential of **1** for radiopharmaceutical application.[2] Complex **1** can be prepared in a single-step procedure from aqueous $[^{99m}TcO_4]^-$ in the presence of CO and $BH_4^-$ as a reducing agent.[3] Unfortunately, the published preparation of $[^{99m}Tc(OH_2)_3(CO)_3]^+$, relying on gaseous carbon monoxide, is unsuitable for use in commercial radiopharmaceutical "kits". Thus, the challenge was to find a solid, air-stable source of carbon monoxide, possibly acting at the same time as the reducing agent.

Compounds which release CO under well-defined conditions and which obey these physicochemical restrictions are extremely rare.[4] They would not only be interesting for the medical application of organometallic precursors such as **1**, but could also lead to a novel type of reaction for the preparation of carbonyl complexes due to the high potential availability of CO in water. We report here the first commercially feasible preparation of an organometallic transition-metal complex in physiological media, using a boron-based carbonylating agent which acts as a CO source and a reducing agent at the same time.

The so-called boranocarbonates, such as the potassium salt $K_2[H_3BCO_2]$ **2**, were described for the first time by Malone and Parry in 1967. They were reported at the time to release CO at elevated temperatures in water.[5] This remarkable behavior has scarcely been further studied, probably due to the difficulties in handling borane carbonyl, $H_3BCO$ **3**, a pyrophoric gas which is the immediate precursor to the boranocarbonate anion.

**Scheme 1**



Originally, $H_3BCO$ **3** was synthesized from $B_2H_6$ and CO either in an autoclave reaction[6] or at atmospheric pressure catalyzed by ethers.[7] Ethers such as dimethoxyethane catalyze the rate-determining step of diborane bridge cleavage in the preparation of **3**. The ether in the adduct $H_2B(HBH_3)(OR_2)$ or $H_3BOR_2$ is then readily substituted by CO. Compound **3** is subsequently reacted with ethanolic KOH to give **2**.[5] Although the reaction yields are fairly good, working under pressurized conditions with pyrophoric gases at low temperatures is not convenient, particularly for larger-scale preparation. We have found[8] that $H_3BCO$ **3** can be prepared continuously from commercially available $H_3B{\cdot}THF$ solutions and reacted in situ with an alcoholic solution of potassium hydroxide to give $K_2[H_3BCO_2]$. The key to the preparation is the control of the equilibrium between $H_3BCO$ and $H_3B{\cdot}THF$. THF is selectively condensed from the gas stream at −50 °C, while $H_3BCO$ (bp −64 °C) passes on, carried by a stream of carbon monoxide. Subsequently, this gas mixture is directly bubbled through an ethanolic solution of KOH at −78 °C. Nucleophilic attack of $[OH]^-$ at the highly electrophilic carbon in $H_3BCO$ leads to the formation of **2** in high yield.[8] If required, $H_3BCO$ itself can be isolated in a cold trap at −78 °C. This novel preparation of **2** and **3** is more convenient than the high pressure or ether-catalyzed procedures (Scheme 1) and can be scaled up to quantities of several grams of $H_3BCO$ or $K_2[H_3BCO_2]$, respectively.

It is remarkable that the characteristics of **3** bear strong resemblance to those of cationic transition-metal carbonyls such as $[Ru(OH_2)_3(CO)_3]^{2+}$ which also often reversibly add $[OH]^-$ to coordinated CO with formation of the corresponding metallocarboxylic acids.[9] The reactivity of **3** toward water can thus be paralleled with highly Lewis acidic transition metals, a rare behavior for main group carbonyl compounds. Hence, compound **2** would probably better be attributed as a boranocarboxylate; however, electron count of "$BH_3$" and "O" accounts for the origin of boranocarbonate.

Crystals[10] of $[K(cryptand)]H_3BCO_2H$ **4** were obtained after dissolution of **2** in a THF solution of the cryptand 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane. The structure of the anion, which forms hydrogen-bonded dimers, is shown in Figure 1. The hydrogen atoms of the boranocarbonate anion were located and fully refined, while those of the cryptand ligand were treated with a riding model. The structure of the anion pair is remarkably similar to the gas-phase dimeric structure of acetic acid:[12,13] hence, the C═O distance is 1.251(3) Å (cf. 1.25(3) Å in acetic acid) and the C−O distance is 1.356(3) Å (cf. 1.36(4)

---

[*] Author for correspondence. E-mail: ariel@aci.unizh.ch.

[†] University of Zürich.

[‡] Paul Scherrer Institute.

(1) (a) Waibel, R.; Alberto, R.; Willuda, J.; Finnern, R.; Schibli, R.; Stichelberger, A.; Egli, A.; Abram, U.; Mach, J.-P.; Plueckthun, A.; Schubiger, P. A. *Nature Biotechnol.* **1999**, *17*, 897−901. (b) Alberto, R.; Schibli, R.; Abram, U.; Johannsen, B.; Pietzsch, H.-J.; Schubiger, P. A. *J. Am. Chem. Soc.* **1999**, *25*, 6076−6077. (c) Hoepping, A.; Reisgys, M.; Brust, P.; Seifert, S.; Spies, H.; Alberto, R.; Johannsen, B. *J. Med. Chem.* **1998**, *41*, 4429−4432.

(2) (a) Alberto, R.; Schibli, R.; Waibel, R.; Abram, U.; Schubiger, P. A. *Coord. Chem. Rev.* **1999**, *190−192*, 901−919. (b) Schibli, R.; Katti, K. V.; Higginbotham, C.; Volkert, W. A.; Alberto, R. *Nucl. Med. Biol.* **1999**, *26*, 711−716. (c) Egli, A.; Alberto, R.; Tannahill, L.; Schibli, R.; Abram, U.; Schaffland, A.; Waibel, R.; Tourwe, D.; Jeannin, L.; Iterbeke, K.; Schubiger, P. A. *J. Nucl. Med.* **1999**, *40*, 1913−1917.

(3) Alberto, R.; Schibli, R.; Egli, A.; Abram, U.; Kaden, Th. A.; Schubiger, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 7987−7988.

(4) Although homoleptic metal−carbonyl complexes fulfill some of these conditions, they are not suitable for our purposes, as the metal would later compete with the technetium for the biomolecule.

(5) (a) Malone, L. J.; Parry, R. W. *Inorg. Chem.* **1967**, *6*, 817−822. (b) Malone, L. J.; Manley, M. R. *Inorg. Chem.* **1967**, *6*, 2260−2262.

(6) Carter, J. C.; Parry, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 2354−2358.

(7) Mayer, E. *Monatsh. Chem.* **1971**, *102*, 940−945.

(8) Carbon monoxide was slowly bubbled through 30 cm$^3$ of a 1 M $H_3B{\cdot}THF$ solution. The gas stream was passed over a reflux condenser at −50 °C and then bubbled through a solution of 2.8 g KOH in 200 cm$^3$ ethanol in a Schlenk tube at −78 °C. After 2 h the Schlenk tube was disconnected and heated to reflux for about 1 h. **2** precipitates as a white solid in large amounts and was filtered and washed with cold ethanol and diethyl ether to yield 1.26 g (43%) of analytically pure product. $\delta_H$ (200 MHz, $D_2O$, 25 °C) 0.80 (1:1:1:1 quartet, $^1J(^1H-^{11}B) = 80$ Hz; 1:1:1:1:1:1:1 septet, $^1J(^1H-^{10}B) = 27$ Hz). $\delta_C$ (50 MHz, $D_2O$, 25 °C) 215.4 (1:1:1:1 quartet, $^1J(^{13}C-^{11}B) = 64$ Hz. $\delta_B$ (160 MHz, $D_2O$, 25 °C) −33.8. Other properties as in ref 5a.

(9) Funaioli, T.; Cavazza, C.; Marchetti, F.; Fachinetti, G. *Inorg. Chem.* **1999**, *38*, 3361−3368.

(10) Crystal data for **4**: colorless blocks, triclinic space group $P\bar{1}$, $T = 183$ K, $a = 11.1315(11)$ Å, $b = 11.4183(11)$ Å, $c = 12.4438(13)$ Å, $\alpha = 106.269(12)°$, $\beta = 105.153(12)°$, $\gamma = 111.573(11)°$, $Z = 2$, R1 = 0.0448, wR2 = 0.0988, GOF = 0.821, structure solution (direct) with SHELXS97, full-matrix least squares refinement on $F^2$ (SHELXL97).[11]

(11) Sheldrick, G. M. *SHELXS97*, University of Göttingen, 1990. Sheldrick, G. M. *SHELXL97*, University of Göttingen, 1997. Zsolnai, L.; Huttner, G. *ZORTEP*, University of Heidelberg, 1994.

(12) Karle, J.; Brockway, L. O. *J. Am. Chem. Soc.* **1944**, *66*, 574−584.

10.1021/ja003932b CCC: $20.00

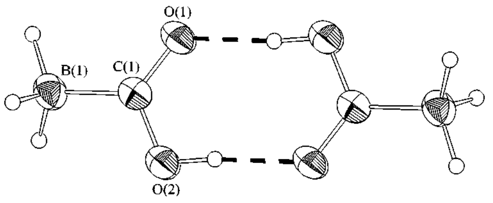
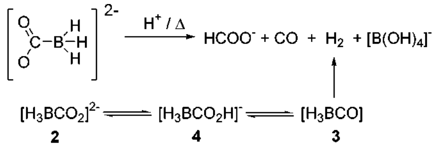


**Figure 1.** ZORTEP[11] representation of two anions of **4**, forming a hydrogen-bonded dimer. Selected bond lengths [Å] and angles [deg]: B(1)−C(1) 1.602(4), C(1)−O(1) 1.251(3), C(1)−O(2) 1.356(3), O(1)−C(1)−O(2) 116.9(2), O(2)−H(4) 0.94(3), O(2)−O(1)′ 2.730(2), O(2)−H(4)−O(1)′ 173(3).

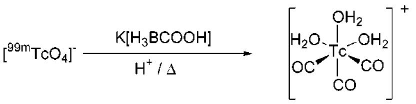
### Scheme 2



Å in acetic acid). Similar dimeric structures are formed by the related compounds $H_3NH_2BCO_2H$[14] and $Me_3NH_2BCO_2H$.[15] The aforementioned metallocarboxylic acids also very often exist in the solid state as hydrogen-bridged dimers.[16]

Aqueous solutions of **2** are strongly alkaline (pH > 11) and quite stable toward heating, but the addition of a borate buffer (pH 9.4−10.4 at 25 °C) allows the observation of the decomposition with half-lives in the order of tens of minutes at 75−90 °C at a nominal pH 10. The only boron-containing product is borate as observed by $^{11}B$ NMR. The production of formate is observed at temperatures above 85 °C, at a rate roughly one-quarter of that of the disappearance of boranocarbonate: otherwise, the only carbon-containing product is carbon monoxide. Although the precise mechanism of formate formation is still unclear, it is likely that it results from intramolecular hydride transfer from boron to carbon. Correspondingly, dihydrogen is produced by protonation of other boranes in the mixture by formic acid. The important reaction beside formation of formate is of course the formation of **3**. Borane carbonyl is indeed formed when boranocarbonate salts are treated with strong acids. We believe that it is also the important intermediate product during decomposition of boranocarbonate in alkaline solution (Scheme 2). $H_3BCO$ is known to be kinetically labile, especially in the absence of carbon monoxide: given the low solubility of carbon monoxide in water (17.74 $\mu$mol $dm^{-3}$ at 25 °C)[18] it is highly likely that any dissociation of $H_3BCO$ in aqueous solution would lead to

### Scheme 3



hydrolysis of the borane portion rather than recombination with carbon monoxide.

Kinetic measurements in buffered solutions show a second-order dependence of the rate of boranocarbonate decomposition on proton concentration. The activation parameters are $\Delta H^{\ddagger}_{353} = +13.4(12)$ kJ $mol^{-1}$, $\Delta S^{\ddagger}_{353} = -121(29)$ $kJ^{-1}$ $mol^{-1}$. The enthalpy of activation may be compared to that of O−H bond cleavage in water.[17] Further details of the kinetic and mechanistic studies, and of the coordination chemistry of the boranocarbonate ion, will be reported separately.

Compound **2** is unique in the sense that it combines the possibility of in situ CO formation and reducing properties. We transferred these features to an improved one-pot synthesis of $[^{99m}Tc(OH_2)_3(CO)_3]^+$ without the necessity of an additional reducing agent or of gaseous CO. In fact, a small amount of **2** dissolved in a few ml of aqueous $[^{99m}TcO_4]^-$ gave **1** in yields of >98% after 10 min at 90 °C.[19] Thus, $K_2H_3BCO_2$ can clearly reduce technetium(VII) to technetium(I). The exact mechanism of this surprisingly convenient synthesis of a carbonyl complex remains unclear. However, the low concentrations of CO ($<10^{-5}$ M) and $^{99m}Tc$ ($<10^{-6}$ M) as good as exclude any stepwise mechanism of reduction followed by CO coordination to a hypothetical $[^{99m}Tc(OH_2)_6]^+$ intermediate: the rate constant would be higher than the diffusion limit. Only the concentration of **2** itself is high enough for reaction with $^{99m}Tc$ to occur at a reasonable rate. This implies that **2** "transports" the CO to the metal center, and that CO release and coordination takes place in the same reaction step at the metal. Therefore, in the preparation of $[Tc(OH_2)_3(CO)_3]^+$, potassium boranocarbonate **2** can replace the sodium borohydride and gaseous CO used in the previously described procedure (Scheme 3).

In conclusion, compound **2** represents a unique and synthetically extremely useful combination of moderately powerful reducing agent and in situ CO source in aqueous solution. In conjunction with a suitable buffer (Borax) and a complexing agent for technetium in intermediate oxidation states (tartrate), it can be used to prepare the water-soluble, and water-stable, technetium carbonyl complex $[^{99m}Tc(OH_2)_3(CO)_3]^+$ **1**. Apart from the illustrative preparation of complex **1**, it is expected that compound **2** can not only be used for the preparation of technetium carbonyls in water but also for other metal carbonyl complexes.

**Acknowledgment.** The authors thank Mallinckrodt Med. for financial support

**Supporting Information Available:** Tables of crystallographic data (PDF). An X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA003932B

---

(13) On the other hand, acetic acid has a chain structure in the solid state. Jones, R. E.; Templeton, D. H. *Acta Crystallogr.* **1958**, *11*, 484−487.

(14) Spielvogel, B. F.; Das, M. K.; McPhail, A. T.; Onan, K. D.; Hall, I. H. *J. Am. Chem. Soc.* **1980**, *102*, 6343−6344.

(15) Spielvogel, B. F.; Wojnowich, L.; Das, M. K.; McPhail, A. T.; Hargrave, K. D. *J. Am. Chem. Soc.* **1976**, *98*, 5702−5703.

(16) (a) Bennett, M. A.; Jin, H.; Willis, A. C. *J. Organomet. Chem.* **1993**, *451*, 249−256. (b) Gibson, D. H.; Ding, Y., Andino, J. G.; Mashuta, M. S.; Richardson, J. F. *Organometallics* **1998**, *17*, 5178−5183. (c) Gibson, D. H. *Chem. Rev.* **1996**, *96*, 2063−2095.

(17) The proton concentration in pure water increases with increasing temperature because of the change in $K_w$. Data were taken from ref 18 and corrected for the change in molar volume.

(18) *Handbook of Chemistry and Physics*, 80th ed.; CRC Press: Boca Raton, 1999.

(19) 2 $cm^3$ of a $[^{99m}TcO_4]^-$ generator eluate (0.9% saline) was injected into a 10 $cm^3$ vial containing potassium boranocarbonate (3 mg), sodium potassium tartrate (5 mg), and potassium tetraborate tetrahydrate (5.5 mg) under $N_2$ and heated to 95 °C for 20 min. After cooling, the solution was neutralized with phosphate buffer. According to HPLC, the radiochemical purity of the product is better than 98%.