Inorganica Chimica Acta, 151 (1988) 87–88

A Convenient Method for the Preparation of Antitumor Carboxylato(1,2-diaminocyclohexane)platinum(II) Complexes

ABDUL R. KHOKHAR*, GREGG LUMETTA and
SHERYL L. DORAN

*Department of Medical Oncology, The University of Texas
M. D. Anderson Hospital and Tumor Institute at Houston,
Houston, Tex. 77030, U.S.A.*

(Received August 31, 1987)

In recent years there has been a great deal of effort devoted to developing analogues of the antitumor agent *cis*-dichlorodiammineplatinum(II) (cis-DDP), that would overcome the problems associated with the use of cis-DDP (e.g., host toxicity and resistance to cis-DDP) [1]. Our research group has focused our work on various carboxylato(amine)platinum(II) complexes [2]. During the course of these studies we developed a simple method for preparing such complexes. This method involves the direct reaction of a carbonato(amine)platinum(II) complex with the desired carboxylic acid. This method is outlined here.

Nyman *et al.* [3] reported that $[Pt(CO_3)(PPh_3)_2]$ reacts with R–COOH (R = Me, CF_3, or Ph) to give $[Pt(OCOR)_2(PPh_3)_2]$. We attempted to extend this method to the preparation of platinum(II) amine complexes containing carboxylate ligands. The complex $[Pt(CO_3)(DACH)]$ (DACH = 1,2-diaminocyclohexane) can be prepared via the reaction of $[PtCl_2(DACH)]$ with silver carbonate, as shown below (eqn. (1))

$$[PtCl_2(DACH)] + Ag_2CO_3 \longrightarrow [Pt(CO_3)(DACH)] + 2AgCl \qquad (1)$$

The reaction is carried out in an aqueous solution in a nitrogen atmosphere with the flask protected from light.

In a typical preparation, $[PtCl_2(DACH)]$ (0.46 g, 1.2 mmol) and Ag_2CO_3 (1.0 g, 3.6 mmol) were mixed together in water in a darkened flask in a nitrogen atmosphere. After stirring for 24 h, the AgCl was filtered, and the solution was lyophilized and gave off-white $[Pt(CO_3)(DACH)]$. This complex was purified from methanol and dried *in vacuo* (yield 50%). *Anal.* Calc. for $C_7H_{14}N_2O_3Pt \cdot 2H_2O$: C, 20.74; H, 4.49; N, 6.91. Found: C, 21.11; H, 4.28; N, 6.99%. This carbonate complex has been characterized by infrared spectroscopy. The infrared spectrum (KBr) exhibits three strong bands in the CO stretching region (1600, 1490, and 1330 cm^{-1}). Such a pattern is neither indicative of a unidentate or bidentate coordination of a carbonate ligand [4], so a precise structure for this molecule cannot be assigned at this point.

$[Pt(CO_3)(DACH)] \cdot 2H_2O$ reacts with monocarboxylic or dicarboxylic acids to form carboxylato(DACH)platinum(II) complexes, according to eqn. (2)

$$[Pt(CO_3)(DACH)] + 2RCOOH \longrightarrow [Pt(OCOR)_2(DACH)] + H_2O + CO_2\uparrow \qquad (2)$$

This provides a very clean route to such carboxylato(DACH)platinum(II) complexes, since the carboxylato complex is the only product of the reaction. The carbonic acid formed decomposes to water and carbon dioxide, which is given off as a gas. The preparation of [Pt(mal)(DACH)] (mal = malonate) in this manner is described here as an example.

$[Pt(CO_3)(DACH)] \cdot 2H_2O$ (0.3407 g, 0.841 mmol) was dissolved in water and malonic acid (0.0873 g, 0.841 mmol) was added. During the course of the reaction, carbon dioxide was evolved. After stirring for 30 min, the solution was evaporated to dryness under reduced pressure using a rotary evaporator to give a white crystalline solid. This was washed with cold water then ethanol and dried *in vacuo* to give [Pt(mal)(DACH)] (0.25 g, 69%). *Anal.* Calc. for $C_9H_{16}N_2O_4Pt \cdot H_2O$: C, 25.17; H, 4.19; N, 6.81. Found: C, 25.36; H, 3.84; N, 6.48%. Infrared spectrum (KBr): ν(C=O) 1665 and 1630 cm^{-1}, ν(C–O) 1380 cm^{-1}.

$[Pt(CBDCA)(DACH)] \cdot H_2O$ (CBDCA = 1,1-cyclobutanedicarboxylate) has also been prepared by this method. *Anal.* Calc. for $C_{12}H_{20}N_2O_4Pt \cdot H_2O$: C, 30.70; H, 4.69; N, 5.97%. Found: C, 31.10; H, 4.70; N, 5.99%. Infrared spectrum (KBr): ν(C=O) 1615 cm^{-1}, ν(C–O) 1372 cm^{-1}.

To summarize, we have demonstrated that $[Pt(OCOR)_2(DACH)]$ complexes can be synthesized via the reaction of the carbonate complex $[Pt(CO_3)(DACH)]$ with carboxylic acids. This method is advantageous because it avoids the presence of coproducts in the reaction mixture, since the carbonic acid formed decomposes to carbon dioxide and water.

Acknowledgement

This work was supported by grant CA 41581 from the National Cancer Institute.

---

*Author to whom correspondence should be addressed.

0020-1693/88/$3.50

References

1 M. P. Hacker, E. B. Douple and I. H. Krakoff (eds.), in 'Platinum Coordination Complexes in Cancer Chemotherapy', Martin Nijhoff, Boston, 1984.

2 A. R. Khokhar, I. H. Krakoff, M. P. Hacker and J. J. McCormak, *Inorg. Chim. Acta, 108*, 63 (1985).

3 C. J. Nyman, C. E. Wymore and G. Wilkinson, *J. Chem. Soc. A,* 561 (1968).

4 K. Nakamoto, 'Infrared and Raman Spectra of Inorganic and Coordination Compounds', 3rd edn., Wiley, New York, 1978, p. 243.