A New Synthetic Method for Diaminomalonatoplatinum Type Complexes and the Unexpected Behaviour of [$PtCl_2$(*trans*-dach)]

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Malonato, or 2-substituted malonato (Mal)** diaminoplatinum complexes are a class of second-generation cisplatin analogues [1, 2] which are being studied extensively because of the interesting biological properties conferred to the complexes by these leaving groups [1–3]. One of these complexes, namely carboplatin, has recently been granted a product licence in some countries [1].

These complexes can be synthesized in aqueous media by either routes (i) or (ii) [4]:

(i) *cis*-$[PtI_2A_2] \xrightarrow{AgNO_3}$ *cis*-$[PtA_2(H_2O)_2](NO_3)_2 \xrightarrow{M_2Mal}$ $[PtA_2Mal]$

(ii) *cis*-$[PtI_2A_2] \xrightarrow{Ag_2SO_4}$ *cis*-$[PtA_2SO_4]^{\dagger} \xrightarrow{BaMal}$ $[PtA_2Mal]$

In both routes, however, solubility problems often make working up tedious. There is therefore a need for an alternative preparative procedure for these complexes. We now report that $[PtA_2Mal]$ can be obtained via a general route which involves reaction of *cis*-$[PtCl_2A_2]$ with M_2Mal in DMF.

Typical Procedure. Preparation of Carboplatin

cis-$[PtCl_2(NH_3)_2]$ (0.4002 g) was dissolved with heating in 20 ml of DMF and 0.1950 g of 1,1-cyclobutanedicarboxylic acid was added to this solution, followed by 26.8 ml of 0.1 N aqueous KOH. The solution was heated in an unstoppered flask at 60 °C for 20 h, cooled and filtered. Addition of ether gave carboplatin in 70% yield (based on cisplatin). Alternatively the solution was concentrated *in vacuo* to about 2 ml giving the 1:1 DMF adduct†† of carboplatin in 80% yield.

With minor differences in the working up, this procedure works successfully both for other $MalH_2$ (malonic, 2-hydroxy-, and 2-ethylmalonic acids) and for other amines or diamines. LiOH or NaOH can also be used. *cis*-$[PtI_2(NH_3)_2]$ gave carboplatin in only 40% yield. The use of DMA as a solvent also produced low (35%) yields. Typical yields are presented in Table I. The compounds were characterized by elemental analysis (C, H, N, Pt) and by comparison of their mass-FAB and infrared spectra with those of samples prepared by traditional methods. In particular, the presence of ν(C=O) in the 1670–1620 cm^{-1} region is in agreement with the coordinated nature of the carboxylato ligand.

TABLE I. Typical Yields for the Preparation of Diaminomalonatoplatinum from the Corresponding Dichloro Complexes in DMF

A_2	$MalH_2$	MOH	Yields (%)[a]
$(NH_3)_2$	CBDCA	LiOH	65
		KOH	80
	malonic acid	KOH	50
	hydroxymalonic acid	KOH	50
en	CBDCA	KOH	50
	malonic acid	NaOH	60
cis-dach	CBDCA	KOH	55
trans-dach	CBDCA	any	<20[b]
	malonic acid	KOH	<20[b]
NNO	CBDCA	KOH	60

[a]Based on the starting diaminodichloro complex. [b]Approximate, see text.

One interesting aspect emerging from this investigation is the different reactivities displayed by [$PtCl_2$(*trans*-dach)] and [$PtCl_2$(*cis*-dach)]. In fact under our conditions only the latter gave the expected product with coordinated Mal, whereas with the *trans*-dach derivative a mixture of products, with a predominance of the ionic species [Pt(*trans*-dach)$(H_2O)_2$](mal) (ν(COO) 1590 and 1410 cm^{-1}), was obtained. Different reactivities of these two isomeric platinum complexes have been observed in other instances, such as in their reaction with d(GpG) [7] or with Me_2SO [8], and have been attributed to the

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**Abbreviations: cisplatin, *cis*-diamminodichloroplatinum(II); carboplatin, diammino(1,1-cyclobutanedicarboxylate)-platinum(II); $MalH_2$, malonic, or 2-substituted malonic acids; CBDCA, 1,1-cyclobutanedicarboxylic acid; A, amine, or 1/2 diamine; dach, 1,2-diaminocyclohexane; en, 1,2-ethylenediamine; NNO, *N*-(2-hydroxyethyl)-1,2-ethylenediamine; M, alkali metal.

†This formula stands for a diaminosulphato Pt complex and it is not a description of its structure, see ref. 5.

††The presence of solvated, rather than coordinated, DMF in this sample was confirmed by comparison of its infrared spectrum with that of other DMF adducts [6].

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different steric hindrance exhibited by the two ligands [7–9]. Alternative explanations, however, involving different solvation or the conformational freedom of the chelate ring of the *cis*-dach complexes (as opposed to the rigidity of the *trans*-dach case) [10] can also be put forward. These different reactivities may also be related to the different biological properties displayed by the two isomeric dach–Pt complexes [7, 11].

Work is in progress to elucidate the different reactivities of various Pt complexes with diastereoisomeric diamines.

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References

1 C. F. J. Barnard, M. J. Cleare and P. C. Hydes, *Chem. Br., 22,* 1001 (1986).
2 A. Pasini and F. Zunino, *Angew. Chem., 99,* 632 (1987); *Angew. Chem., Int. Ed. Engl., 26,* 615 (1987).
3 For instance, S. K. Mauldin, I. Husain, A. Sancar and S. G. Chaney, *Cancer Res., 46,* 2876 (1986).
4 R. C. Harrison, C. A. McAuliffe and A. M. Zaki, *Inorg. Chim. Acta, 46,* L15 (1980).
5 T. G. Appleton, R. D. Berry, C. A. Davis, J. R. Hall and H. A. Kimlin, *Inorg. Chem., 23,* 3515 (1984); H. A. Meinema, F. Verbeek, J. W. Marsman, E. J. Bulten, J. C. Dabrowiak, B. S. Krishnam and A. L. Spek, *Inorg. Chim. Acta, 114,* 127 (1986).
6 G. Raudaschl, B. Lippert and J. D. Hoeschele, *Inorg. Chim. Acta, 78,* L43 (1983); G. Raudaschl, B. Lippert, J. D. Hoeschele, H. E. Howard-Lock, C. J. L. Lock and P. Pilon, *Inorg. Chim. Acta, 106,* 141 (1985).
7 K. Inagaki and Y. Kidani, *Inorg. Chem., 25,* 1 (1986).
8 G. Natile and F. P. Fanizzi, personal communication.
9 M. Noji, K. Okamoto and Y. Kidani, *J. Med. Chem., 24,* 508 (1981); J. F. Vollano, S. Al-Baker, J. C. Dabrowiak and J. E. Schurig, *J. Med. Chem., 30,* 716 (1987).
10 E. Cesarotti, M. Gullotti, A. Pasini and R. Ugo, *J. Chem. Soc., Dalton Trans.,* 757 (1977); M. Gullotti, G. Pacchioni, A. Pasini and R. Ugo, *Inorg. Chem., 21,* 2006 (1982).
11 W. R. Leopold, R. P. Batzinger, E. C. Miller and R. H. Earhart, *Cancer Res., 41,* 4368 (1981); F. P. Fanizzi, F. P. Intini, L. Maresca, G. Natile, R. Quaranta, M. Coluccia, L. Di Bari, D. Giordano and M. A. Mariggió, *Inorg. Chim. Acta, 137,* 45 (1987).