Available online at www.sciencedirect.com
SCIENCE DIRECT®
J. Chem. Thermodynamics 36 (2004) 321–323
JCT
www.elsevier.com/locate/jct

Energetics of the interaction of the antitumour agent titanocene dichloride with glycine: enthalpy of formation of $[Ti(\eta^5\text{-}C_5H_5)_2(OOCCH_2NH_3)_2]Cl_2$

Paulo M. Nunes [a,b], Manuel E. Minas da Piedade [a,c,*]

[a] *Centro de Química Estrutural, Complexo Interdisciplinar, Instituto Superior Técnico, 1049-001 Lisboa, Portugal*
[b] *Escola Superior Agrária de Santarém, Sector de Química, Quinta do Galinheiro, Apartado 310, 2001-904 Santarém, Portugal*
[c] *Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal*

Received 4 July 2003; accepted 8 January 2004

Abstract

The standard molar enthalpy of formation of $[Ti(\eta^5\text{-}C_5H_5)_2\ (OOCCH_2NH_3)_2]Cl_2$ in the crystalline state, at $T = 298.15$ K, was determined as $\Delta_f H^\circ_m\{[Ti(\eta^5\text{-}C_5H_5)_2(OOCCH_2NH_3)_2]Cl_2, cr\} = -(1447.6 \pm 8.1)\ kJ \cdot mol^{-1}$, by reaction-solution calorimetry. A discussion of the energetics of the direct interaction of the antitumour agent $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ with glycine is also presented.

Keywords: Enthalpy of formation; Thermochemistry; Reaction-solution calorimetry; Antitumour agents; Metallocenes

1. Introduction

Some metallocene dichloride complexes of the early transition metals, $M(\eta^5\text{-}C_5H_5)_2Cl_2$ (M = Ti, V, Nb, Mo), have been extensively studied as potential antitumour agents [1,2]. The titanium derivative, $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$, in particular, has proved to be one of the most efficient complexes of this type against a variety of tumours [1–5], and it is the first complex of a transition metal other than platinum to have been introduced into phase II clinical trials [4–6]. In a number of cases titanocene dichloride was found to be at least as active and less toxic than cisplatin, *cis*-$[Pt(NH_3)_2Cl_2]$, a drug that has been used in the treatment of several types of human cancer for the last 25 years [1]. However, in contrast to the well-characterised platinum-based anticancer drugs, the active species responsible for the antitumour properties of $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ *in vivo* has not been identified, and the mechanism for the therapeutic action of metallocenes is poorly understood [4,5]. It has nevertheless, been established that the titanium species is carried into the cells upon intravenous administration, thus suggesting that, *in vivo*, $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ may be stabilised by interaction with a biomolecule. Proteins or enzymes that are relevant for the function and synthesis of nucleic acids have been considered possible binding targets for the titanocene dichloride [4–6]. This fostered the synthesis of a number of model complexes, $[Ti(\eta^5\text{-}C_5H_5)_2(aa)_2]Cl_2$ (aa = α-amino-acid), aiming to gain insight into the reactivity of $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ towards biological molecules that possess both oxygen and nitrogen donor groups [7–9]. These complexes have also been found to exhibit antitumor activity, although less pronounced than that of the parent $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ [6].

In this paper, we report the determination of the standard enthalpy of formation of the glycine containing complex $[Ti(\eta^5\text{-}C_5H_5)_2(OOCCH_2NH_3)_2]Cl_2$ in the crystalline state, by reaction-solution calorimetry. Based on this result, the energetics of the direct interaction of $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ with glycine is discussed, in light of a possible *in vivo* stabilisation and transport of the metallocene dichloride, through the formation of a carboxylate coordinated $[Ti(\eta^5\text{-}C_5H_5)_2(protein)]$ species.

* Corresponding author. Fax: +351-21-7500088.
E-mail address: memp@fc.ul.pt (M.E. Minas da Piedade).

0021-9614/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jct.2004.01.002

2. Experimental

Elemental analyses were made with a Fisions Instruments EA1108 apparatus. The FT-IR spectra were carried out in a Jasco 430 spectrophotometer calibrated with polystyrene film. The UV–Vis spectra were recorded in a Jasco V530 instrument. The ^{1}H NMR spectra were obtained at ambient temperature on a Varian 300 MHz spectrometer.

$Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ (Aldrich, mass fraction 0.97) was sublimed prior to use. Glycine (Aldrich, mass fraction >0.985) was dissolved in water at 298 K, precipitated upon addition of ethanol, and dried in vacuum at 133.3 Pa and 303 K. The $[Ti(\eta^5\text{-}C_5H_5)_2(OOCCH_2NH_3)_2]Cl_2$ used in the calorimetric studies was prepared according to the following procedure, which was adapted from the literature [6–8]. A suspension of $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ (2.003 g, 8.05 mmol) and glycine (1.19 g, 15.9 mmol) in 12 cm^3 of methanol (José Manuel Gomes dos Santos, mass fraction 0.995) was kept under magnetic stirring inside a Schlenk tube, under nitrogen atmosphere, during 5 h, at 284 K. The precipitated orange solid was filtered off, washed 10 times with 5 cm^3 of chloroform (Pronalab, mass fraction 0.99) to remove any remaining $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$, then five times with 5 cm^3 of methanol, and finally dried in vacuum at 133.3 Pa and 303 K. The mass fractions of C, H, and N in $TiC_{14}H_{20}N_2O_4Cl_2$, obtained by elemental analysis were: calculated C, 0.4213; H, 0.0505; N, 0.0702; found C, 0.4218; H, 0.0508; N, 0.0696 (average of two measurements). The ^{1}H NMR spectrum in D_2O was as follows (chemical deviations, δ, relative to tetramethylsilane and using water as the internal standard): δ/ppm = 6.60 (s, C_5H_5); 3.70 (s, CH_2). The UV–Vis spectrum in distilled and deionised water showed a local maximum at $\lambda = 372$ nm, the intensity increasing sharply for shorter wavelengths due to the charge transfer transitions typical of bis(cyclopentadienyl) complexes. The main peaks in the infrared (IR) spectrum, in KBr were: $\bar{\nu}/cm^{-1} = 3425$ ms, 3080 ms, 1673 vs, 1442 m, 1129 ms, 840 s. The ^{1}H NMR, UV–Vis and IR results are in good agreement with those published in the literature [7,8].

The reaction-solution calorimetric experiments were performed using the apparatus previously described [10,11]. The calorimetric solvent was an $HCl \cdot 3.45H_2O$ aqueous solution (Panreac p.a.). In a typical experiment the sample was sealed in a thin walled glass ampoule and weighed to $\pm 10^{-5}$ g on a Mettler AT201 balance. The reaction or solution process under study was started by breaking the glass ampoule in 125 cm^3 of the calorimetric solvent. This was preceded by an electrical calibration, in which a potential difference of ca. 2.6 V was applied to a 48 Ω resistance during ca. 200 s.

The final state of the reaction of $[Ti(\eta^5\text{-}C_5H_5)_2(OOCCH_2NH_3)_2]Cl_2$ with concentrated hydrochloric acid ($HCl \cdot 3.45H_2O$, Panreac p.a.), in conditions as similar as possible to those of the reaction-solution calorimetric experiments, was determined by UV–Vis spectroscopy. A volume of 2.5 cm^3 of $HCl \cdot 3.45H_2O$ was added to 2.5 cm^3 of a $1.211 \cdot 10^{-2}$ mol · dm^{-3} aqueous solution of $[Ti(\eta^5\text{-}C_5H_5)_2(OOCCH_2NH_3)_2]Cl_2$. The visible spectrum of the resulting mixture matched that of a stoichiometrically identical solution of $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ and glycine in $HCl \cdot 3.45H_2O$.

3. Results and discussion

The standard atomic masses recommended by the IUPAC Commission in 2001 were used in the calculation of all molar quantities [12].

Reaction-solution calorimetric measurements of the enthalpies of the reactions

$$[Ti(\eta^5\text{-}C_5H_5)_2(OOCCH_2NH_3)_2]Cl_2\,(cr) + 2HCl \cdot 3.45H_2O\,(aq) = Ti(\eta^5\text{-}C_5H_5)_2Cl_2\,(cr) + 2HOOCCH_2NH_3Cl\,(aq) \quad (1)$$

$$HOOCCH_2NH_2\,(cr) + HCl \cdot 3.45H_2O\,(aq) = HOOCCH_2NH_3Cl\,(aq) \quad (2)$$

led to the results in tables 1 and 2, from which $\Delta_r H^\circ_m(1) = -(26.7 \pm 2.3)$ kJ · mol^{-1} and $\Delta_r H^\circ_m(2) = -(18.04 \pm 0.86)$ kJ · mol^{-1} were derived. The uncertainties quoted represent twice the standard deviation of the mean.

In the UV–Vis spectroscopy experiments carried out to determine the final state of reaction (1) it was found that $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ was very slightly soluble in $HCl \cdot 3.45H_2O$ (see Section 2). However, breaking ampoules containing stoichiometric amounts of this complex in $HCl \cdot 3.45H_2O$ led to $\Delta_{sol}H^\circ_m = 0$ within the experimental error. This indicated that the enthalpic effect associated with the presence of an insignificant amount of $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ in solution at the end of reaction (1) could be neglected and the complex assumed to be formed in the crystalline state.

TABLE 1
Results of the calorimetric study of reaction (1)

m^a/g	ε^b / (J · K^{-1})	$\Delta T_{ad}{}^c$/K	$-\Delta_r H^\circ_m(1)^d$ / (kJ · mol^{-1})
0.11893	432.52	0.0173	25.11
0.09935	436.88	0.0171	30.01
0.11549	437.77	0.0170	25.72
0.13153	436.96	0.0181	24.00
0.06709	432.12	0.0112	28.79

[a] Mass of $[Ti(\eta^5\text{-}C_5H_5)_2(OOCCH_2NH_3)_2]Cl_2$.
[b] Energy equivalent of the reaction-solution calorimeter.
[c] Adiabatic temperature change.
[d] Standard molar enthalpy of reaction (1).

TABLE 2
Results of the calorimetric study of reaction (2)

m^a/g	ε^b / (J · K^{-1})	$\Delta T_{ad}{}^c$/K	$-\Delta_r H_m^\circ(2)^d$ / (kJ · mol^{-1})
0.04372	421.23	0.0239	17.29
0.04505	426.67	0.0252	17.92
0.04323	438.84	0.0253	19.28
0.04380	413.51	0.0240	17.01
0.04289	435.83	0.0227	17.32
0.04280	442.13	0.0250	19.39

[a] Mass of glycine.
[b] Energy equivalent of the reaction-solution calorimeter.
[c] Adiabatic temperature change.
[d] Standard molar enthalpy of reaction (2).

Based on the $\Delta_r H_m^\circ(1)$ and $\Delta_r H_m^\circ(2)$ values indicated above it was possible to derive the enthalpy of the standard state reaction:

$$\mathrm{Ti(\eta^5\text{-}C_5H_5)_2Cl_2\ (cr) + 2HOOCCH_2NH_2\ (cr) = [Ti(\eta^5\text{-}C_5H_5)_2(OOCCH_2NH_3)_2]Cl_2\ (cr)} \quad (3)$$

as $\Delta_r H_m^\circ(3) = -(9.4 \pm 2.9)$ kJ · mol^{-1}. Using $\Delta_f H_m^\circ$ [Ti(η^5-C_5H_5)$_2$Cl$_2$, cr] = −(383.2 ± 7.5) kJ · mol^{-1} [13] and $\Delta_f H_m^\circ$ (HOOCCH$_2$NH$_2$, cr) = −(527.5 ± 0.5) kJ · mol^{-1} [14], it is finally concluded that $\Delta_f H_m^\circ$ {[Ti(η^5-C_5H_5)$_2$-(OOCCH$_2$NH$_3$)$_2$]Cl$_2$, cr} = −(1447.6 ± 8.1) kJ · mol^{-1}.

The analysis of the energetics of reaction (3) indicates that, at least in the solid state, there is a slightly favourable (−9.4 kJ · mol^{-1}) enthalpic interaction between Ti(η^5-C_5H_5)$_2$Cl$_2$ and glycine. The fact that this interaction is weak supports the observation that the aminoacid ligands in the complex rapidly dissociate in water and in the presence of nucleotides. It also supports the suggestion that the *in vivo* stabilisation of titanocene dichloride through the formation of a carboxylate coordinated [Ti(η^5-C_5H_5)$_2$(protein)] species may not occur [4].

Acknowledgements

This work was supported by Fundação para a Ciência e Tecnologia (Project POCTI/199/QUI/35406).

References

[1] I. Haiduc, C. Silvestru, Coord. Chem. Rev. 99 (1990) 253–290.
[2] P. Kopf Maier, in: B.K. Keppler (Ed.), Metal Complexes in Cancer Chemotherapy, VCH, Weinheim, 1993, pp. 259–296.
[3] P. Kopf Maier, Eur. J. Clin. Pharmacol. 47 (1994) 1–16.
[4] M.M. Harding, G. Mokdsi, Curr. Med. Chem. 7 (2000) 1289–1303.
[5] E. Meléndez, Crit. Rev. Oncol. Hemat. 42 (2002) 309–315.
[6] P. Kopf Maier, I.C. Tornieporth-Oetting, Biometals 9 (1996) 267–271.
[7] T.M. Klapötke, H. Köpf, I.C. Tornieporth-Oetting, P.S. White, Angew. Chem. Int. Ed. Engl. 33 (1994) 1518–1519.
[8] T.M. Klapötke, H. Köpf, I.C. Tornieporth-Oetting, P.S. White, Organometallics 13 (1994) 3628–3633.
[9] I.C. Tornieporth-Oetting, P.S. White, Organometallics 14 (1995) 1632–1636.
[10] H.P. Diogo, M.E. Minas da Piedade, J.J. Moura Ramos, J.A. Simoni, J.A. Martinho Simões, J. Chem. Educ. 69 (1992) 940–942.
[11] H.P. Diogo, M.E. Minas da Piedade, J.A. Martinho Simões, C.J. Teixeira, Organomet. Chem. 632 (2001) 188–196.
[12] IUPAC Commission on Atomic Weights and Isotopic Abundances. Available from <http://www.chem.qmul.ac.uk/IUPAC/AtWt/>.
[13] A.R. Dias, J.A. Martinho Simões, Polyhedron 7 (1988) 1531–1544.
[14] V.P. Vasil'ev, V.A. Borodin, S.B. Kopnyshev, Russ. J. Phys. Chem. 65 (1991) 29–32 (Engl. Transl.).

JCT 03/097