

Stability of Aqueous Carboplatin Solutions Under Illumination

Montserrat Pujol¹, Josefina Part¹, Maria Trillas², and Xavier Domènech^{2,*}

¹ Facultat de Farmàcia, Departament de Farmàcia, Unitat de Fisicoquímica, Avda Diagonal s/n, E-08028 Barcelona, Spain

² Facultat de Ciències, Departament de Química, Unitat de Química Física, Universitat Autònoma de Barcelona, E-08193 Bellaterra, Spain

Summary. The stability of carboplatin in aqueous solutions at different experimental conditions was studied. It was observed that the degradation rate of carboplatin under illumination increases notably with respect to the rate obtained in the dark. The time course of carboplatin in solution follows a first-order kinetics with rate constants that depend on the incident light intensity and little with temperature. The quantum yield of the carboplatin degradation lies between 0.05 and 0.2 depending on the experimental conditions. From the results obtained in the present work it is concluded that carboplatin is degraded under illumination by means of a photoaquation process.

Keywords. Kinetics; Carboplatin; Photoaquation.

Stabilität wäßriger Carboplatin-Lösungen unter Beleuchtung

Zusammenfassung. Es wurde die Stabilität wäßriger Carboplatin-Lösungen unter verschiedenen experimentellen Bedingungen untersucht. Dabei wurde festgestellt, daß die Zersetzungsgeschwindigkeit bei Belichtung gegenüber der Zersetzung im Dunklen ansteigt. Die Reaktion folgt erster Ordnung und hängt stark von der Lichtintensität und nur wenig von der Temperatur ab. Je nach experimentellen Bedingungen liegt die Quantenausbeute zwischen 0.05 und 0.2. Die Ergebnisse erlauben den Schluß, daß die Zersetzung durch Belichtung über einen Photoaquationsprozeß verläuft.

Introduction

Cisplatin (*cis*-diaminedichloroplatinum (II)) is a well-known compound used as antitumor agent in cancer chemotherapy [1]. Despite its wide use, certain pharmaceutical problems associated with the poor stability of the aqueous solutions of this cytostatic compound have been detected [2, 3]. This is the reason that other Pt-related compounds also with antineoplastic activity have been proposed [4]. In this way, carboplatin (1,1-cyclobutanedicarboxylatoplatinum (II)) is one of the compounds suggested as alternative to cisplatin, due to its high stability in aqueous solutions [5]. However, it must be considered that carboplatin similar to these platinum complexes can be sensible to light, promoting photoaquation [6, 7]. In this paper the photodegradation of carboplatin in aqueous solutions at different

experimental conditions is investigated. From the obtained experimental data, the kinetics and the mechanism of the process are analysed.

Experimental

Carboplatin and cisplatin of analytical grade were purchased from Bristol-Myers and Wasserman and were used without further purification. Double-distilled water was used throughout. All other chemicals were, at least, of reagent grade and used as received. Once prepared, the carboplatin solutions were stored, at 4 °C and protected from light. Aqueous solutions containing a mixture of *cis*-[Pt(NH₃)₂Cl(H₂O)]⁺ and *cis*-[Pt(NH₃)₂(H₂O)₂]²⁺ were prepared by incubating cisplatin in pure water [8].

All experiments were carried out in an open thermostated Pyrex cell of 50 ml of capacity. In the photochemical experiments a 250 W Xe lamp (Applied Photophysics) was used as light source. In those experiments where intense UV-irradiation was required a Hg high-pressure vapour lamp of 125 W was used (Philips HPK 125). The intensity of incident light inside the cell was measured using an uranyl oxalate actinometer.

Carboplatin disappearance in solution was monitored by HPLC by comparing the peak area of the drug with standard aqueous solutions. A liquid chromatograph with an isocratic pump and diode array UV-light detector (Hewlett Packard, HP-1090), coupled to an integrator (Hewlett Packard, HP-3396) was used for the HPLC assay. A spherisorb-Ph column (25 cm × 4.6 mm i.d., 5 µm particle size) was used as stationary phase. The mobile phase was 2% methanol and 98% water.

Results and Discussion

Under illumination, the concentration of carboplatin in solution (*c*) readily decreases with time following a first-order kinetics. For example, Fig. 1 shows the corresponding ln *c* vs. time plots for different initial concentrations of carboplatin at 25 °C. As can be seen, the plots give straight lines with the same slope within the experimental error, i.e., $5.8 \times 10^{-3} \text{ min}^{-1}$, $6.0 \times 10^{-3} \text{ min}^{-1}$ and $5.9 \times 10^{-3} \text{ min}^{-1}$, for $2.15 \times 10^{-3} \text{ mol l}^{-1}$, $1.08 \times 10^{-3} \text{ mol l}^{-1}$ and $0.54 \times 10^{-3} \text{ mol l}^{-1}$, respectively. In Table 1, the rate parameters (rate constant and $t_{0.5}$) for carboplatin photodegradation at different experimental conditions are summarized. It must be pointed out that the rate constant increases with increasing light intensity and practically does not vary with temperature within the temperature range comprised between 25 °C and 60 °C.

In fact, the rate of carboplatin degradation can be expressed as made up of two contributions,

$$r = K_{th}c + K_{pH}c,$$

where K_{th} and K_{pH} are the thermal and photochemical rate constants of the process, respectively. However, it must be said that in the dark the aqueous solutions of carboplatin are very stable. As can be seen from data in Table 1, the rate constant of carboplatin degradation in the dark at 60 °C is $5.6 \times 10^{-5} \text{ min}^{-1}$, that is 100-times lower than the rate constant of the process under illumination at the same experimental conditions. At lower temperatures the rate constant of carboplatin degradation decreases. So, at 37 °C the rate constant of the process in the dark is $2.8 \times 10^{-5} \text{ min}^{-1}$ [9], while under illumination it is $5.7 \times 10^{-3} \text{ min}^{-1}$. As a consequence, K_{th} can be neglected and

$$r = K_{pH}c.$$

The photochemical rate constant, K_{pH} , can be related to the light intensity absorbed per mol of carboplatin by means of the following expression [10],

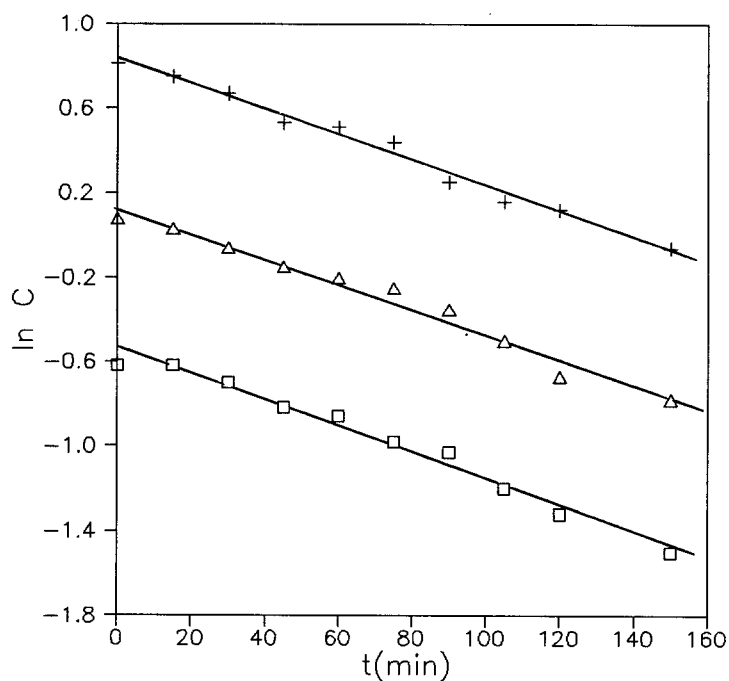


Fig. 1. $\ln c$ vs. t plots for carboplatin solutions at different concentrations: $2.15 \times 10^{-3} \text{ mol l}^{-1}$ (+), $1.08 \times 10^{-3} \text{ mol l}^{-1}$ (Δ) and $0.54 \times 10^{-3} \text{ mol l}^{-1}$ (\square) under illumination; temperature 25°C , initial $pH = 5.0$

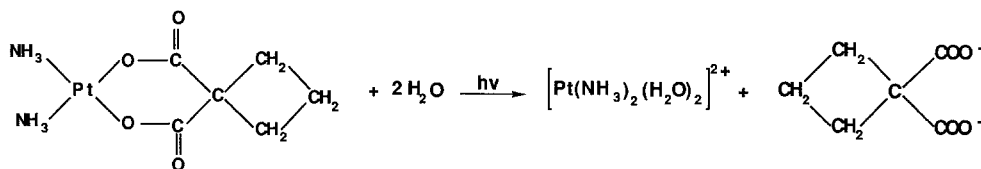
Table 1. Rate-parameters and quantum yield (ϕ) of the carboplatin photo-degradation at different initial concentrations of carboplatin (c_i), light intensities (I) and temperatures (T)

$c_i \times 10^3$ (mol l^{-1})	$I \times 10^6$ (Eins min^{-1})	T ($^\circ\text{C}$)	$K \times 10^3$ (min^{-1})	$t_{0.5}$ (h)	ϕ
1.08	4.20	25	2.0	5.7	0.052
1.08	5.25	25	3.4	3.4	0.069
1.08	6.00	25	6.0	1.9	0.11
1.08	7.00	25	7.5	1.6	0.12
1.08	8.40	25	10.4	1.1	0.13
1.08	6.00	37	5.7	2.0	0.10
1.08	6.00	50	5.9	2.0	0.11
1.08	6.00	60	5.7	2.1	0.10
1.08	dark	60	0.056	207	—
0.54	6.00	25	5.9	1.9	0.054
2.15	6.00	25	5.8	2.0	0.21

$$K_{pH} = (\phi I)/(c_i V),$$

where ϕ is the quantum yield of the carboplatin photodegradation, I the intensity expressed as moles of incident photons per minute, c_i the initial concentration of carboplatin and V is the solution volume. From this last expression, the quantum yield of carboplatin photodegradation at different experimental conditions has been deduced (see Table 1).

From chromatograms obtained of the carboplatin solutions illuminated at different times, it has been observed the appearance of a peak that grows parallel to the decrease of the peak corresponding to carboplatin. From the analysis of the chromatograms of blank solutions, this peak has been assigned to *cis*-diaminediaquo platinum(II), $[\text{Pt}(\text{NH}_3)_2(\text{H}_2\text{O})_2]^{2+}$. This confirms that the photoaquation is the process responsible of the degradation of carboplatin under illumination:



In fact, during illumination of the carboplatin solution at neutral to acid pH s, an increase of pH is noticed. This change of pH can be accounted for considering the acid-base equilibria established in solution, between the 1,1-cyclobutanedicarboxylate anion and their protonated forms ($pK_1 \approx 2$ and $pK_2 \approx 7$ [11]).

The photoaquation of carboplatin depends on the initial pH . In Fig. 2, the percentage of carboplatin photodegraded from an initial $1.08 \times 10^{-3} \text{ mol l}^{-1}$ solution of carboplatin after 90 min of illumination at 25°C at different initial pH are represented. As can be seen, in acid media there is a strong decrease of the yield

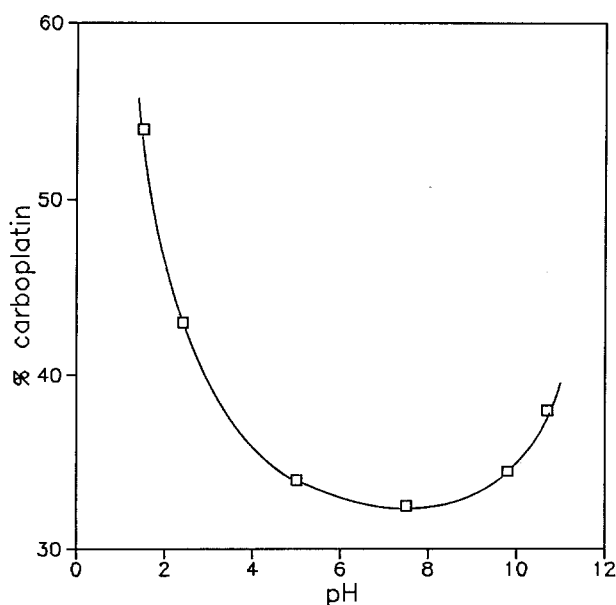
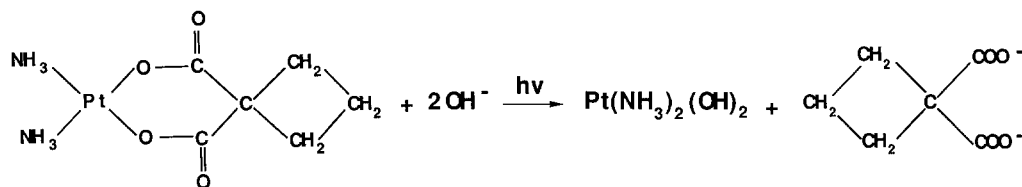


Fig. 2. Percentage of carboplatin photodegraded after 90 min of illumination from an initial $1.08 \times 10^{-3} \text{ mol l}^{-1}$ solution at different initial pH s; temperature = 25°C

of the carboplatin photoaquation with increasing pH , attaining a minimum value at neutral pH after which it slightly increases. The increment of the percentage of carboplatin degradation indicates that the OH^- ions are the species that displace the 1,1-cyclobutanedicarboxylate anion from carboplatin in alkaline media, in a similar way as for cisplatin aqueous solutions [6]:



For intense UV-irradiation the appearance of fine black paricles suspended in the carboplatin solution have been observed after some minutes of illumination. This phenomenon, which also takes place in illuminated cisplatin solutions [7], is indicative of the formation of black platinum(II) oxide. This oxide is generated when carboplatine has been fully aquated, obtaining the complex $\text{Pt(H}_2\text{O)}_4^{2+}$ which is converted to PtO afterwards.

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