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Characterization of reactions of antimoniate and meglumine antimoniate with a guanine ribonucleoside at different pH

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Abstract

It has been shown previously that Sb^V forms mono- and bis-adducts with adenine and guanine ribonucleosides, suggesting that ribonucleosides may be a target for pentavalent antimonial drugs in the treatment of leishmaniasis. In the present work, the reactions of antimoniate ($KSb(OH)_6$) and meglumine antimoniate (MA) with guanosine 5′-monophosphate (GMP) have been characterized at 37 °C in aqueous solution and two different pH (5 and 6.5), using ESI(−)-MS and ^1H NMR. Acid and base species for both 1:1 and 1:2 Sb^V–GMP complexes were identified by ESI(−)-MS. The ^1H NMR anomeric region was explored for determining the concentrations of mono- and bis-adducts. This allows for the determination of stability constants for these complexes (5900 L mol^{-1} for 1:1 complex and 370 L mol^{-1} for 1:2 complex, at pD 5 and 37 °C). Kinetic studies at different pH indicated that formation and dissociation of both 1:1 and 1:2 Sb–GMP complexes are slow processes and favored at acidic pH (2150 L mol^{-1} h^{-1} for the rate constant of 1:1 complex formation and 0.25 h^{-1} for the rate constant of 1:1 complex dissociation, at pD 5 and 37 °C). When MA was used, instead of antimoniate, formation of 1:1 Sb–GMP complex occurred, but with a slower rate constant. Assuming that MA consists essentially of a 1:1 Sb–meglumine complex, a stability constant for MA could also be estimated (8600 L mol^{-1} at pD 5 and 37 °C). Thermodynamic and kinetic data are consistent with the formation of 1:1 Sb–ribonucleoside complexes in vertebrate hosts, following treatment with pentavalent antimonial drugs.

Introduction

The pentavalent organoantimonial complexes, meglumine antimoniate (MA) and sodium stibogluconate, are the first line drugs for the treatment of all forms of leishmaniasis. Despite their clinical use for more than half a century, the mode of action of these drugs remains poorly understood (Berman 1997; Demicheli & Frezard 2005). It is still not clear whether the final active form of pentavalent antimonials is Sb^V or Sb^{III}. It has been reported that part of Sb^V is reduced *in vivo* into more toxic Sb^{III} (Goodwin & Page 1943; Burguera *et al.* 1993; Shaked-Mishan *et al.* 2001). Recent studies also indicated that thiols may act as a reducing agent in this conversion (Frézard *et al.* 2001; Ferreira *et al.* 2003; Yan *et al.* 2003). On the other hand, the formation of a complex between

adenine ribonucleoside and Sb^V has been reported (Demicheli *et al*. 2002). This was the first report of a physiologically relevant biomolecule capable of forming a stable complex with Sb^V (Demicheli & Frezard 2005). Circular dichroism data indicated the formation of a 1:2 Sb–adenosine complex and the absence of complexation with 2′-deoxyadenosine. Furthermore, complexation was found to occur at pH 5 but not at pH 7, suggesting that it may take place preferentially in acidic biological compartments. Two recent studies performed with guanine and adenine ribonucleosides using ESI-MS and ^{1}H NMR techniques allowed the identification of both mono- and bis-adducts (Chai *et al*. 2005; Demicheli *et al*. 2006). The large changes for H_2' NMR resonance suggested that –OH groups in the ribose are the binding sites for Sb^V probably via ring chelation at C2′ and C3′. This was also supported by the fact that no significant shift of proton resonance was observed for deoxy-ribonucleosides and dApG dinucleotide in the presence of Sb^V (Chai *et al*. 2005).

Despite the recent progress achieved in the understanding of the interactions between Sb^V and nucleosides, detailed kinetic and thermodynamic studies are still necessary in order to evaluate the pharmacological relevance of this reaction. Moreover, such investigation is expected to improve our knowledge on the chemistry of pentavalent organoantimonial complexes in aqueous solution.

In this paper, guanine 5′-monophosphate (GMP) was taken as a model of purine ribonucleoside to characterize kinetically and thermodynamically the reaction of these biomolecules with Sb^V using ESI(−)-MS and ^{1}H NMR. The antimonial drug, MA, was also evaluated for its ability transfer Sb^V to the ribonucleoside. The pharmacological implications of this reaction are discussed.

Materials and methods

Materials

Guanosine 5′-monophosphate disodium salt (GMP) was obtained from Sigma Chemical Co (>99% purity). Potassium hexahydroxoantimonate ($KSb(OH)_6$ or antimoniate) was obtained from Fluka Chemie GmbH (>99% purity). N-methyl-D-glucamine (>99% purity) and $SbCl_5$ (99% purity) were obtained from Aldrich Chemical Co. All other reagents were of at least reagent grade. Double-distilled-deionized water was used throughout the experiments.

Synthesis of meglumine antimoniate

Meglumine antimoniate was synthesized as previously described (Demicheli *et al*. 2003) from equimolar amounts of N-methyl-D-glucamine and pentavalent antimony oxyhydrated. The resulting product contained approximately 30% antimony by weight, as determined plasma emission spectroscopy (ICP-OES), using a Perkin-Elmer Optima 3000 plasma emission spectrometer.

ESI mass spectrometric analyses

ESI-Q-ToF mass spectrometry analyses were carried out using a Q-ToF Micro^{TM} (Micromass, UK) equipped with an electrospray ionisation source operated in negative ion mode. Capillary voltage was 2.5–3.5 kV and sample cone voltages were 30–60 V. Mass spectrometer calibrations were made by using sodium iodide with cesium iodide in the 100–2000 m/z range. Antimoniate/nucleoside solutions were prepared in water at pH 5 at 1:2 molar ratio. For study at pH less than 5, the antimoniate/nucleoside mixture was diluted 1:2 (v/v) with 0.1% trifluoroacetic acid (TFA). Samples were introduced by using a syringe pump with flow rates of 5–10 μL min^{-1}. MS/MS experiments were performed by collision induced dissociation (CID) and were carried out by using argon as collision gas and collision energies in the range of 20–50 eV. Data were analysed by MassLynx® 4.0 software. Each species is indicated with the m/z value of the first peak of its isotopic cluster.

^{1}NMR analyses

^{1}H NMR spectra for GMP and its Sb(V)-complexes were obtained on a Brüker DRX400-*AVANCE* spectrometer operating at 400.129 MHz using D_2O as solvent. TMS (3-(trimethylsilyl) propionic-2,2,3,3-d_4 acid, sodium salt) was used as an internal reference.

Solutions were prepared from GMP and antimoniate or meglumine antimoniate in 0.1 mol/L KCl in D_2O. pD was adjusted using a DCl solution in D_2O. The value of pD was obtained from pH measurements and calculated as: pD = pH + 0.4.

Dissociation was induced, after reaching reaction equilibrium, by diluting the mixture from 7.6 to 1 mM nucleoside concentration. The kinetics of complex formation and dissociation were studied at 37 °C and pD 5 and 6.5. The proportion of each species (free GMP, 1:1 Sb–GMP complex, 1:2 Sb–GMP complex) was calculated by integration of the corresponding H1′ signal.

Determination of apparent association and dissociation rate constants

k_{f1} and k_{d2} were determined from the kinetics of formation and dissociation of Sb–GMP complexes, respectively, in initial conditions, using the following equations:

$$\ln\{([Sb]_{tot} - [SbL])/([L]_{tot} - [SbL])\} = ([Sb]_{tot} - [L]_{tot})k_{f1}t + \ln([Sb]_{tot}/[L]_{tot})$$

$$\ln([SbL_2]) = k_{d2}t + \ln(([SbL_2]_0)$$

where $[Sb]_{tot}$ and $[L]_{tot}$ are the total molar concentrations of antimony and GMP in the solution, [SbL] and $[SbL_2]$ are the molar concentrations of 1:1 and 1:2 Sb–GMP complexes, respectively, at the time t and $[SbL_2]_0$ is the molar concentration of 1:2 Sb–GMP complex at time zero. k_{f2} and k_{d1} were determined from the kinetics of formation and dissociation of Sb–GMP complexes, respectively, in conditions of small variation of [SbL] and [L], using the following equations:

$$(d[SbL_2]/dt) = k_{f2}[SbL][L] - k_{d2}[SbL_2]$$

$$(d[SbL_2]/dt) + (d[L]/dt) = k_{d1}[SbL] - k_{f1}[Sb][L]$$

where [L] is the molar concentration of free nucleoside.

Results

Characterization of Sb–GMP complexes using ESI(−)-MS and ^{1}H-NMR

Figure 1a shows the Electrospray Ionization Mass Spectrometry spectrum obtained in the negative

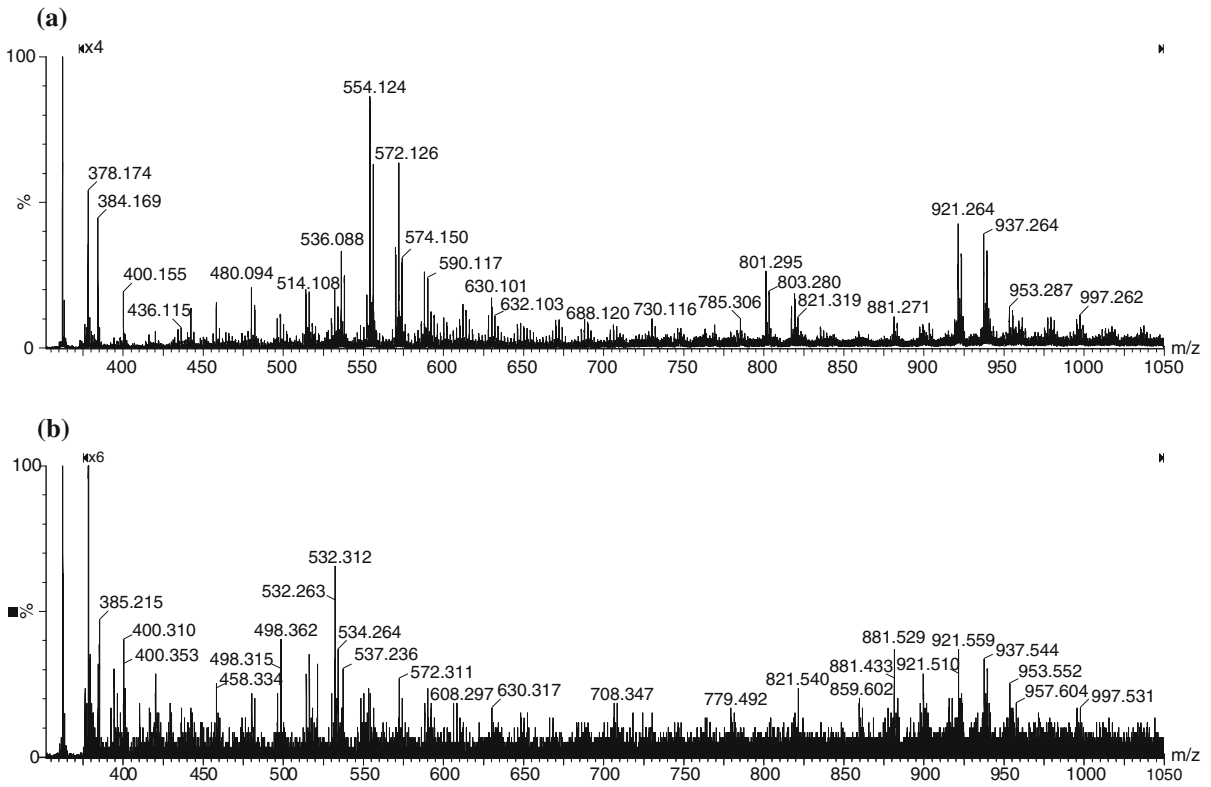

Figure 1. Negative ESI mass spectra obtained for a solution of 7.5 mM antimoniate and 15 mM GMP in water after 3 h-incubation at 25 °C (a) and following 1:2 (v/v) dilution with TFA 0.1% (b).

Table 1. Assignment of most relevant ions detected in the ESI(−)-MS spectrum in aqueous solutions of antimoniate and GMP at a 1:2 molar ratio.

Ionic species	*m/z*
GMP^-	362
$[(GMP)Sb(O)(OH)\text{-}2H]^-$	514
$[(GMP)Sb(OH)_3\text{-}2H]^-$	532
$[(GMP)Sb(O)_2Na\text{-}2H]^-$	536
$[(GMP)Sb(OH)_2Na\text{-}2H]^-$	554
$[(GMP)Sb(OH)_4Na\text{-}2H]^-$	572
$[(GMP)_2Sb(OH)Na\text{-}4H]^-$	881
$[(GMP)_2Sb(O)Na_2\text{-}4H]^-$	903
$[(GMP)_2Sb(OH)_2Na_2\text{-}4H]^-$	921
$[(GMP)_2Sb(OH)_3Na_2\text{-}3H]^-$	937

mode (ESI(−)-MS) for 15 mM GMP after incubation for 3 h at 25 °C and pH 5 with 7.5 mM potassium hexahydroxoantimonate (antimoniate). The assignment of the main peaks is reported in Table 1. ESI spectrum is constituted essentially by peaks due to free GMP, 1:1 Sb–GMP and 1:2 Sb–GMP complexes. Most complexes were found to contain Na^+, presumably as a result of interaction with negatively charged phosphate group. These complexes were confirmed by CID experiments, in which losses of Na^+ ion was verified (data not shown). Furthermore, prominent clusters of ions related to the natural isotopic distribution of Sb (^{121}Sb:$^{123}Sb = 57{:}43$) were identified.

Strikingly, the two 1:1 Sb–GMP species with *m/z* of 532($[(GMP)Sb(OH)_3]^-$) and 572($[(GMP)Sb(OH)_4Na]^-$) and the two 1:2 Sb–GMP species with *m/z* of 881($[(GMP)_2Sb(OH)Na]^-$) and 921($[(GMP)_2Sb(OH)_2Na_2]^-$) represent the acid and base species, respectively, which are in equilibrium according to the following reactions:

$$[(GMP)Sb(OH)_4]^{2-} + H^+ \leftrightarrow [(GMP)Sb(OH)_3]^- + H_2O \quad (1)$$

$$[(GMP)_2Sb(OH)_2]^{3-} + H^+ \leftrightarrow [(GMP)_2Sb(OH)]^{2-} + H_2O \quad (2)$$

This model is further supported by the fact that, when the Sb/GMP solution was diluted 1:2 (v/v) with 0.1% TFA, the peak intensities of 532 and 881 species increased compared to those of the other species (Figure 1b). Figure 2 shows the the H1′ region (5.4–6.2 ppm) of ^{1}H-NMR spectra obtained for GMP in D_2O and a mixture of GMP

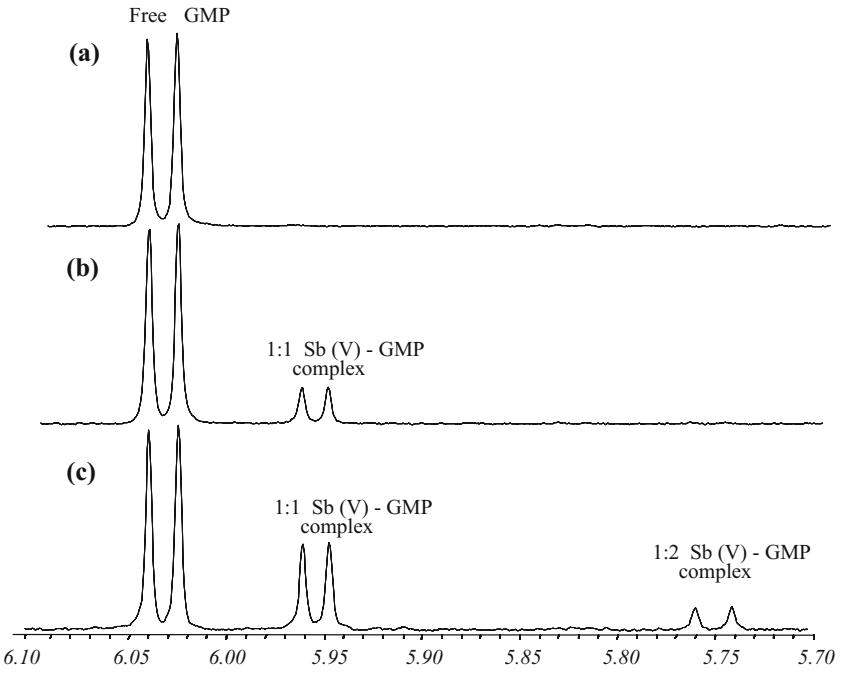

Figure 2. H1′ region of the ^{1}H NMR spectra obtained for 7.6 mM GMP in the absence (a) and in the presence of 3 mM antimoniate after 1 h (b) and 6 h (c) incubation at 37 °C and pD 6.5.

Table 2. Apparent association (k_{f1}, k_{f2}) and dissociation (k_{d1}, k_{d2}) rate constants and stability constants (K_1, K_2)* for 1:1 and 1:2 Sb–GMP complexes at 37 °C in 0.1 M KCl in D_2O.

pD	k_{f1} (L mol^{-1} h^{-1})	k_{f2} (L mol^{-1} h^{-1})	k_{d1} (h^{-1})	k_{d2} (h^{-1})	[a]K_1 (L mol^{-1})	[b]K_2 (L mol^{-1})
5	2150	400	0.25	0.51	5900	370
6.5	88	5.2	0.0053	0.0055	–	–

[a]K_1 = [SbGMP]/[Sb][GMP]; [b]K_2 = [Sb(GMP)$_2$]/[SbGMP][GMP]; *Experimental errors for these parameters did not exceed 20%.

and antimoniate in D_2O at 7.6 mM and 3 mM final concentrations, respectively, after 1 h- and 6 h-incubation at 37 °C and pD 6.5. These spectra allowed for the identification of NMR resonances of 1:1 Sb–GMP and 1:2 Sb–GMP complexes and, after integration of anomeric signals, for the determination of the proportion of the three different species.

Stability constant for Sb–GMP complexes

As illustrated in Figure 3, when antimoniate and GMP were incubated at 37 °C and pD 5 at a Sb/GMP molar ratio of 1:2 (4.3 mM GMP), the reaction equilibrium was reached within 24 h. From these data, the following stability constants for 1:1 and 1:2 Sb–GMP complexes were determined:

$$K_1 = [\mathrm{SbGMP}]/[\mathrm{Sb}][\mathrm{GMP}] \quad \text{for } \mathrm{Sb} + \mathrm{GMP} \leftrightarrow \mathrm{SbGMP} \qquad (3)$$

$$K_2 = [\mathrm{Sb(GMP)_2}]/[\mathrm{SbGMP}][\mathrm{GMP}] \quad \text{for } \mathrm{SbGMP} + \mathrm{GMP} \leftrightarrow \mathrm{Sb(GMP)_2} \qquad (4)$$

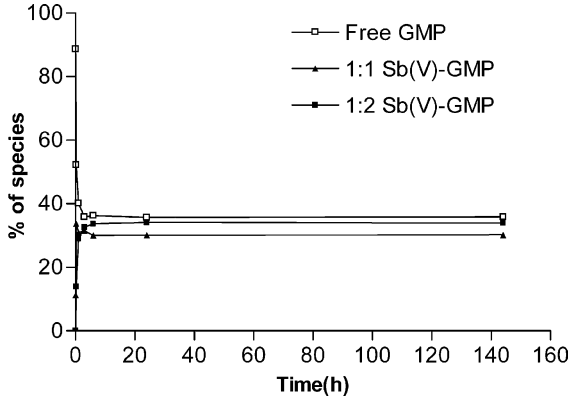

Figure 3. Kinetics of formation of 1:1 and 1:2 Sb–GMP complexes at pD 5 and 37 °C after mixing of antimoniate and GMP at 2.2 mM and 4.3 mM final concentrations, respectively. The proportion of the different species was determined from ^{1}H NMR spectrum by integration of anomeric signals.

Table 2 displays the values calculated for K_1 and K_2.

Kinetic parameters for the formation and dissociation of Sb–GMP complexes

Figure 4a shows the kinetics of formation of Sb–GMP complexes at 37 °C and pD 6.5, after mixing antimoniate and GMP at 3 mM and 7.6 mM final concentrations, respectively. From these data, assuming second-order reactions, apparent association rate constants for reactions 3 (k_{f1}) and 4 (k_{f2}) could be determined (Table 2). When antimoniate/GMP aqueous solution was recovered after 7 days and then diluted at 1 mM final nucleoside concentration, complex dissociation was induced, as shown in Figure 4b. Assuming first-order reactions, apparent dissociation rate constants for reactions 3 (k_{d1}) and 4 (k_{d2}) could be determined (Table 2). This experiment was repeated at pD 5 and the resulting kinetic constants are also displayed in Table 2. These data revealed a strong pH-dependence for complex association and dissociation rate constants, both processes being markedly favored at acidic pH.

Reaction between meglumine antimoniate and GMP

When GMP was incubated with the antimonial drug, MA, instead of potassium antimoniate, in addition to reaction (4), the following reaction and equilibrium constant (K_3) were considered:

$$\mathrm{MA} + \mathrm{GMP} \leftrightarrow \mathrm{SbGMP} + \mathrm{M} \quad \text{with} \quad K_3 = [\mathrm{SbGMP}][\mathrm{M}]/[\mathrm{MA}][\mathrm{GMP}] \qquad (5)$$

where M represents N-methyl-glucamine (ligand in MA).

This model is based on the assumptions that MA consists essentially of a 1:1 Sb–M complex (Demicheli *et al.* 1999; Demicheli & Frézard 2005)

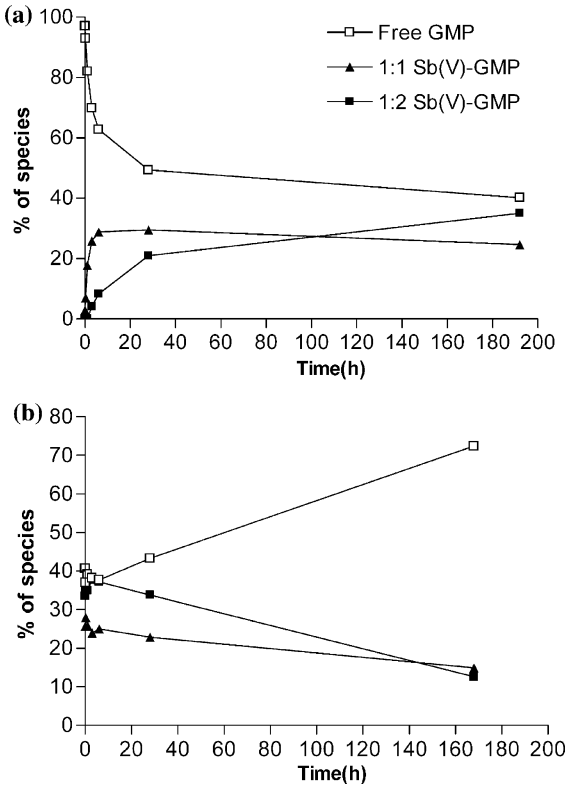

Figure 4. Kinetics of formation (a) and dissociation (b) of 1:1 and 1:2 Sb–GMP complexes at 37 °C and pD 6.5 in KCl 0.1 M. First, 7.6 mM GMP and 3 mM antimoniate were incubated for 7 days at 37 °C (a). Then, the resulting solution was diluted to 1 mM GMP concentration to induced dissociation (b). The proportion of the different species was determined from ^{1}H NMR spectrum by integration of anomeric signals.

and does not form significant amount of M–Sb–GMP ternary complex.

In order to evaluate the 1:1 Sb–GMP species formed in the MA/GMP mixture, both ESI(−)-MS and ^{1}H NMR experiments were performed. Figure 5 shows the ESI(−)-MS spectra obtained for 2.1 mM MA, in the absence and in the presence of 4.2 mM GMP after incubation for 1 h at 37 °C. The spectrum obtained for MA/GMP mixture shows the same peaks as antimoniate/GMP mixture (m/z at 514, 532, 554 and 572), in addition to new peaks related to 1:1 Sb–M complexes ($[MSb(O) - 4H]^-$ at 328, $[MSb(OH)_2 - 4H]^-$ at 346 and $[MSb(OH)_3 - 3H]^-$ at 364) and to M–Sb–GMP ternary complexes ($[MSb(OH)GMP - 4H]^-$ at m/z 691,$[MSb(OH)_2GMP - 3H]^-$ at m/z 709). On the other hand, ^{1}H NMR spectrum for MA/GMP showed anomeric signals with exactly the same chemical shifts and coupling constants as those of antimoniate/GMP (data not shown), suggesting that ternary complexes are minor species. Figure 6 shows the kinetics of formation of 1:1 and 1:2 Sb–GMP complexes at 37 °C and pD 6.5, after mixing MA and GMP at 3 mM and 7.6 mM concentrations, respectively. From these data, apparent association rate constants could be determined. The values obtained for these parameters, in addition to those determined at pD 5, are displayed in Table 3. Considering that, in these experimental conditions, the concentration of non-complexed antimoniate is negligible compared to total antimony concentration, the equilibrium constants K_2 and K_3, could also be determined (Table 3).

Discussion

In the present work, the complexation of Sb^V with GMP has been characterized thermodynamically and kinetically in conditions of temperature and pH close to physiological ones. This study represents an extension of recent works performed by our group (Demicheli *et al.* 2002, 2006) and others (Chai *et al.* 2005) on the interaction of Sb^V with nucleosides. Both mono- and bi-adducts were identified following reaction of Sb^V with the purine ribonucleosides adenosine, AMP, guanosine and GMP. In the study of Chai *et al.* (2005), the kinetics of formation of Sb–GMP 1:1 and 1:2 complexes from antimoniate and sodium stibogluconate were investigated at pH 5, using the same methodology as that used in the present work. Importantly, our work gives new insights into the acid–base properties of Sb–GMP complexes (using ESI(−) MS) as well as into the influence of pH on the kinetics of formation and dissociation of mono- and bi-adducts. Moreover, it reports for the first time a value for the stability constant of MA (see below).

We report here that association and dissociation rates of mono- and bi-adducts are slow and pH-dependent, both being increased at acidic pH. The pH-dependence of the rate of formation of 1:1 Sb–GMP (reaction 3) may be attributed to the acid–base properties of Sb^V in aqueous solution. $Sb(OH)_5$ and $Sb(OH)_6^-$ are considered to be the predominant acid–base Sb^V species in aqueous solution (Filella & May 2003), which are in equilibrium according to the following equation:

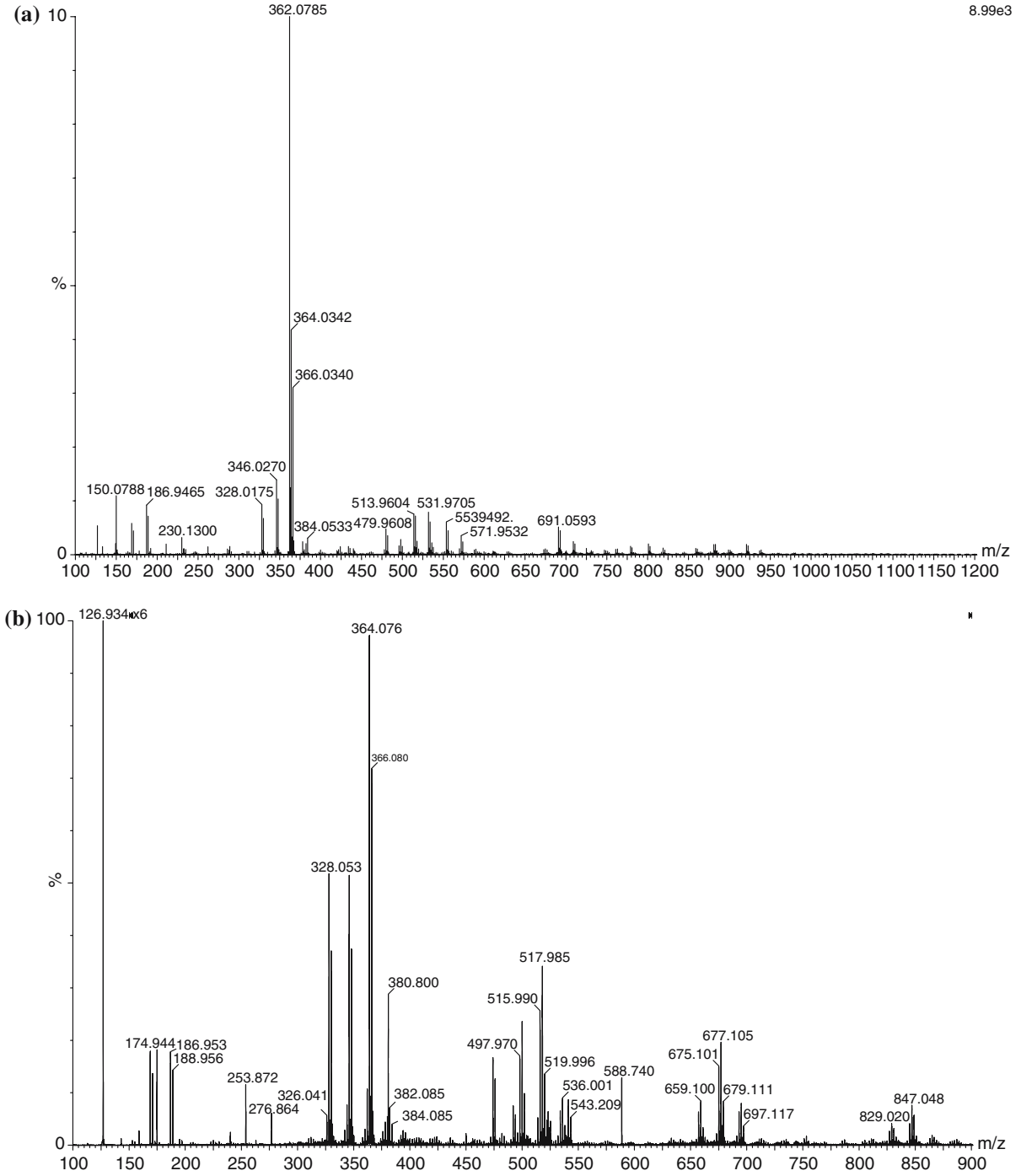

Figure 5. Negative ESI mass spectra obtained for meglumine antimoniate solution in water at 2.1 mM Sb and pH 5, in the absence (b) or in the presence (a) of GMP after 1 h- incubation at 37 °C.

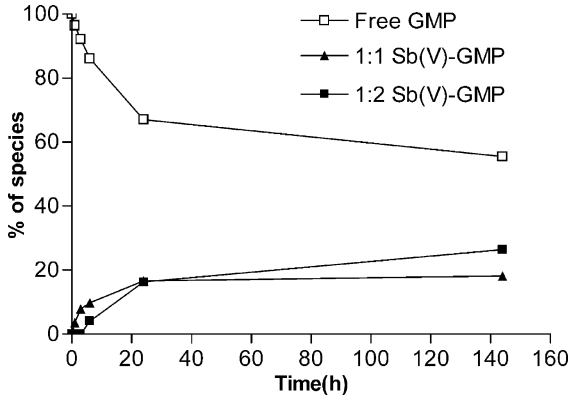

Figure 6. Kinetics of formation of 1:1 and 1:2 Sb–GMP complexes at 37 °C and pD 6.5, after mixing meglumine antimoniate and GMP at final concentrations of 3 mM and 7.6 mM, respectively. The proportion of the different species was determined from ^{1}H NMR spectrum by integration of anomeric signals.

Table 3. Apparent association rate constants (k_{f1}^{app}, k_{f2}) and equilibrium constants (K_2, K_3)* for reactions of meglumine antimoniate with GMP at 37 °C in 0.1 M KCl in D_2O.

pD	k_{f1}^{app} (L mol^{-1}h^{-1})	k_{f2} (L mol^{-1} h^{-1})	[a]K_3 (L mol^{-1})	[b]K_2 (L mol^{-1})
5	260	375	0.68	225
6.5	7.7	5.2	–	–

[a]K_3 = [SbGMP][M]/[MA][GMP]; [b]K_2 = [Sb(GMP)$_2$]/[SbGMP][GMP]; *Experimental errors for these parameters did not exceed 20%.

$$Sb(OH)_5 + H_2O \leftrightarrow Sb(OH)_6^- + H^+$$

Therefore, our data suggests that $Sb(OH)_5$ may be the reactive form of Sb^V.

By analogy, the fact that the rate of formation of 1:2 Sb–GMP complex (reaction 4) is also favored at acidic pH suggests that the acid form $[(GMP)Sb(OH)_3]^-$ at m/z 332 may be the reactive species.

The fact that the rates of dissociation of both 1:1 and 1:2 Sb–GMP complexes are much slower at neutral pH indicates that the deprotonated forms of the complexes ($[(GMP)Sb(OH)_4]^{2-}$ and $[GMP)_2Sb(OH)_2]^{3-}$) are much less subject to dissociation than the protonated ones ($[(GMP)Sb(OH)_3]^-$ and $[(GMP)_2Sb(OH)]^{2-}$).

According to these data, reactions (3) and (4) can be more fully described by the following equations:

$$Sb(OH)_5 + (H)_2GMP^- \leftrightarrow [GMP\,Sb(OH)_3]^- + 2H_2O \quad (7)$$

$$[GMP\,Sb(OH)_3]^- + (H)_2GMP^- \leftrightarrow [(GMP)_2Sb(OH)]^{2-} + 2H_2O \quad (8)$$

Complexation of Sb^V in the form of MA was found to slow down the formation of the 1:1 Sb–GMP complex and to turn the metal less available for complexation with the nucleoside. Determination of K_3 relies on the assumption that MA does not form significant amount of ternary complex in the presence of GMP. This assumption was supported by the lack of specific signal detected for such species in the NMR spectrum and by the observation that k_{f2} and K_2 showed about the same values with antimoniate (Table 2) and MA (Table 3).

Assuming a 1:1 reaction between antimoniate (Sb) and N-methyl-glucamine (M) to form MA, an apparent stability constant for MA (K^{MA}) could also be calculated at pD 5 and 37 °C as follows:

$$K^{MA} = [MA]/[Sb][M] = K_1/K_3 = 8600 \text{ L mol}^{-1}$$

In order to evaluate the possible implications of the present results for the pharmacology of pentavalent antimonial drugs, one should consider first the physiological conditions in which *Leishmania* parasite develops. *Leishmania* parasites reside and multiply within macrophage phagolysosomes, which are acidic compartment with a pH of about 5 (Alexander & Russel 1992). The mode of entry of Sb^V has not yet been characterized. Sb^V may reach the parasite either by diffusion through macrophage plasma membrane, the cytosol and, then, the phagolysosome membrane. Alternatively, Sb^V may reach the phagolysosome compartment by phagocytosis, following interaction with some surface glycoprotein. The pH-dependence of the rate of formation of Sb–ribonucleoside indicates that this reaction will be kinetically favored within acidic biological environments. Moreover, since *Leishmania* is a true auxothroph for purine, purine ribonucleosides are expected to be present, in significant amount, within phagolysosomes. Taking into account the values determined for K_1, K_2 and K_3 and assuming a MA concentration of 1 mM and a nucleoside concentration at least 10-fold lower, one can infer that, at pD 5 and 37 °C, about 63% of nucleoside will be in the form of 1:1 Sb–nucleoside complex

and only 0.5% in the form of 1:2 Sb–nucleoside complex. Moreover, in the presence of 0.1 mM nucleoside, an initial rate of formation of the 1:1 Sb-complex of about 0.025 mmol L^{-1} h^{-1} is expected. Given that after a short exposure to antimonial drug, macrophages were found to retain antimony for several days (Roberts *et al*. 1995), one expect indeed that such complex would be formed in vertebrate hosts following treatment with pentavalent antimonial drugs. To explain the leishmanicidal action of Sb^V, two hypotheses can be raised. Such complex might act as an inhibitor of the *Leishmania* purine transporters (Vasudevan *et al*. 1998; Carter *et al*. 2000). Alternatively, these complexes might penetrate inside the parasite, encountering a neutral pH-environment and then interfere with the purine salvage pathway, like the purine analog, allopurinol (Marr 1991).

According to the present study, Sb–ribonucleoside complexes remained kinetically ''trapped'' at neutral pH. Whether this peculiar property applies to other pentavalent organoantimonial complexes, such as meglumine antimoniate, and contributes to their pharmacological properties, should be investigated in future works. On the other hand, ribose-containing compounds may also find applications in the development of pH-controlled release systems for Sb^V.

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