Ranitidine Bismuth(III) Citrate

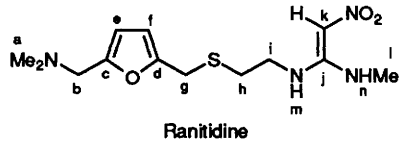
Peter J. Sadler* and Hongzhe Sun
Department of Chemistry, Birkbeck College, University of London, Gordon House and Christopher Ingold Laboratories, 29 Gordon Square, London WC1H 0PP, UK

A variety of amines have been shown to solubilize bismuth(III) citrate, [Bi(Hcit)], and the nature of the adduct **1** between it and ranitidine [*N,N*-dimethyl-5-(3-nitromethylene-7-thia-2,4-diazaoctyl)furan-2-methanamine], which is currently on clinical trial as an antiulcer drug, has been investigated by ^{1}H and ^{13}C NMR spectroscopy and polarography. Complex **1** undergoes a structural transition in aqueous solution with an associated pK_a of 6.2. Ranitidine appears to be involved in second-co-ordination-sphere interactions with polymeric bismuth(III) citrate species *via* the $HNMe_2^+$ group for which the pK_a is raised from 8.64 to 8.90, whereas the pK_a of the diaminonitroethene group of ranitidine (2.2) is unaffected. In solutions of **1** in $(CD_3)_2SO$ this interaction increases the rate of NH exchange compared to free ranitidine. The chemical properties of **1** in aqueous solution differ from those previously reported for the potassium ammonium adduct, colloidal bismuth subcitrate, a drug in current clinical use. Complexation of both citrate and ranitidine to Bi^{III} in acidic solutions (pH 2.5–3) was detected by polarography, which demonstrated the existence of rapid deprotonation equilibria for bismuth(III) citrate complexes in the range pH 1–5.8. Since antiulcer drugs are subjected to low-pH environments in the stomach, such equilibria may be relevant to the biological activity of ranitidine bismuth citrate.

Bismuth compounds have been used for treating gastrointestinal disorders for more than 200 years.[1] Recently the effectiveness of bismuth has been attributed to its bacteriocidal activity towards *Helicobacter pylori*, a microorganism which has been implicated in the pathogenesis of gastric and duodenal ulcer disease.[1]

There has been particular interest for drug use in forms of bismuth(III) citrate solubilized by ammonium and potassium hydroxides. They are the basis of so-called colloidal bismuth subcitrate present, for example, in the drugs Telen (Byk Gulden) and De-Nol (Gist Brocades).[2] The crystal structures of several adducts in this class have been determined.[3–8] They contain stable dinuclear units $[(cit)BiBi(cit)]^{2-}$ (H_4cit = citric acid = 3-carboxy-3-hydroxypentane-2,5-dioic acid) with additional O^{2-}, OH^- and H_2O ligands, and these subunits aggregate further *via* bridging citrate ligands and a network of hydrogen bonds involving citrate, ammonium ions and water. In these compounds, Bi^{III} has a high co-ordination number of 9, and there are short bismuth–alkoxide (C–O^- of citrate) bonds of *ca.* 2.13 Å. The stereochemical role played by the bismuth(III) lone pair of electrons is particularly notable. The high solubility of these bismuth citrate compounds in water has been attributed to the presence of channels in the aggregates.[7]

In addition to the well established organic histamine (imidazole-4-ethanamine) H_2-receptor antagonists such as cimetidine and ranitidine [*N,N*-dimethyl-5-(3-nitromethylene-7-thia-2,4-diazaoctyl)furan-2-methanamine], bismuth compounds can also be efficacious in the treatment of peptic ulcers, and recently an adduct† of ranitidine with bismuth citrate (ranitidine bismuth citrate) has entered clinical trials.[9] This compound is highly water-soluble, but no chemical studies of it have yet been published. In this paper we consider the solubilization of bismuth citrate by a variety of amines and also investigate the properties of ranitidine bismuth citrate (referred to as complex **1**). Solution ^{1}H and ^{13}C NMR spectroscopy were chiefly employed, but we also demonstrate that polarography provides a very sensitive method for detection of interactions of both citrate and ranitidine with Bi^{III}



Ranitidine

Experimental

Materials.—Bismuth citrate [Bi(Hcit)], ranitidine, ranitidine hydrochloride and ranitidine bismuth citrate‡ were supplied by Glaxo. The salt $Bi(NO_3)_3{\cdot}5H_2O$ (Aldrich, A. R.), iron(III) citrate (Fluka-Garantie), citric acid monohydrate (Aldrich, A. R.), trisodium citrate (Aldrich, A. R.), $NaNO_3$ (Aldrich, 99.999%), NaOD (Goss) and DCl (Aldrich) were used as received.

NMR Spectroscopy.—Proton and ^{13}C-{^{1}H} NMR spectra were recorded on JEOL GSX270, GSX500 and Bruker AM400 spectrometers at 270, 500 and 400 MHz, respectively, for ^{1}H, and 67.5, 125 and 100 MHz, respectively, for ^{13}C, using 5 mm tubes, *ca.* 0.6 cm^3 of solution, at ambient temperature (*ca.* 297 K) unless otherwise stated. Typical ^{1}H spectral accumulation conditions were 16 K points, 32 scans, 45–60° pulses, and relaxation delay of 2–3 s, and for ^{13}C, 16 K points, relaxation delay 2.0 s, 6000–30 000 scans and 45° pulses. The chemical shift reference for ^{1}H and ^{13}C was internal sodium 2,2,3,3-tetradeuterio-3-trimethylsilyl propionate for D_2O solutions, and tetramethylsilane for dimethyl sulfoxide (dmso) solutions.

† We use the term 'adduct' to cover possible first- and second-co-ordination-sphere interactions between ranitidine and bismuth citrate; since the interactions turn out to be second sphere, the term 'complex salt' could also be used.

‡ Ranitidine bismuth citrate is an amorphous solid containing ranitidine, bismuth and citrate in the approximate molar ratio 0.84:1:0.94.

There was no evidence for binding of the reference to Bi^{III} under the conditions used (checks carried out using dioxane as secondary reference).

For determination of pK_a values, Henderson–Hasselbalch curves were fitted to experimental data using the KALEIDAGRAPH numerical analysis program[10] (Sinergy Software) on an Apple Macintosh SE/30 computer. Adjustments of pH* (see below) in D_2O solutions were made using NaOD or DCl.

To investigate the extent of solubilization of bismuth citrate by amines, known amounts of the amines were added to a suspension of [Bi(Hcit)] (8 mg, 20 μmol) in D_2O (1 cm^3) which was stirred and heated if necessary at a temperature between ambient and 368 K for 2–60 min until a clear solution was obtained. To determine the apparent equilibrium constant, the relative amounts of citrate and amine in the equilibrium solution were measured by integration of ^1H NMR peaks.

Polarography.—Differential pulse polarograms were recorded on either a model 264 EG & G polarographic analyzer/stripping voltameter or a Metrohm instrument at *ca.* 289 K using a three-electrode system with a Ag–AgCl reference electrode, dropping mercury electrode and auxiliary platinum electrode, and 30 μmol dm^{-3} bismuth solutions. The ionic strength was maintained at *ca.* 0.5 mol dm^{-3} with $NaNO_3$ as the supporting electrolyte. We report potentials relative to Ag–AgCl which is + 0.222 V relative to the normal hydrogen electrode.

Infrared Spectroscopy.—Spectra were recorded as Nujol mulls between KBr plates on a Perkin-Elmer 1700 IR FT spectrometer.

pH *Measurements.*—These were made using a Corning pH meter 145 equipped with an Aldrich micro combination electrode calibrated with Aldrich buffer solutions at pH 4, 7 and 10. The pH meter readings for D_2O solutions are recorded as pH* values, *i.e.* uncorrected for the effect of deuterium on the glass electrode.

Results and Discussion

Solubilization of [Bi(Hcit)].—We determined the amounts of various amines which were required to solubilize [Bi(Hcit)], Table 1. From the integration of the peaks in ^1H NMR spectra of the supernatants from mixtures of amines and bismuth citrate, apparent equilibrium constants were calculated on the assumption that 1:1 complexes are formed [equation (1)]. It

$$[Bi(Hcit)](s) + amine \rightleftharpoons [Bi(cit)]\cdot Hamine \quad (1)$$

can be seen (Table 1) that the constants correlate to some extent with the pK_a values of the amines, the strongest bases being the most effective solubilizing agents. Ethylenediamine is more effective than its pK_a values would predict, suggesting that other factors such as first- or second-co-ordination sphere binding of the amine may also be involved. Although we were able to solubilize [Bi(Hcit)] with Na_2CO_3 and $NaHCO_3$ (mol ratios *ca.* 1:2) in water, the resulting solutions were unstable, giving rise to precipitates within a few hours. This contrasts with solutions obtained using the above amines which remained clear and stable for > 1 week, again suggesting that the amine is involved in interactions in solution.

Infrared Spectroscopy.—The solid-state IR spectra of [Bi(Hcit)] and ranitidine bismuth citrate, complex **1**, are shown in Fig. 1. The most notable difference is the presence of a sharp band at 3455 cm^{-1} in the spectrum of [Bi(Hcit)] assignable to the C(3)O–H stretch which is absent in the spectrum of **1**. Such a band is also present for $Na_3(Hcit)$ and a mechanical admixture of bismuth citrate and ranitidine but absent for iron(III) citrate (Fig. 1). These data show that **1** is not simply a mixture of ranitidine and [Bi(Hcit)] and suggest that solubilization of [Bi(Hcit)] by ranitidine leads to deprotonation and co-ordination of the citrate C(3)OH group allowing the formation of a six-membered chelate ring, as also expected for Fe^{III}, but not for Na^+.

Table 1 Correlation between the solubilization of [Bi(Hcit)] by various amines and their pK_a values. An apparent equilibrium constant (K) for formation of a 1:1 complex was determined by NMR measurements of the citrate: amine mol ratio in solution

Amine	Ratio[a]	pH[b]	K/dm^3 mol^{-1}	pK_a[c]
Pyridine	1:5	6.9	0.3	5.24
Imidazole	1:2	6.5	0.5	7.03
Ranitidine	1:2	6.9	1.5	8.64
Triethylamine	*d*	*d*	1.94	10.75
1,2-Diaminoethane	1:0.5	8.4	*e*	9.89, 7.08
Dimethylamine	1:2	10.7	*e*	10.80

[a] Molar ratio bismuth:amine required for complete solubilization of [Bi(Hcit)]. The amine was added in 0.5 mol ratio steps. [b] Of clear solution, except pH* for imidazole, ranitidine and pyridine. [c] Values from ref. 11. [d] Not determined, poor solubility of amine in water. [e] Citrate and amine resonances overlapped.

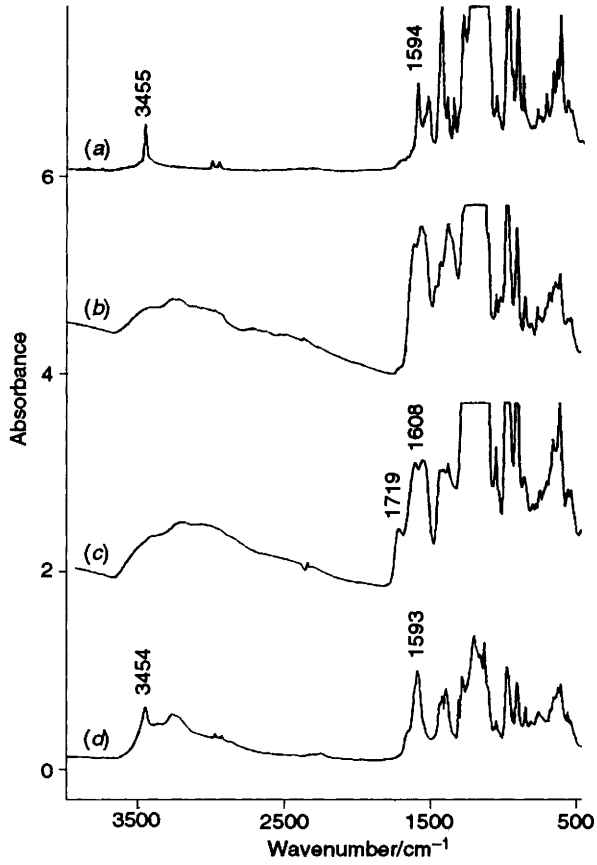


Fig. 1 Infrared spectra of (*a*) [Bi(Hcit)], (*b*) complex **1**, (*c*) [Fe^{III}(Hcit)] and (*d*) $Na_3(Hcit)$. The absence of a sharp OH stretch in (*b*) and (*c*) is notable, and the peak at 1719 cm^{-1} in (*c*) suggests the presence of uncomplexed carboxyl groups in the iron(III) complex

NMR Spectroscopy.—Comparison of pH* *Dependence of Complex* **1** *and Ranitidine.* The ^1H NMR spectrum of complex **1** in D_2O is shown in Fig. 2 together with the resonance assignments[12] (the atom labelling is the same as that used previously[12]). The chemical shifts of resonances for H_a, H_b, H_e, H_f and citrate protons of **1** are pH*-dependent, and the pH* dependence of the chemical shift of the ^1H NMR resonance for

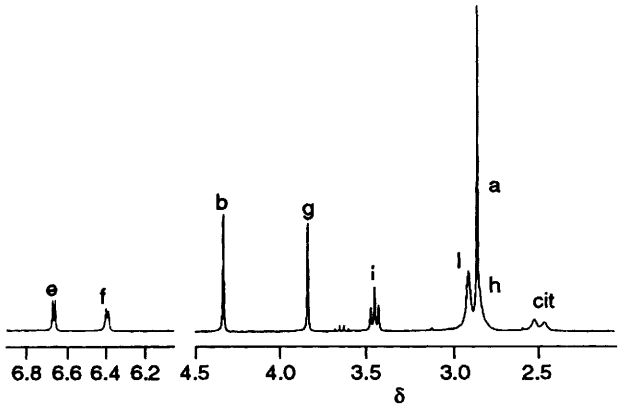


Fig. 2 The 270 MHz ^{1}H NMR spectrum of complex **1** in D_2O, pH* 4.5. One of the broadened AB doublets of citrate is overlapped with the H_a, H_b and H_i resonances of ranitidine. Resonance H_k is absent due to exchange with deuterium. The quartet at δ 3.65 is due to ethanol impurity. The labelling scheme is shown in the text

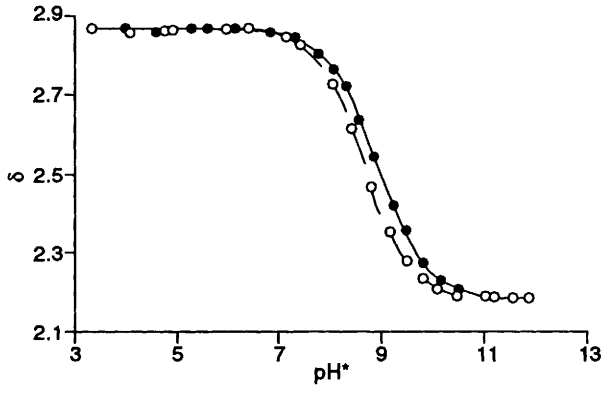


Fig. 3 Dependence of the ^{1}H NMR chemical shift of the NMe_2 (a) protons of complex **1** (●) and ranitidine (○), both as 20 mmol dm^{-3} solutions in D_2O, showing the increase in pK_a of this group in **1**

the NMe_2(a) group of ranitidine alone is compared to that for complex **1** in Fig. 3. The curves were fitted using pK_a values of 8.64 ± 0.01 and 8.90 ± 0.01 for ranitidine and **1**, respectively. The increase in pK_a was not due to ionic strength effects since the pK_a of ranitidine in the presence of a ten-fold molar excess of sodium nitrate was found to be the same as that in water alone (data not shown).

Thus, there is no clear evidence for an inner-sphere interaction between ranitidine and bismuth under these conditions, but the stabilization of the protonated group NMe_2H^+ in solutions of complex **1** relative to ranitidine alone can be attributed to hydrogen-bonding interactions with bound citrate. It is clear that such outer-sphere interactions can play a major role in determining the structure of bismuth(III) carboxylate complexes. For example, Breeze *et al.*[13] have recently shown in their X-ray crystallographic work on ammine and amine adducts of tetrakis(trifluoroacetato)bismuthate(III) complexes that outer-sphere hydrogen-bonding interactions between NH and carboxylate oxygens determine both the stability of the complexes and the geometry around Bi^{III}. In crystal structures of ammonium adducts of bismuth(III) citrate such as $[NH_3]_4[Bi(cit)(Hcit)(H_2O)_2]\cdot H_2O$ there is close contact between NH_4^+ ions and citrate and water oxygen atoms in the lattice.[4]

Fig. 4 shows the ^{1}H NMR chemical shifts of the citrate resonances of complex **1** over the pH* range 4–12. Below pH* 3.5 a precipitate formed which is likely to contain BiOCl as has been observed for colloidal bismuth subcitrate solutions.[2]

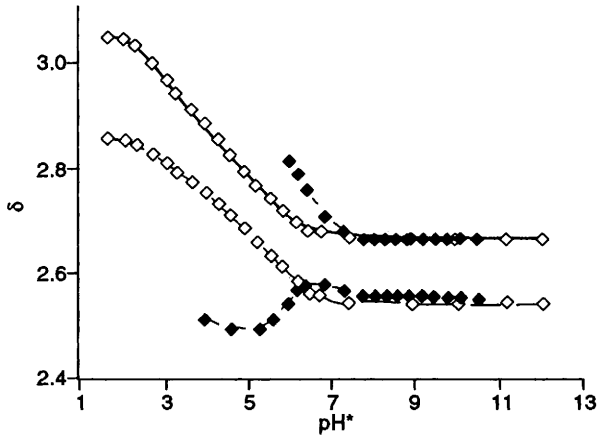


Fig. 4 Dependence of the chemical shifts of the major citrate CH_2 ^{1}H NMR resonances of complex **1** (◆) and citrate alone (◇) on pH*. Above pH* *ca.* 7.5 the shifts are almost identical, suggesting these resonances from solutions of **1** represent unbound citrate. At low pH* values (< 4, 20 mmol dm^{-3}) solutions of **1** give rise to precipitates. The low-field citrate peaks for **1** are overlapped with ranitidine peaks at pH* < *ca.* 6

Above pH* 7.5 it can be seen that the shifts of the citrate resonances are almost identical to those of citrate alone. From this it might be reasoned that at pH* > 7.5 citrate is not bound to Bi^{III} but is displaced by OH^- or O^{2-}, a conclusion which others have made for ammonium adducts of bismuth citrate based on similar data.[4,7] However, there is evidence from ^{13}C NMR and polarographic data (see below) that, in the case of **1**, bismuth citrate complexes are also present in solution at high pH* implying that their ^{1}H resonances are too broad to observe. This illustrates a difference between **1** and ammonia adducts with bismuth citrate. The broadening of the citrate ^{1}H NMR resonances is likely to be due to the presence of different forms of bound citrate in intermediate exchange on the ^{1}H NMR time-scale.

The ^{13}C NMR spectra of complex **1** in D_2O at various pH* values are shown in Fig. 5(*a*). Marked changes are seen for citrate resonances in the region δ 175–200 [CO_2^-, C(1), C(5) and C(6)], 75–90 [CO^-, C(3)] and 47–55 [CH_2, C(2) and C(4)]. At pH* > 5.8 the CO_2^- [C(1), C(5) and C(6)], CO [C(3)] and CH_2 [C(2), C(4)] regions suggest that there is a major form of bound citrate present plus at least two other minor forms, such that at pH* 8.6 the major form accounts for about 50% of the citrate and has chemical shifts close to that of unbound citrate at the same pH*, Fig. 5(*b*). The chemical shifts of the minor citrate peaks were largely unaffected by pH* changes, whereas those for the major peaks of bound citrate were fitted by pK_a values of 6.22 ± 0.05 [C(6)], 6.21 ± 0.05 [C(3)] and 6.21 ± 0.05 [C(2), C(4)] respectively. The value calculated for the C(1), C(5) curve was slightly higher (6.66) but is subject to greater error because the shift change is much smaller. These can be contrasted with pK_3 for citrate alone of 5.64 (pK_1 and pK_2 being 2.89, 4.34, respectively).[14] The measured pK_a could represent deprotonation of bound citrate, but it seems unlikely that this would give rise to shifts which are the same as for unbound citrate. One possibility is that the deprotonation of Bi-bound H_2O or OH^- is occurring, giving rise to additional Bi–O(H)–Bi bridges, displacement of citrate from Bi, and rapid exchange (on the NMR time-scale) of unbound and bound citrate. The presence of substantial amounts of Bi-bound citrate in solutions of **1** at high pH* is quite distinct from the reported behaviour of colloidal bismuth subcitrate, for which the citrate ligands are 'hardly co-ordinated' at pH > 7.[7] This can be attributed to the presence of different cations (ranitidine *versus* ammonium) and to the different Bi:citrate mol ratios in these two preparations (greater than or approximately equal to 1:1 for complex **1**, and < 1.0:1 for the subcitrate).

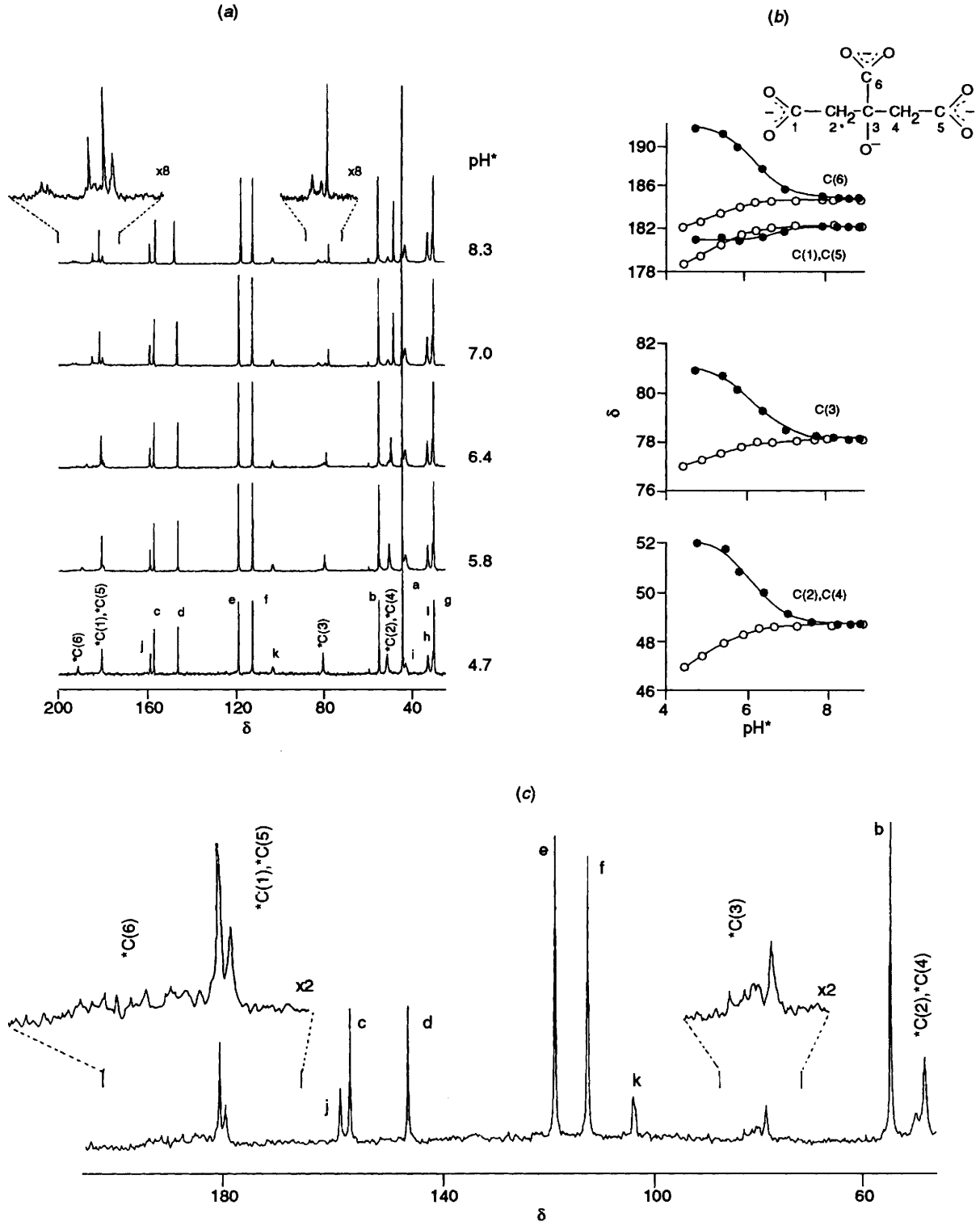


Fig. 5 (*a*) The 67.5 MHz ^{13}C-{^{1}H} NMR spectra of 0.2 mol dm^{-3} complex **1** in D_2O at various pH* values. The labelling scheme for ranitidine peaks is as before; resonances for bound citrate are labelled *C(1), *C(5), *C(2), *C(4), *C(3) and *C(6). The broadening of resonance k is due to exchange of the associated proton with deuterium, and that of l is due to restricted rotation around the double bond. (*b*) Comparison of the pH* dependences of the ^{13}C NMR chemical shifts of the major (most intense) citrate resonances of **1** (●) together with those of citrate alone (○). (*c*) The 100 MHz ^{13}C-{^{1}H} NMR spectrum of 50 mmol dm^{-3} complex **1**, pH 6.2. The peaks marked * were not observed in reported spectra of the ammine adduct $K_{4.75}[NH_4]_{0.25}[Bi_2(cit)_2(Hcit)]\cdot 14H_2O$ under similar conditions[4]

The aggregation properties of complex **1** are also different from those of colloidal bismuth subcitrate. In order to compare ^{13}C NMR spectra of **1** directly with published spectra of the ammine adducts $K_{4.75}[NH_4]_{0.25}[Bi_2(cit)_2(Hcit)]\cdot 14H_2O$ and colloidal bismuth subcitrate under similar conditions[4] we also recorded the ^{13}C-{^{1}H} NMR spectrum of 50 mmol dm^{-3} **1** in D_2O, pH* 6.2 [Fig. 5(*c*)]. This clearly showed the presence of peaks for different forms of bound citrate at δ 180.4 [C(6)],

175–196 [C(1), C(5), a band of broad peaks], 80–84 [C(3), at least three-peaks] and 51 [C(2), C(4)], which are similar to the peaks for **1** at 0.2 mol dm^{-3}. In contrast ammine adducts of bismuth(III) citrate have been reported to give rise to only one set of peaks (over the range pH* 4–9) and, even at very high concentration (220 mg cm^{-3}, *ca.* 0.4 mol dm^{-3}), colloidal bismuth subcitrate does not exhibit additional peaks for other types of bound citrate at pH* 6.2.[7] Again this shows that the ammine/amine plays a role in determining the structural forms of bismuth citrate which are present in the adducts. These forms are likely to be different for different adducts and therefore their biological activities may differ.

The ^{13}C NMR spectra of a 0.7 mol dm^{-3} solution of complex **1** at 293, 313 and 343 K, pH 8.6 (data not shown), gave evidence for chemical exchange between the different forms of bound citrate with broadening and shifting of peaks (at higher temperatures). In contrast, over this temperature range the CH_3 and CH_2 peaks of ranitidine l, h, i became sharper due to the known increase in rotation rate about the ethene bond.[15]

In order to investigate possible interactions of the NMe_2H^+ group of ranitidine with bismuth and citrate in solutions of complex **1** we lyophilized solutions of **1** in water at various pH values, and of ranitidine at the same pH value, and redissolved the solids in $(CD_3)_2SO$. A comparison of spectra for pH 4.3 solutions is shown in Fig. 6; those for pH 5.7 solutions were similar. The most notable differences are for peaks from protons at the dimethylaminomethylfuran end of ranitidine. The NMe_2H^+ proton does not give rise to an observable signal for **1**, and the peaks for $H_{a,b,e,f}$ are shifted by > 0.3 ppm. The absence of the NH peak did not appear to be due to the presence of more water in the sample of **1** since addition of further water (up to 1 mol dm^{-3}) to the ranitidine sample in dmso still allowed observation of this peak (data not shown). It can be concluded that outer-sphere hydrogen-bonding occurs between the NMe_2H^+ group and bismuth citrate species including bound H_2O, OH^- or O^{2-} ligands. Such hydrogen-bonding might be expected to decrease the rate of NH exchange and therefore sharpen the NH ^1H NMR resonance, but in the present case there is presumably a dynamic equilibrium between the different types of hydrogen-bonded structures and between hydrogen-bonded and non-hydrogen-bonded ranitidine which leads to line broadening.

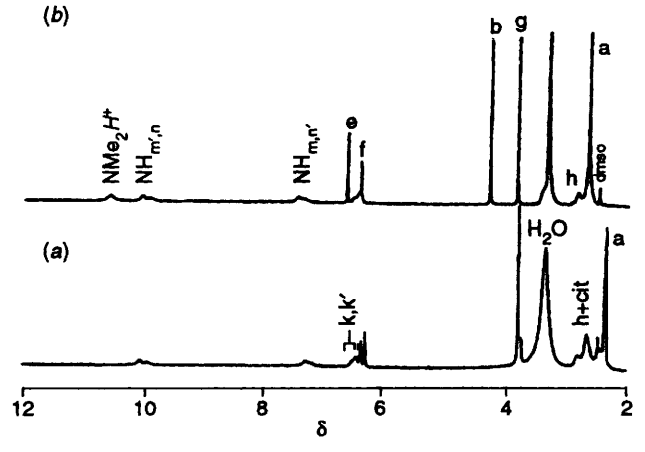


Fig. 6 Comparison of the ^1H NMR spectra of samples of (*a*) complex **1** and (*b*) ranitidine, which had been prepared by dissolving in water at pH 4.3, followed by lyophilization and redissolution in $(CD_3)_2SO$. The absence of an observable NMe_2H^+ peak for **1** is notable, as are the shifts of $H_{a,b,e,f}$ suggesting that the dimethylaminomethylfuran end of ranitidine is involved in interactions with bismuth citrate species. The H_2O peak is larger in (*a*) but probably contains contributions from H_2O or OH ligands. Addition of water to the sample in (*b*) (to 1 mol dm^{-3}) still allowed observation of NMe_2H^+. The protons NH_n and NH_m are involved in internal hydrogen bonding, and the resonances for the *Z* and *E* isomers are labelled with unprimed and primed letters (k, k', m, m', n, n')[16]

Polarography.—We studied solutions containing $Bi(NO_3)_3$ and citric acid in a 1:10 mol ratio, $Bi(NO_3)_3$ and ranitidine hydrochloride in a 1:10 mol ratio, and $Bi(NO_3)_3 \cdot 5H_2O$, citric acid and ranitidine in a 1:10:10 mol ratio at various pH values in the range 1–8 with $NaNO_3$ (0.5 mol dm^{-3}) as a supporting electrolyte. Bismuth nitrate alone at pH 1 gave rise to single peak at −0.03 V. Above pH 2 this peak decreased in intensity and a second peak appeared at −0.13 V, and by pH 4 both these peaks were broad and weak, consistent with the known

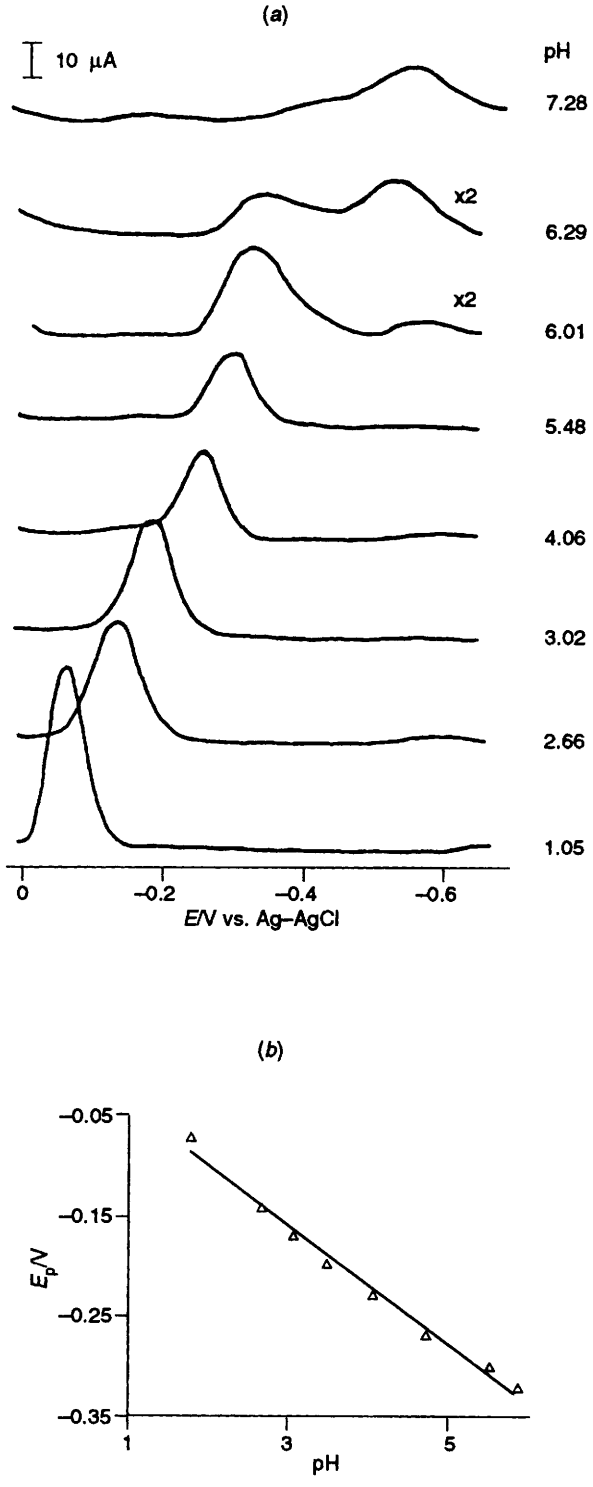


Fig. 7 (*a*) Differential pulse polarograms for an aqueous solution containing Bi^{3+} and citric acid in a 1:10 mol ratio as a function of pH. (*b*) Linear dependence of peak shift on pH showing that reduction is accompanied by the uptake of one proton

tendency[2,17] for hydrolysis to give a mixture of hydroxo species such as $[Bi(OH)_2]^+$, $Bi(OH)_3$, $[Bi(OH)_4]^-$ and $[Bi_6(OH)_{12}]^{6+}$. In the presence of 10 mol equivalents of citric acid only a single peak was observed from pH 1 to 5.5, which showed an approximate linear shift of 59 mV per pH unit, Fig. 7. These data suggest that reduction is accompanied by the uptake of one proton, and that there is a rapid deprotonation equilibrium between at least two species which are being reduced, *e.g.* $[Bi(Hcit)] \rightleftharpoons [Bi(cit)]^- + H^+$. At pH > 5.8 a second peak appeared at *ca.* −0.55 V and the initial peak decreased in intensity, Fig. 7. These data suggest that at least two types of bismuth(III) citrate complexes exist under these conditions.

Polarograms from a mixture of $Bi(NO_3)_3$ and ranitidine hydrochloride in a 1:10 mol ratio contain three peaks at pH 1.73, assignable to reduction of Bi^{3+} (−0.06 V) and of RNO_2H^+ (−0.47 V) and RNO_2 (−0.80 V) of ranitidine. The latter two peaks have a similar pH dependence to that for free ranitidine, with a corresponding pK_a value of 2.2 ± 0.05, showing that the nitro group is not involved in bismuth(III) complexation. At pH 2.7 two 'Bi^{3+}' peaks are detected, Fig. 8(*a*), one assignable to Bi^{3+} ions (−0.08 V, I), and the other (−0.22 V) to a bismuth(III)-ranitidine complex (II). By pH 4.7 both these peaks are very broad and barely detectable.

It is known that Bi^{III} has a high affinity for both nitrogen and sulfur as ligands, as well as oxygen.[17] Thus the thioether S, amine N, and furan O of ranitidine are all potential donors for Bi^{III}. The strongest interaction may involve formation of an NMe_2–furan O five-membered chelate ring. Comparative studies of citrate and ranitidine complexation to Bi^{III} cannot be made by NMR spectroscopy under the same conditions as those used for polarography since at the higher concentrations needed for NMR hydrolysis is dominant (precipitation of BiOCl).

Polarograms obtained from solutions of $Bi(NO_3)_3$, citric acid and ranitidine in a mol ratio 1:10:10, Fig. 8(*b*), suggest that at pH 2.7 both bismuth–citrate and –ranitidine species are present (overlapping peaks at −0.16 and −0.21 V). The differential pulse polarogram of a 0.1 mmol dm^{-3} solution of complex **1** in 0.1 mol dm^{-3} $NaNO_3$ (pH 5.80) showed a peak at −0.28 V, similar to that of bismuth citrate alone under similar conditions (−0.3 V), and also similar to the polarogram of a Bi^{3+}–citrate mixture in a 1:10 mol ratio at pH 5.8, as described above. Thus ranitidine does not bind directly to Bi^{III} in solutions of **1** under these conditions, in agreement with NMR data.

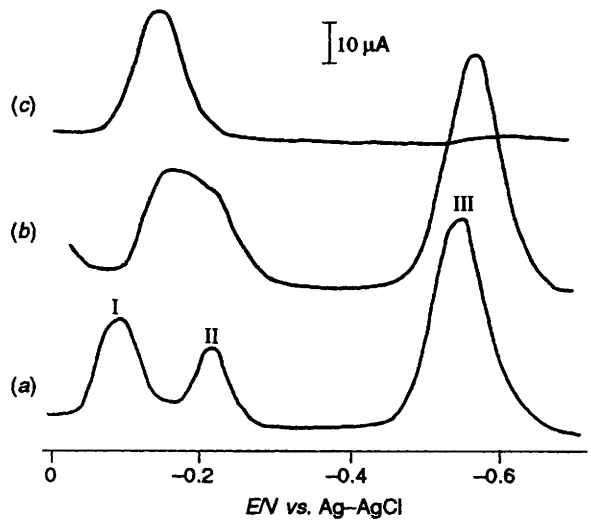


Fig. 8 Differential pulse polarograms for solutions containing (*a*) Bi^{3+} and ranitidine hydrochloride, mol ratio 1:10, pH 2.70, (*b*) Bi^{3+}, citric acid and ranitidine hydrochloride, mol ratio 1:10:10, pH 2.69, and (*c*) Bi^{3+} and citric acid, mol ratio 1:10, pH 2.66. Peak assignments for (*a*): I, Bi^{3+}; II, Bi^{3+}–ranitidine; III, RNO_2 (ranitidine). The Bi^{3+} peak at *ca.* −0.15 V in (*b*) appears to contain contributions from both Bi^{3+}–citrate and –ranitidine species

Conclusion

Ranitidine is one of many amines, including ammonia, which can solubilize [Bi(Hcit)]. The primary function of the amine seems to be to deprotonate the citrate hydroxyl group which allows formation of a six-membered chelate ring. We have not been able to crystallize the adduct with ranitidine, complex **1**, but the infrared data are consistent with hydroxyl deprotonation. From recently reported crystal structures of bismuth(III) citrate complexes stabilized by ammonium ions as counter cations it seems likely that the species in solution are dinuclear units of the type $[(cit)BiBi(cit)]^{2-}$ with additional oxide, hydroxide and water ligands depending on the pH, and further aggregation into networks *via* hydrogen bonding by bridging citrates, water and counter cations. The structures of the aggregates are important in determining the properties, *e.g.* solubility and long-term stability, of solutions of the adducts. Therefore the chemical (and biological) properties of bismuth citrate adducts containing different counter cations are likely to differ significantly. Complex **1** appeared to release about half of the bound citrate at high pH in a process with an apparent pK_a of *ca.* 6.2. This may be due to the formation of complexes such as $[Bi_6O_4(OH)(cit)_3(H_2O)_3]^{3-}$ which has a lower bismuth:citrate ratio of 1:0.5, and is known to be stable at alkaline pH.[6] This behaviour is quite distinct from that of the ammonium adduct colloidal bismuth subcitrate which is reported to release nearly all of the bound citrate at pH > 7.[7] The increase in the pK_a of the terminal NMe_2H^+ group of ranitidine by 0.26 units in **1** compared to ranitidine alone provided evidence for second-sphere hydrogen-bonding interactions between ranitidine and bismuth citrate species in solutions of complex **1**, and such interactions were also apparent from ^1H NMR studies of the NH resonances of **1** in dmso compared to ranitidine alone. Using differential-pulse polarography, which is a powerful method for investigating complexation of Bi^{III} in aqueous solution[17] at low concentrations where NMR measurements are difficult, we were able to detect inner-sphere complexation of ranitidine to Bi^{III} at low pH (2) even in the presence of citrate, but not at higher pH, in agreement with NMR data. Two distinct types of bismuth(III) citrate species were detectable over the range pH 1–7, and the lower-pH form was found to be involved in a rapid deprotonation equilibrium. Since antiulcer drugs are subjected to low-pH environments in the stomach, such protonation equilibria may be relevant to the biological activity of ranitidine bismuth citrate.

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