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Short Communication

Differential pulse polarographic determination of cimetidine†

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Introduction

Cimetidine is a competitive histamine H_2-receptor antagonist that inhibits gastric acid secretion and is used for the treatment of peptic ulcers [1]. Its determination in plasma, urine and other biological media by high-performance liquid chromatography has been reported [2–4], and its physicochemical and spectroscopic properties investigated [5] with a view to its analysis by UV spectrometry and chromatography. The polarographic determination of cimetidine has apparently not been studied. This paper describes the polarographic behaviour of cimetidine complexed with Co(II) ions as a means of determining it at low concentrations.

Experimental

Apparatus

A three electrode cell with a dropping mercury electrode and a saturated calomel electrode was used in the polarographic analyser previously described [6]. The water-jacketed polarographic cell was maintained at 20±0.1°C. The capillary characteristic was 0.67 mg s^{-1} in 0.1 M KCl in open circuit at a mercury height of 90 cm. Polarographic curves were recorded in differential pulse mode with a scan rate of 5 mV s^{-1}. The scan was from −0.700 to −1.500 V vs SCE. The mercury column height was 90 cm and the modulation amplitude was 50 mV. pH measurements were done with a Corning model 12 research pH meter and the purity of water was controlled by a Yellow Spring

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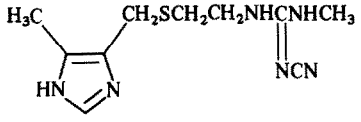
Instruments model 31 conductivity bridge. Solutions for polarography were deoxygenated with nitrogen gas, which was also directed above the solution during the scan.

Reagents and solutions

Cimetidine was kindly donated by Smith, Kline & French Laboratories and tested for purity by UV, IR and NMR spectroscopy. All other solutions were prepared with reagent grade chemicals. The Co(II) solutions were prepared from $Co(NO_3)_2.6H_2O$.

Results and Discussion

In the molecular skeleton of cimetidine there are two C=N, one C=C and one C≡N bonds that are theoretically reducible. The reduction of the compound was studied in



Britton–Robinson buffers at various pH values. At pH < 5, ill-defined d.p.p. peaks were observed, but they were of little value for quantitative analysis. The polarographic inactivity of the imidazole nucleus has been reported by Clark *et al.* [7]. When Co(II) ions were added to the 0.1 M KCl solution containing cimetidine, two peaks were observed (Fig. 1) at −0.980 V and at −1.370 V vs SCE. The former peak was due to the catalytic reduction of cimetidine and the latter to the reduction of the Co(II) ion. This was shown by adding increasing amounts of cimetidine to a solution containing a fixed amount of Co(II). The mechanism of the catalytic reduction was thought to be similar to the hydrogen discharge catalytic mechanism. Normally it is expected that the formation of a stable metal ion complex shifts the reduction potential of the central metal ion to more negative values [8]. In this case the height of the more positive peak increased linearly with cimetidine concentration and was also affected by Co(II) concentration (Fig. 2). This unusually sensitive peak was used for quantitative cimetidine determinations over the range 0.02–2 $\mu g\ ml^{-1}$.

As the catalytic peak current was a function of the free metal ion concentration, an excess of Co(II) was used. At high Co(II) concentrations, the d.p.p. peak of the cimetidine complex moved to more positive potentials while the reduction potential of the more negative peak was unaffected. On the other hand the linear range of peak current versus cimetidine concentration decreased at higher Co(II) concentrations. The concentration of Co(II) should thus be no larger than is necessary to obtain a wide linear range, but it should also be enough to provide sensitivity to lower cimetidine concentrations. The best concentration of Co(II) is therefore a matter of choice depending on the purpose of the analysis.

The current used for the determination of cimetidine was studied as a function of mercury column height (h) and temperature. Changes of the peak current with h and $h^{1/2}$ showed that the catalytic current was controlled by the adsorption of cimetidine on the dropping mercury electrode. The temperature coefficient of the peak current was *ca.* 1.3% $°C^{-1}$ (Fig. 3). This temperature coefficient and the mercury column height experiments indicate that the process was not entirely diffusion controlled.

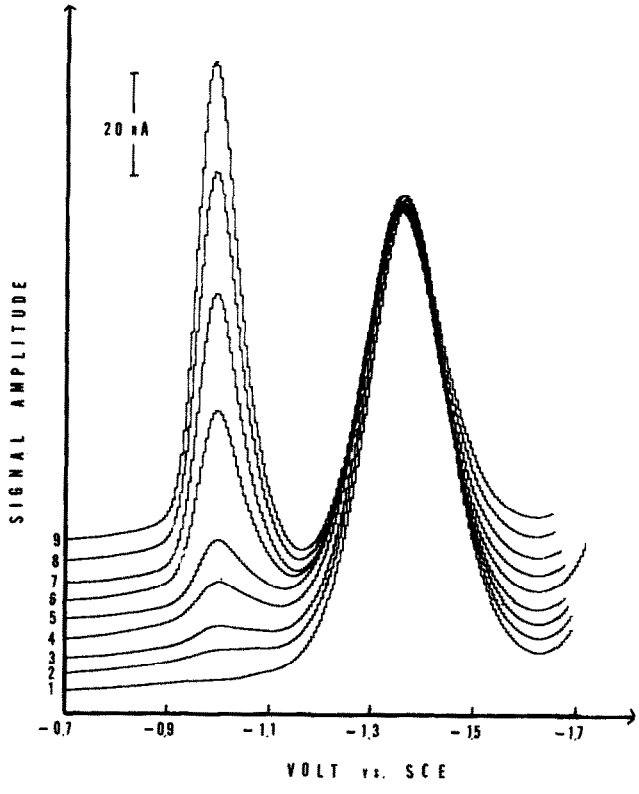


Figure 1
Variation of d.p.p. peak height with cimetidine concentration. (1) 0, (2) 0.2, (3) 0.38, (4) 0.74, (5) 1.23, (6) 2.93, (7) 4.57, (8) 6.16 and (9) 7.70×10^{-6} M cimetidine in 0.1 M KCl and 1.4×10^{-4} M Co(II).

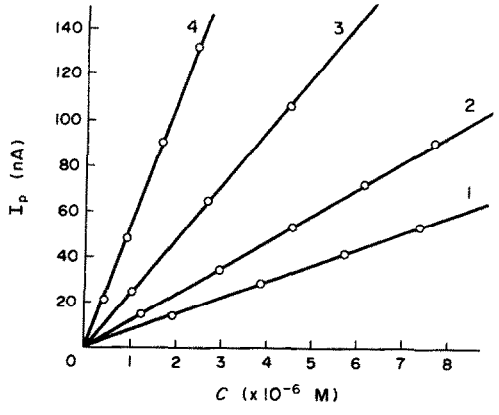


Figure 2
Variation of peak currents with concentration of cimetidine at (1) 1.0, (2) 1.4, (3) 4.0 and (4) 10×10^{-4} M cobalt (II).

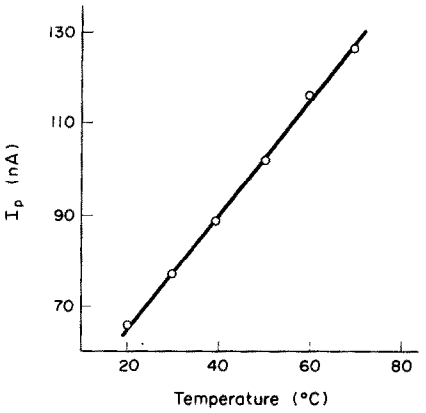


Figure 3
Variation of peak current of 1.10×10^{-5} M cimetidine with temperature at −0.980 V vs SCE in 1.0×10^{-4} M Co(II).

The reversibility of the electrode reactions was demonstrated by several methods: peak potentials did not vary with drop time or temperature, and the wave heights in forward and reverse scan were almost equal [9]. No attempt was made to determine the number of electrons transferred in the electrode reaction, but the electrode mechanism may be similar to that found for nickel (II)–ethylenediamine complexes [10].

Cimetidine is marketed in tablet form under the name "Tagamet". Successful determinations of the cimetidine content of "Tagamet" tablets are shown in Table 1. The further application of the method to the analysis of cimetidine in biological fluids will be published separately.

Table 1
Estimation of cimetidine in film-coated tablets

	mg cimetidine per tablet (content 200 mg)	
No. of tablets analysed	d.p.p. method	Spectrophotometric method [11]
5	199.5	—
10	199.8	—
20	200.6	—
Mean	200.0	198.4
Standard deviation	0.55	—
Recovery (%)	100.0	99.2

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