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Short Communication

# POTENTIOMETRIC DETERMINATION OF SOME COMMON ALKALOIDS WITH A PICRATE-SELECTIVE ELECTRODE

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*Summary.* Potentiometric methods are described for the determination of alkaloids, based on the formation of insoluble alkaloid picrate salts, using a picrate ion-selective indicating electrode. Micro-amounts of strychnine, papaverine, quinine and cocaine were determined by direct potentiometry and titrimetrically, using Gran plots, with average errors of about 4% and 2%, respectively. The method was successfully applied to pharmaceutical preparations.

The commonest procedure for the determination of alkaloids in pharmaceutical preparations includes precipitation by making the solution alkaline with ammonia, extraction with chloroform, evaporation to dryness, and weighing the residue. Such methods are fairly accurate but demand toxic reagents and are time-consuming. Alkaloids are also determined by spectrofluorimetry [1] and differential pulse polarography [2].

In this communication, potentiometric methods are described for the determination of several alkaloids with picrate ions, either by direct potentiometry or by potentiometric titration, using as indicator electrode the recently described picrate ion-selective electrode [3—5]. The method is based on the formation of insoluble alkaloid picrates. Both versions are sensitive, rapid, fairly accurate and simple, and were employed successfully for the determination of papaverine and quinine in pharmaceutical preparations. The method, properly modified, can be used for the determination of many alkaloids.

## *Experimental*

*Instrumentation.* The electrodes, the reaction cell and the recording system were the same as previously reported [3].

*Reagents.* All solutions were prepared with deionized twice-distilled water and reagent-grade substances, except where stated.

Standard picrate solutions were prepared by neutralizing suitable picric acid solutions with sodium hydroxide to the appropriate pH value. All picrate solutions were stored in amber bottles. The picric acid used (Merck 99.8%) was standardized against standard sodium hydroxide solution.

Solutions of strychnine sulfate, papaverine hydrochloride, quinine hydrochloride, and cocaine hydrochloride (0.0100 M) were prepared by dissolving pure (Merck) substances in water. More dilute standard solutions were prepared by dilution.

*Method 1.* (For the direct potentiometric determination of alkaloids with sodium picrate.) Pipet into the reaction cell a 10.00-ml aliquot of the sample and 10.00 ml of standard sodium picrate solution. Start the stirrer, and after the potential has stabilized to ±0.1 mV (ca. 7 min) record the millivoltmeter reading ($E_2$). Repeat the procedure replacing the sample with 10.00 ml of water ($E_1$).

For strychnine samples in the ranges $2.00 \times 10^{-4}$—$2.00 \times 10^{-3}$ M and $4.00 \times 10^{-3}$—$2.00 \times 10^{-2}$ M, the sodium picrate solutions used were $3.00 \times 10^{-3}$ and $3.00 \times 10^{-2}$ M, respectively, at pH 5.8. For papaverine samples in the ranges $2.00 \times 10^{-4}$—$1.00 \times 10^{-3}$ M and $1.00 \times 10^{-3}$—$1.00 \times 10^{-2}$ M, the sodium picrate solutions used were $1.50 \times 10^{-3}$ and $1.50 \times 10^{-2}$ M, respectively, at pH 3.5. For quinine and cocaine samples in the range $1.00 \times 10^{-3}$—$1.00 \times 10^{-2}$ M, a $1.50 \times 10^{-2}$ M sodium picrate solution at pH 6.0 was used.

After the completion of the reaction, the free picrate concentration, [P], is calculated from $[P] = [P]_0 \text{ antilog } (\Delta E/S)$, where $[P]_0$ is the initial picrate concentration, $\Delta E = E_2 - E_1$, and $S$ is the slope of the potential vs. log [P] curve.

*Method 2.* (For the titrimetric determination of alkaloids with sodium picrate, using a Gran plot.) Pipet into the reaction cell a 15.00-ml aliquot of the sample, start the stirrer and titrate with a standard sodium picrate solution. Reach the region of the equivalence point with 3 or 4 large increments of titrant, and then take 5—6 additional values of the cell potential vs. titrant volume in the range 10—100% beyond the equivalence volume.

Calculate the factor $F = (V_0 + V)10^{E/S}$, where $V_0$ is the initial volume, $V$ is the volume of titrant added, and $E$ is the cell potential [6]. The plot $F$ vs. ml of titrant added is linear with the $x$-intercept at the equivalence volume. The line is calculated by a least-squares fit.

Clean the reaction cell and the reference electrode with acetone and the picrate electrode with water, and wipe with soft paper after each measurement.

*Results and discussion*

The optimum pH for each alkaloid was calculated from $pH \leqslant 12 - pK_b$, where $K_b$ is the dissociation constant of the alkaloid. At this pH value the alkaloid is nearly 100% in the cationic form (protonated).

Determinations on aqueous alkaloid solutions of known concentrations by direct potentiometry gave the results shown in Table 1. The average recovery of strychnine was about 97%; similar results were obtained with a phosphate buffer of pH 5.8. The average recovery of papaverine was 99%; similar results were obtained with a phthalate buffer of pH 3.5. For papaverine solutions in the range $1 \times 10^{-4}$—$2 \times 10^{-4}$ M no precipitate was visible in the reaction cell, although $\Delta E$ values were obtained. The average recovery of quinine was 96%. The large negative error in the first (20 μmol) quinine sample is due to the solubility of the picrate salt. The positive errors in the determination of cocaine are due to the response of the picrate electrode to

TABLE 1

Results for aqueous solutions of alkaloids by direct potentiometry

| Alkaloid | Picrate (μmol) | Alkaloid (μmol) | | Error (%) |
|---|---|---|---|---|
| | | Taken | Found[a] | |
| Strychnine sulfate, | 30.0 | 4.00 | 3.88 | −3 |
| $2C_{21}H_{22}N_2O_2 \cdot H_2SO_4 \cdot 5H_2O$, | 30.0 | 8.00 | 8.16 | +2 |
| M.w. 856.96 | 30.0 | 20.0 | 19.0 | −5 |
| | 300 | 40.0 | 38.0 | −5 |
| | 300 | 140 | 134 | −4 |
| | 300 | 200 | 198 | −1 |
| Papaverine hydrochloride, | 15.0 | 2.00 | 1.98 | −1 |
| $C_{20}H_{21}NO_4 \cdot HCl$, | 15.0 | 4.00 | 3.92 | −2 |
| M.w. 375.9 | 15.0 | 10.0 | 9.6 | −4 |
| | 150 | 40.0 | 39.2 | −2 |
| | 150 | 70.0 | 70.7 | +1 |
| | 150 | 100 | 101 | +1 |
| Quinine hydrochloride, | 150 | 20.0 | 17.2 | −14 |
| $C_{20}H_{24}N_2O_2 \cdot HCl \cdot 2H_2O$, | 150 | 40.0 | 37.2 | −7 |
| M.w. 396.9 | 150 | 70.0 | 72.1 | +3 |
| | 150 | 100 | 101 | +1 |
| Cocaine hydrochloride, | 150 | 20.0 | 22.6 | +13 |
| $C_{17}H_{21}NO_4 \cdot HCl$, | 150 | 40.0 | 42.0 | +5 |
| M.w. 339.81 | 150 | 70.0 | 71.4 | +2 |
| | 150 | 100 | 102 | +2 |

[a]Single measurements.

the protonated form of cocaine. The picrate electrode exhibits near-Nernstian response to various quaternary ammonium compounds [7]. This was also true for most of the cations of the alkaloids tested.

In semi-automatic potentiometric titrations with liquid-membrane ion-selective electrodes, there is usually a blank. For better accuracy, an alternative is to carry out the titration manually and treat the results by Gran's method [8, 9]. Gran plots were used here to establish the equivalence point for two reasons: (a) before the equivalence point, the reaction is not fast enough so that obtaining a full titration curve is time-consuming; (b) in dilute solutions, the break at the end-point is too shallow for successful calculations of the end-point. Figure 1 shows typical titration curves for strychnine and the corresponding Gran plots.

Titrimetric determinations on aqueous alkaloid solutions of known concentrations gave the results shown in Table 2. The relative standard deviations were 0.30 and 0.34% for $1.07 \times 10^{-2}$ and $1.07 \times 10^{-3}$ M strychnine solutions, and 0.32 and 1.5% for $5.33 \times 10^{-3}$ M papaverine and quinine solutions, respectively ($n = 3$).

*Applications.* The proposed methods were applied to the determination of papaverine and quinine in two pharmaceutical preparations. Thirty papaverine hydrochloride tablets (Knoll) and ten quinine hydrochloride tablets

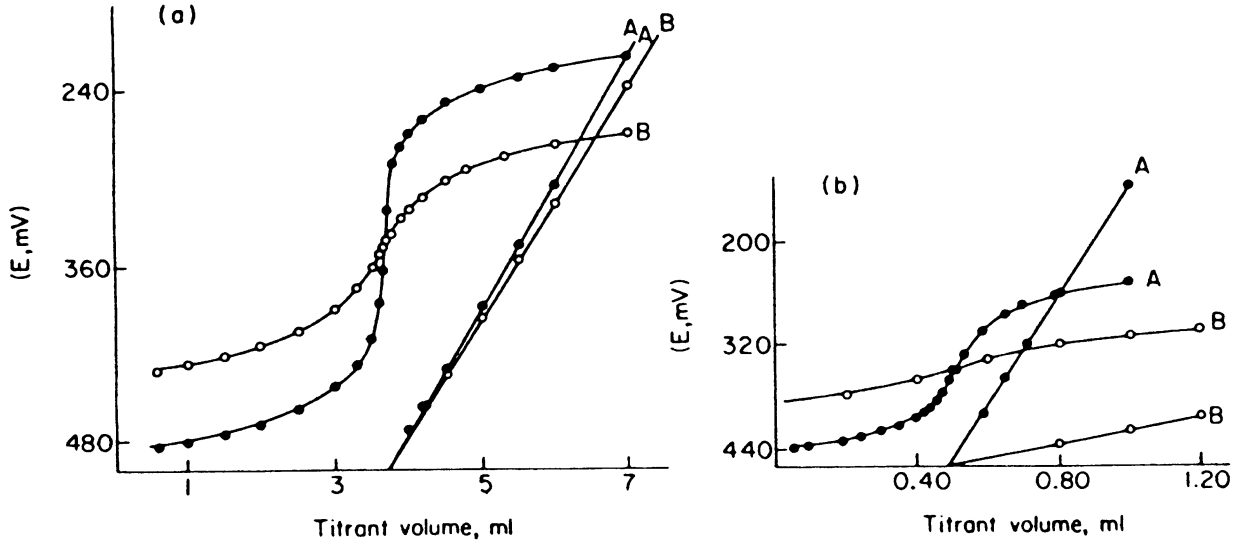


Fig. 1. Titration curves for the titration of 15 ml of strychnine sulfate with sodium picrate and the corresponding Gran plots. In (a): (A) $2 \times 10^{-2}$ M strychnine sulfate with $8 \times 10^{-2}$ M sodium picrate; (B) $2 \times 10^{-3}$ M strychnine sulfate with $8 \times 10^{-3}$ M sodium picrate; for curve B, factor $F$ in the $y$-axis was multiplied by 10. In (b): (A) $2.67 \times 10^{-3}$ M strychnine sulfate with $8 \times 10^{-2}$ M sodium picrate; (B) $2.67 \times 10^{-4}$ M strychnine sulfate with $8 \times 10^{-3}$ M sodium picrate.

(Boehringer—Mannheim) were powdered and extracted with 400 ml of water. After filtering, the volume was adjusted to 500.0 ml in a volumetric flask. The samples were analyzed by a standard [10] and the proposed potentiometric methods. The results are summarized in Table 3.

TABLE 2

Titrimetric potentiometric determination of alkaloids with sodium picrate

| Alkaloid | Concentration range (M) | Picrate[a] (M) | Alkaloid ($\mu$mol) | | Error (%) |
|---|---|---|---|---|---|
| | | | Taken | Found[b] | |
| Strychnine sulfate | $2.67 \times 10^{-4}$—$2.00 \times 10^{-3}$ | $8.00 \times 10^{-3}$ | 4.00 | 3.92 | −2.0 |
| | | | 16.0 | 15.6 | −2.5 |
| | | | 30.0 | 29.2 | −2.7 |
| | $2.67 \times 10^{-3}$—$2.00 \times 10^{-2}$ | $8.00 \times 10^{-2}$ | 40.0 | 39.2 | −2.0 |
| | | | 160 | 154 | −3.8 |
| | | | 300 | 294 | −2.0 |
| Papaverine hydrochloride | $1.33 \times 10^{-3}$—$1.00 \times 10^{-2}$ | $4.00 \times 10^{-2}$ | 20.0 | 19.9 | −0.5 |
| | | | 80.0 | 80.8 | +1.0 |
| | | | 150 | 151 | +0.7 |
| Quinine hydrochloride | $1.33 \times 10^{-3}$—$1.00 \times 10^{-2}$ | $4.00 \times 10^{-2}$ | 20.0 | 18.0 | −10.0 |
| | | | 80.0 | 79.3 | −0.9 |
| | | | 150 | 151 | +0.7 |
| Cocaine hydrochloride | $2.67 \times 10^{-3}$—$2.00 \times 10^{-2}$ | $8.00 \times 10^{-2}$ | 40.0 | 41.7 | +4.2 |
| | | | 80.0 | 82.2 | +2.8 |
| | | | 140 | 140 | — |
| | | | 300 | 298 | −0.7 |

[a]The pH of the sodium picrate solution was about 6 for the titration of strychnine, quinine and cocaine, and 3.5 for the titration of papaverine. [b]Single measurements.

TABLE 3

Comparison of results by the potentiometric and gravimetric methods for the determination of papaverine and quinine in pharmaceutical preparations

| Pharmaceutical preparation | Alkaloid ($\mu$mol)[a] | | |
|---|---|---|---|
| | Standard method | Direct potentiometry | Titrimetric method |
| Papaverine hydrochloride tablets | 756 (35) | 707 (12) | 640 (10) |
| Quinine hydrochloride tablets | 729 (95) | 788 (6) | 783 (17) |

[a]The numbers in parentheses are the differences between two measurements.

In conclusion, the proposed potentiometric methods are faster and simpler than the standard methods. They can also be applied to other alkaloids which give insoluble picrate salts. Efforts to determine atropine, codeine and morphine were unsuccessful because of the great solubility of their picrate salts. The $K_{so}$ of the atropine picrate salt was calculated to be $1.5 \times 10^{-5}$ at 26°C.

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