

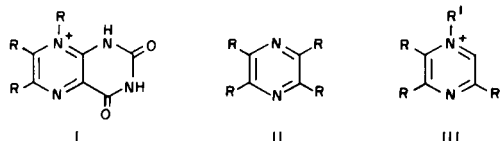
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The pK_1 and pK_2 values and the polarographic half-wave reduction potentials for a series of methyl substituted pyrazines are reported, together with the reduction potentials of several of their *N*-alkyl derivatives. There is a linear inverse relationship between pK_1 and $E_{1/2}$ for the pyrazines.

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It is known that alkyl groups at the 7-position of 6,7,8-trialkylmiazines (*e.g.* I, shown in the protonated form) have high prototropic reactivity in acidic (and basic) solution [1] and as part of a study of this phenomenon we have examined the properties of alkylpyrazines II and pyrazinium salts III, which are closely related but simpler compounds. The pK_1 and pK_2 values of six methyl substituted pyrazines (II, R = H or Me) are reported herein, together with their polarographic reduction potentials and those of several quaternary salts (III, R = H or Me, R' = Me, Et, or *i*-Pr).



Chia and Trimble [2] determined the protonation constants of a number of methylmiazines using sulfuric acid media and the H_0 acidity function to measure pK_2 . Since Johnson, Katritzky *et al.* [3] have reported that the second protonation of pyrazine itself follows the H_A function more closely than the H_0 function we tested our ionization data for each of the pyrazines against the H_0 , H_A , and H_+ functions [4] and also applied the Bunnett-Olsen treatment [5] to the data. Since the H_+ function was derived for use with cationic bases it would seem, on the face of it, to be the most suitable function for determining pK_2 .

A plot of logarithm of the ionization ratio against acidity function should be linear and of unit slope; we find that this condition is closely obeyed for the H_+ function (average slope for the seven compounds shown in Table 1 is 0.975) but not for H_0 (average slope 0.761) or H_A (average slope 0.732). Furthermore, the difference between pK_1 and pK_2 for the seven pyrazines is almost constant ($\Delta pK = 6.34 \pm 0.16$), whereas with H_0 there is a small drift and with H_A (or with the Bunnett-Olsen treatment) there is a large drift in ΔpK .

There are few series reported in the literature where the effect of substituents on symmetrical diprotic acids or bas-

Table 1
Basicity Constants of Pyrazine and its Methyl Derivatives in Water, 25°

| Pyrazine | pK_1 | pK_2 |
|---------------|--------|--------|
| Unsubstituted | 0.57 | -5.51 |
| 2-Methyl | 1.41 | -4.89 |
| 2,3-Dimethyl | 2.24 | -4.17 |
| 2,5-Dimethyl | 1.99 | -4.42 |
| 2,6-Dimethyl | 2.11 | -4.48 |
| Trimethyl | 2.65 | -3.60 |
| Tetramethyl | 3.61 | -2.73 |

Table 2
Polarographic Half-Wave Potentials of Alkylpyrazines in Water at pH 6.85; Volts

| Pyrazine | Ionic Strength | |
|--------------------|----------------|--------|
| | 0.14 | 1.00 |
| 2-Methyl | -0.875 | -0.858 |
| 2,3-Dimethyl | -0.909 | -0.894 |
| 1-Methyl cation | -0.767 | — |
| 1-Ethyl cation | -0.752 | — |
| 1-Isopropyl cation | -0.729 | — |
| 2,5-Dimethyl | -0.897 | -0.876 |
| 1-Ethyl cation | -0.763 | — |
| 2,6-Dimethyl | -0.901 | 0.884 |
| Tetramethyl | -0.976 | -0.940 |

es has been determined, particularly when the substituents are equidistant, or almost so, from the two acidic or basic sites. The first and second dissociations of alkyl and aryl phosphoric acids and of 5-substituted isophthalic acids are such series and there a constant difference between pK_1 and pK_2 has either been inferred or measured [6,7]; these results lend further support to the pK_2 values determined using the H_+ function and they are the ones we report in Table 1. Despite our using a different acidity function the values of Chia and Trimble are not greatly different from ours, whereas the values calculated using H_A are all much less negative. Of the five compounds common to the two studies the greatest difference is 0.36 pK units (for 2,3-dimethylpyrazine); the values for pK_1 are in

reasonable agreement with those reported earlier [2,8,9].

The polarographic reduction potential of the alkylpyrazines and a number of their *N*-alkyl derivatives are given in Table 2. Increasing the ionic strength of the medium is known to increase the polarographic reduction potential of pyrazine (make it less negative) [10] and this is the effect we observe. It can be seen that cation formation also has the expected effect, which is to make reduction easier. Increasing the number of methyl groups in the pyrazine ring makes the polarographic reduction more difficult and it is interesting to note that there is an inverse linear correlation between the basicity constants of methylpyrazines and their reduction potentials; a plot of pK_1 against $E_{1/2}$ gives an excellent straight line, correlation coefficient 0.997.

EXPERIMENTAL

The pK_1 values and the polarographic reduction potentials (A.C. modulation method) were determined in aqueous solution as previously described [11]. The acidity functions that were used to determine pK_2 are those given by Rochester [5]; corrections for medium effects on the spectra of the mono- and di-cations at the two wavelengths used for the measurements were made by extrapolating the absorbance values measured in regions of high and low acidity to the regions of partial ionization [12]. The extrapolated lines had almost the same slopes in all cases, indicating that the medium had almost the same effect on the spectrum of the mono- and di-cations.

The pyrazines were commercially available; the quaternary salts were synthesized as follows.

1,2,3-Trimethylpyrazinium Iodide.

2,3-Dimethylpyrazine (0.15 g) was refluxed with 10 ml of methyl iodide for 2 hours. Evaporation and recrystallization (ethyl acetate) of the solid residue gave 2.2 g (63%) of yellow crystals, mp 187-188°; nmr (deuterium oxide): δ 8.98 (1H, b), 8.70 (1H, b), 4.34 (3H, s), 2.88 (6H, s).

Anal. Calcd. for $C_7H_{11}IN_2$: C, 33.62; H, 4.43; N, 11.20; I, 50.75. Found: C, 33.76; H, 4.45; N, 11.09; I, 50.61.

1-Ethyl-2,3-dimethylpyrazinium Iodide.

This compound was prepared using ethyl iodide and the above procedure. Recrystallization (ethanol) gave a 53% yield of product, mp 140-141°; nmr (deuterium oxide): δ 9.02 (1H, b), 8.72 (1H, b), 4.78 (2H, q),

2.92 (3H, s), 1.64 (3H, t).

Anal. Calcd. for $C_8H_{13}IN_2$: C, 36.38; H, 4.96; N, 10.61; I, 48.05. Found: C, 36.10; H, 5.05; N, 10.50; I, 47.80.

1-Isopropyl-2,3-dimethylpyrazinium Iodide.

Prepared using isopropyl iodide as above except that the mixture was heated under pressure for three days. Recrystallization (ethanol/ethyl acetate) gave a 20% yield of product, mp 215-216°; nmr (deuterium oxide): δ 8.98 (1H, b), 8.78 (1H, b), 5.28 (1H, m), 2.98 (3H, s), 2.88 (3H, s), 1.75 (6H, d).

Anal. Calcd. for $C_9H_{15}IN_2$: C, 38.86; H, 5.44; N, 10.07; I, 45.63. Found: C, 38.77; H, 5.42; N, 9.96; I, 45.70.

1-Ethyl-2,5-dimethylpyrazinium Iodide.

Prepared using ethyl iodide and 2,5-dimethylpyrazine as above except that the mixture was allowed to react for a week at room temperature. Recrystallization (ethanol/ethyl acetate) gave a 33% yield of product, mp 200-201°; nmr (deuterium oxide): 9.12 (1H, b), 8.80 (1H, b), 4.65 (2H, q), 2.88 (3H, s), 2.75 (3H, s), 1.60 (3H, t).

Anal. Calcd. for $C_8H_{13}IN_2$: C, 36.38; H, 4.96; N, 10.61; I, 48.05. Found: C, 36.28; H, 4.90; N, 10.75; I, 47.95.

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