Chemical Reactions of Omeprazole and Omeprazole Analogues. III. Protolytic Behaviour of Compounds in the Omeprazole System

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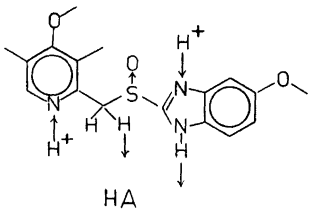
pK_a values have been measured for a variety of omeprazole analogues. Owing to the poor stability of the compounds, a rapid potentiometric method was developed for the determination of pK_a values. The experimental results were used in various correlations to enable the rapid and accurate estimation of pK_a values for analogues and intermediates in the chemical transformations of omeprazole.

For the understanding of the pH dependence of the very complex system of reactions of omeprazole and its degradation products, knowledge of the protolytic behaviour of these compounds is essential. This will be given in the present part of the work. Analogues of omeprazole will be treated first, and then the protolytic behaviour of some intermediates will be discussed.

Omeprazole (HA) (Scheme 1) is protolytically active in at least four reactions:



HA

Scheme 1.

1. It can accept a proton on the pyridine nitrogen atom. A pK_a of 3.98 for this equilibrium can be measured by the method outlined in the Experimental section. The dependence of this pK_a on substituents on the pyridine ring and on the benzimidazole ring can be predicted.
2. It can accept a second proton on the N atom of the benzimidazole ring. The pK_a^* = − 0.21 for this equilibrium can be estimated by indirect methods and the pK_a dependence of substituents can be predicted.
3. It can release a proton from the NH group of the benzimidazole ring. Also the pK_a of 8.70 for this equilibrium can be measured and the pK_a dependence on substituents can be predicted.
4. The protons on the CH_2 group are acidic enough to be replaced by deuterium by treatment with D_2O and NaOD. The pK_a for these protons is, however, too high to be of interest in our case and will not be considered further.

At pH values in the range 1–4, most of the analogues of omeprazole are protonated. This protonation occurs preferentially at the pyridine nitrogen atom and only to a very small extent on the benzimidazole nitrogen atoms. The reason for this is that the pK_a-lowering effect of a RCH_2SO group in the 2-position of the benzimidazole ring is more pronounced than that of a $RSOCH_2$ group in the 2-position of the pyridine ring. Since unsubstituted pyridine and unsubstituted benzimidazole have about the same pK_a value the CH_2SO chain will make the pK_a values of the two rings very different, with the preferential protonation of the pyridine nitrogen as a result.

Prediction of pK_a for omeprazole analogues

Effects of substituents in the pyridine ring. Methods have been given by Perrin, *et al.*[1] for the prediction of pK_a values for various compounds. However, these general methods, based on Hammett's σ-values, are somewhat crude for the present purpose. We have therefore applied the method of analogy to the problem: two closely related reactions exhibit the same dependence on structural variations.

A reaction closely related to the release of a proton from a protonated pyridine ring in omeprazole analogues is the release of a proton from simple protonated pyridines. pK_a values for substituted pyridines are available,[2] and are usually reliable. From pK_a values for monosubstituted pyridines, PyR, and pyridine, PyH, we can readily calculate Δpy(R) values, defined by eqn. (1), for different groups R in different positions of the ring. A few such values are given in Table 1.

$$\Delta py(\mathrm{R}) = \mathrm{p}K_a(\mathrm{PyH}) - \mathrm{p}K_a(\mathrm{PyR}) \quad (1)$$

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Table 1. Δ*py*(R) values for some substituents in the pyridine ring.

R	Position		
	3	4	5
CH_3	−0.63[a]	−0.76	−0.47
C_2H_5	–	−0.80	−0.33
CH_3O	–	−1.35	+0.23
C_6H_5	–	−0.12	+0.43
Cl	–	+1.40	+2.42
CH_3CO	–	+1.72	+1.97

[a] See the text.

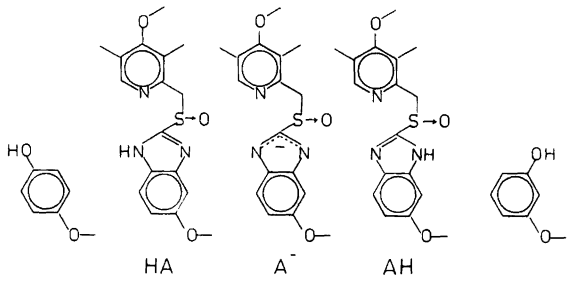
The Δ*py*(R) values are pyridine analogues of Hammett's σ(R) values, and show the same type of additivity. This means that eqn. (1) is valid, but with the same type of exceptions, e.g. for compounds with restricted resonance due to steric hindrance or strong hydrogen bonding. The good additivity of the Δ*py*(R) values is seen from a regression between found pK_a values for di- and tri-substituted pyridines and values calculated with the aid of eqn. (1) using Δ*py*(R) values obtained from monosubstituted pyridines. In this regression, 83 values were used, which were nearly all of the available values, from Ref. 2, ranging from −2.27 to +9.44. Compounds for which we could expect strong steric interactions were excluded. An intercept of 0.09 and a slope of 0.985 ± 0.011, in good agreement with the expected values 0 and 1 were obtained. The standard deviation for this inhomogeneous experimental material was 0.28, which is of the same magnitude as the differences between experimental values reported for the same compounds. It is thus possible to predict pK_a values for different pyridines with about the same accuracy as measured values. However, if *ortho* effects are expected, the additivity rules should be applied with caution.

An inspection of the pK_a values of the 2,3-, 2,4-, and 2,5-dimethylpyridines compared with that of 2-methylpyridine reveals that Δ*py*(4-CH_3) and Δ*py*(5-CH_3) have their expected values, whereas Δ*py*(3-CH_3) is −0.63 instead of the expected −0.47. This is probably the result of steric effects. Since all of the omeprazole analogues of interest have a CH_2 group in the 2-position, the value of −0.63 for a 3-CH_3 group has been used in our calculations (Table 2). For substituents in the 4-position with a free electron pair (e.g. $NHCOCH_3$, SCH_3) no reliable pK_a values for monosubstituted pyridines were available. Δ*py*(R) values for the substituents of this type used in the present investigation were therefore obtained from the regression line given in Table 2. However, Δ*py*(R) values for this type of substituent can be expected to be linearly dependent on the σ_p^+ values[3] for the substituents. This is shown in Fig. 1, which can be used to determine Δ*py*(R) values for other substituents of this type.

In the present case we found excellent additivity for all compounds tested (Table 2), with the exception of the 3,5-dimethyl-4-methoxy compound, which has a pK_a value about one unit lower than that expected from the additivity rule. An inspection of the X-ray structure of omeprazole reveals that the O–CH_3 bond is perpendicular to the pyridine ring and that the resonance is therefore restricted.

The pK_a value (p$K_{H_2A^+}$) for the release of a proton from a protonated pyridine ring in omeprazole analogues is, to some extent, also dependent on the substituent in the benzimidazole ring, as will be discussed later.

Effects of substituents on the benzimidazole ring. The pK_a value (pK_{HA}) for the release of a proton from the benzimidazole ring of omeprazole analogues is usually more complicated to predict than is that for the release of a proton from a protonated pyridine, First, a substituted benzimidazole can often exist as two rapidly interchanging isomers with a common anion (Scheme 2). Another complicating factor is that very few pK_a values have been measured for benzimidazoles. We therefore had to use another analogous reaction for the predictions. Such a reaction is the release of a proton from a substituted phenol (Scheme 2).



Scheme 2.

The problem of isomerism was solved in the following way. Assume that we have two isomeric acids HA and AH with the common anion A^-. The observable K_a(obs) and the non-observable, but predictable, K_a(HA) and K_a(AH) are defined in eqn. (2). Here $f^{\pm}$ is the mean activity coefficient. If these relationships are combined we obtain eqn. (3).

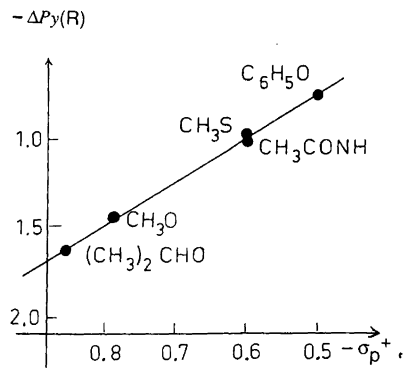
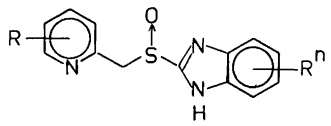


Fig. 1. Plot of Δ*py*(R) values for substituents with free electron pairs vs. σ_p^+ for the corresponding substituents. Δ*py*(R) values are obtained from the regression (Table 2).

Table 2. Observed and calculated $pK_a(1)$ values at 37 °C for the release of a proton from compounds of the type:



R	R^1	Δpy(R)	ΔBi(R^n)	$pK_a(1)$	
				Exp.	Calc.[a]
H	H	0	0	2.89	2.79
H	5-CH_3O	0	−0.01	2.84	2.79
4-CH_3	5-CH_3O	−0.76	−0.61	3.64	3.55
3,4-$(CH_3)_2$	5-CH_3O	−1.39	−0.01	4.21	4.18
3,5-$(CH_3)_2$	5-CH_3O	−1.10	−0.01	3.77	3.89
4,5-$(CH_3)_2$	5-CH_3O	−1.23	−0.01	4.05	4.02
3,4,5-$(CH_3)_3$	5-CH_3O	−1.86	−0.01	4.56	4.65
4-CH_3O	5-CH_3O	−1.48[c]	−0.01	4.27	–
3,5-$(CH_3)_2$	5-CH_3	−1.10	−0.19	3.88	3.92
3-CH_3	5-CH_3, 6-$COOCH_3$	−0.63	0.80	3.28	3.30
3,4-$(CH_3)_2$, 6-$COOCH_3$	5-CH_3, 6-$COOCH_3$	−1.39	0.80	4.09	4.06
3,5-$(CH_3)_2$, 6-$COOCH_3$	5-CH_3, 6-$COOCH_3$	−1.10	0.80	3.71	3.76
4,5-$(CH_3)_2$, 6-$COOCH_3$	5-CH_3, 6-$COOCH_3$	−1.23	0.80	4.01	3.90
3,4,5-$(CH_3)_3$, 6-$COOCH_3$	5-CH_3, 6-$COOCH_3$	−1.86	0.80	4.45	4.53
3,5-$(CH_3)_2$, 4-CH_3O	H	−1.16[b]	0	4.01	3.95
3,5-$(CH_3)_2$, 4-CH_3O	5-CH_3O	−1.16	−0.01	3.98	3.95
3,5-$(CH_3)_2$, 4-CH_3O	5-CH_3	−1.16	−0.19	4.00	3.98
3,5-$(CH_3)_2$, 4-CH_3O	5-Cl	−1.16	0.69	3.85	3.85
3,5-$(CH_3)_2$, 4-CH_3O	5-$COCH_3$	−1.16	1.00	3.84	3.80
	5-$COOCH_3$	−1.16	1.06	3.65	3.79
3,5-$(CH_3)_2$, 4-CH_3O	5-CH_3, 6-$COOCH_3$	−1.16	0.80	3.83	3.83
3,5-$(CH_3)_2$, 4-CH_3O	5-CH_3, 6-$COCH_3$	−1.16	0.74	3.85	3.84
4-CH_3S	5-CH_3O	−0.99[c]	−0.01	3.78	–
4-CH_3CONH	5-CH_3O	−1.02[c]	−0.01	3.81	–
4-C_6H_5O	5-CH_3O	−0.78[c]	−0.01	3.57	–
4-$(CH_3)_2CHO$	5-CH_3O	−1.63[c]	−0.01	4.42	–

[a] $pK_a(1)_{calc.} = 2.79 - \Delta py(R) - 0.15\ \Delta Bi(R^n)$. [b] Mean value for this substitution (obtained from the regression). [c] Calculated value from the regression (see the text).

$$\frac{f^{\pm}[A^-]a_{H_3O^+}}{[HA] + [AH]} = K_a(obs); \quad \frac{f^{\pm}[A^-]a_{H_3O^+}}{[AH]} = K_a(AH); \quad \frac{f^{\pm}[A^-]a_{H_3O^+}}{[HA]} = K_a(HA) \tag{2}$$

$$1/K_a(obs) = 1/K_a(HA) + 1/K_a(AH) \tag{3}$$

The problem of predicting K_a(obs) is thus reduced to the problem of predicting K_a(HA) and K_a(AH). This can be done by a comparison with the corresponding phenols in the following way: denote the group R present in the position given in HA and the corresponding phenol by R^1 and the same group in the isomeric position in AH and the corresponding phenol by R^2. By analogy with the pyridines (see above), we can define ΔP(R) values for the groups by eqn. (4) where Ph stands for a C_6H_4OH residue. pK_a values

$$\Delta P(R^1) = pK_a(PhH) - pK_a(PhR^1); \quad \Delta P(R^2) = pK_a(PhH) - pK_a(PhR^2) \tag{4}$$

Table 3. Differences ΔP(R) in pK_a of phenol [pK_a(PhH)] and substituted phenols [pK_a(PhR)] for substituents in different positions.

R	ΔP(R)		
	ortho	*meta*	*para*
H	0	0	0
Br	1.55	0.97	0.63
Cl	1.54	0.88	0.59
F	1.30	0.79	0.09
NO_2	2.77	1.64	2.84
CN	3.14	1.39	2.03
CF_3	–	1.05	1.32
CH_3	−0.22	−0.10	−0.28
CH_3O	0.02	0.35	−0.21
CH_3SO	2.39	1.22	1.71
C_2H_5	−0.20	−0.07	−0.21
CH_3CO	−0.22	0.75	1.95
CH_3OCO	−0.13	0.84	1.75
CH_3CONH	–	0.42	0.30
C_2H_5O	−0.11	0.34	−0.13
$(CH_3)_3C$	−0.63	−0.12	−0.39

of a large number of phenols are available, and they are usually of excellent validity.[4] Calculated $\Delta P(R)$ values for a variety of substituents can be found in Table 3.

From the analogy seen in the release of a proton from a phenol and a benzimidazole we can expect that eqn. (5) is valid, where ϱ is a constant which can be expected to be close to 1. The meaning of K_0 is seen from the following; R = H means that HA and AH are identical and $\Delta P(H) = 0$. Eqn. (3) thus gives eqn. (6), where pK_a(BiH) is the pK_a (obs) value for the compound unsubstituted in the 4–7 positions of the benzimidazole ring.

$$pK_a(HA) = pK_0 - \varrho\Delta P(R^1); \quad pK_a(AH) = pK_0 - \varrho\Delta P(R^2) \tag{5}$$

$$K_0 = 2\,K_a(BiH) \text{ or } pK_0 = pK_a(BiH) - 0.3 \tag{6}$$

If the values in eqn. (5) are introduced into eqn. (3) and K_{obs}(BiR) is defined as the K_a(obs) value for the benzimidazole compound substituted with the group R, we obtain eqn. (7), which can be rearranged to eqn. (8).

$$1/K_{obs}(BiR) = 10^{[pK_0 - \varrho\Delta P(R^1)]} + 10^{[pK_0 - \varrho\Delta P(R^2)]} \tag{7}$$

$$pK_{obs}(BiR) = pK_0 - \varrho\Delta P(R^1) + \log\left(1 + 10^{\varrho[\Delta P(R^1) - \Delta P(R^2)]}\right) \tag{8}$$

If we assign R as R^1 and R^2 in such a way that $\Delta P(R^1) < \Delta P(R^2)$, the argument of the logarithm in eqn. (8) will be within the limits 1–2 and can be denoted by *SF* (statistical factor). We thus obtain eqn. (9).

$$pK_{obs}(BiR) = pK_0 - \varrho\Delta P(R^1) + \log(SF) \tag{9}$$

This equation is valid for omeprazole analogues with hydrogen substituents in the pyridine ring. A substituent in the pyridine ring might be expected to change the pK_a value of the benzimidazole NH group in a way proportional to $\Delta py(R)$. If this is taken into account, eqn. (10) gives the complete expression for the pK_a value (pK_{HA}) for the release of a proton from the benzimidazole ring of an omeprazole analogue. From this equation we can calculate both pK_0 and ϱ' from *experimental* pK_{HA} values. This has been done and the results are given in Table 4. As described above, we can define ΔBi(R) values by eqn. (11).

$$pK_{HA} = pK_0 - \varrho\Delta P(R^1) - \varrho'\Delta py + \log(SF) \tag{10}$$

$$\Delta Bi(R) = pK_a(BiH) - pK_a(BiR) \tag{11}$$

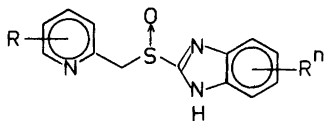
These ΔBi(R) values are not additive, but values for both mono-, di-, and poly-substituted benzimidazoles are readily calculated using the methods outlined above. As for the σ and $\Delta py(R)$ values, the ΔBi(R) values can be used as numerical estimations of the electronic effects of substituents of the benzimidazole ring.

The effect of a substituent in the benzimidazole ring is transferred via the $SOCH_2$ group to the pyridine ring. A substituent in the benzimidazole ring will thus affect the pK_a value of the pyridine ring. This change in pK_a can be expected to be proportional to ΔBi(R). This has already been taken into account in Table 2.

pK_a predictions for the protonated benzimidazole ring

The substituted $pyCH_2SO$ group in omeprazole reduces the pK_a for the release of a proton from the uncharged benz-

Table 4. Observed and calculated $pK_a(2)$ values at 37 °C for the release of a proton from compounds of the type:



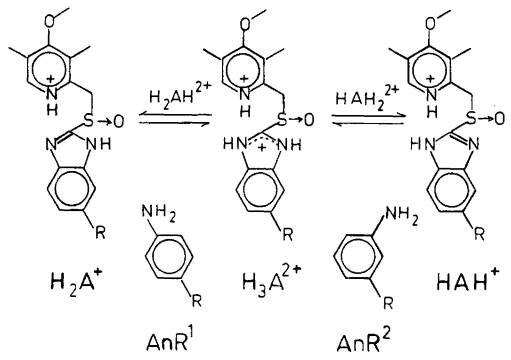
R	R^n	$\Delta P(R)$		log(*SF*)[a]	Δpy	pK_{HA}	
		R^1	R^2			Exp.	Calc.[b]
3,5-$(CH_3)_2$,4-OCH_3	5-C_2H_5	−0.21	−0.07	0.24	−1.16	8.89	8.85
3,5-$(CH_3)_2$,4-OCH_3	5-Br	0.63	0.97	0.16	−1.16	8.01	7.96
3,5-$(CH_3)_2$,4-OCH_3	5-CH_3O	−0.21	0.35	0.11	−1.16	8.70	8.72
3,5-$(CH_3)_2$,4-OCH_3	5-$(CH_3)_3C$	−0.39	−0.12	0.19	−1.16	9.01	8.98
3,5-$(CH_3)_2$,4-OCH_3	5-C_2H_5O	−0.13	0.34	0.13	−1.16	8.61	8.66
3,5-$(CH_3)_2$,4-OCH_3	4,6-$(CH_3)_2$	−0.50	−0.20	0.18	−1.16	9.03	9.07
3,5-$(CH_3)_2$,4-OCH_3	5,6-$(CH_3)_2$	−0.38	−0.38	0.30	−1.16	9.06	9.08
3,5-$(CH_3)_2$,4-OCH_3	5-CF_3	1.05	1.32	0.19	−1.16	7.55	7.58
3,5-$(CH_3)_2$,4-OCH_3	5-CH_3SO	1.22	1.71	0.12	−1.16	7.34	7.35
4-CH_3	5-CH_3O	−0.21	0.35	0.11	−0.76	8.65	8.66
3,4,5-$(CH_3)_3$	5-CH_3O	−0.21	0.35	0.11	−1.86	8.81	8.82
3,5-$(CH_3)_2$,4-OC_2H_5	5-CH_3O	−0.21	0.35	0.11	−1.20	8.79	8.72

[a] $\log(SF) = \log\left(1+10^{0.97[\Delta P(R^1) - \Delta P(R^2)]}\right)$. [b] $pK_{HA}(calc.) = 8.24 - 0.97\Delta P(R^1) - 0.14\Delta py(R) + \log(SF)$.

imidazole ring from 12.86 for unsubstituted benzimidazole[2] to 8.70 for omeprazole, thus by 4.16 units. The same substituent will also reduce the pK_a of the benzimidazolinium ion by about the same. Since the unsubstituted benzimidazolinium ion has pK_a of 5.58[5] we can expect that the nitrogen atom of the pyridine ring will be protonated long before the nitrogen atoms of the benzimidazole ring. In strongly acidic solutions, both the pyridine ring and the benzimidazole ring are protonated. The extent of this protonation is of importance for the reactions in strongly acidic solutions (pH $\leq$ 2). The concentration ionization constant $K^*_{H_3A^{2+}}$ governs this protonation according to eqn. (12).

$$K^*_{H_3A^{2+}} = \frac{([H_2A^+] + [HAH^+])}{[H_3A^{2+}]}[H_3O^+] \quad (12)$$

We have two monoprotonated forms H_2A^+ and HAH^+, and one diprotonated form H_3A^{2+}, connected by the constants $K^*_{H_2AH^{2+}}$ and $K^*_{HAH_2^{2+}}$, as demonstrated in Scheme



Scheme 3.

3. By analogy with the deductions made for the release of a proton from the acids HA and AH we obtain eqn. (13).

$$K^*_{H_3A^{2+}} = K^*_{H_2AH^{2+}} + K^*_{HAH_2^{2+}} \quad (13)$$

The two monocations H_2A^+ and HAH^+ are now compared with the two isomeric anilines AnR^1 and AnR^2. If we are using $\Delta An(R)$ values, obtained from pK_a measurements on monosubstituted aniline, in the same way as the $\Delta P(R)$ values, we obtain eqn. (14).

$$pK^*_{H_3A^{2+}} = pK_0 - \Delta An(R^1) - \log(1 + 10^{[\Delta An(R^2) - \Delta An(R^1)]}) - 0.14\Delta py(R) \quad (14)$$

In this equation we have assumed that $\varrho = 1$, which seems very reasonable. The substitution on the pyridine ring also has some effect upon the $pK^*_{H_3A^{2+}}$ value; this is assumed to be the same as that upon pK_{HA}. Eqn. (14) enables a correlation of $pK^*_{H_3A^{2+}}$ values with structural changes, which together with measurements described in part II,[6] enables a rather good estimation of $pK^*_{H_3A^{2+}}$ values. For omeprazole we can thus estimate $pK^*_{H_3A^{2+}} = -0.21$ at $\mu = 0.5$ M. The error in this estimation is probably < 0.2 pK units.

pK_a predictions for some intermediates in the degradiation of omeprazole

The structure of compounds discussed below are given in Scheme 4. The compound $HE\beta^+$ has one group of protolytic interest, the proton on the NH group of the benzimidazole ring. The pK_a for this reaction has been measured to be about 6.4 in a methanol–water mixture (1:1), and 6.02 from the kinetic results.[7]

The sulfide HS behaves similarly to HA. The electron-withdrawing effect of a $PyCH_2S$ group is, however, much less pronounced than that of a $PyCH_2SO$ group. This makes the benzimidazole NH group in HS a much weaker acid than in HA. The pK_a values have been measured to be about 11.5. The base-weakening effect on the benzimidazole nitrogens is also much less in HS than in HA, and the difference in base strength of the two rings becomes less in HS than in HA. The rules advanced for the calculation of pK_a values for the sulfoxides can therefore not be directly applied to the calculation of pK_a values for the sulfides. Since the sulfide HS is not a reactive species, no attempt was made to develop methods for the calculation of pK_a values for this type of compound. The pK_a value for the sulfide HS corresponding to omeprazole has been measured to be 4.91.

The short-lived *intermediate* HB^+ can, protolytically, be regarded as a phenylenediamine substituted by a strong electron-withdrawing group on the nitrogen atoms. It is thus a very weak base and at the same time a very weak acid, and thus a non-protolyte under most conditions. If the anion resulting from the loss of one of the protons of the two NH groups is temporarily formed, it will abstract a proton from water in a very fast reaction.

The sulfenic acid HC^+ has two protolytic centers of interest. The proton on the NH group is readily released with a pK_a that should be very close to that of $HE\beta^+$, thus about 6 for HC^+ formed from omeprazole. The pK_a value of the groups in HC^+ should be dependent on the substituents on the benzimidazole ring in the same way as the corresponding groups in HA analogues. Since the pyridine ring is closer to the NH group in HC^+ than in HA, the dependence of the pK_a value on the substituents in the pyridine ring should be greater for HC^+ than for HA.

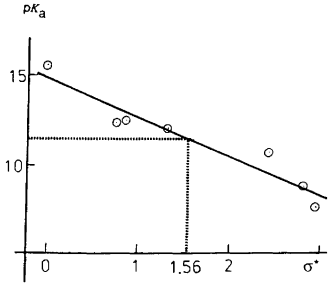
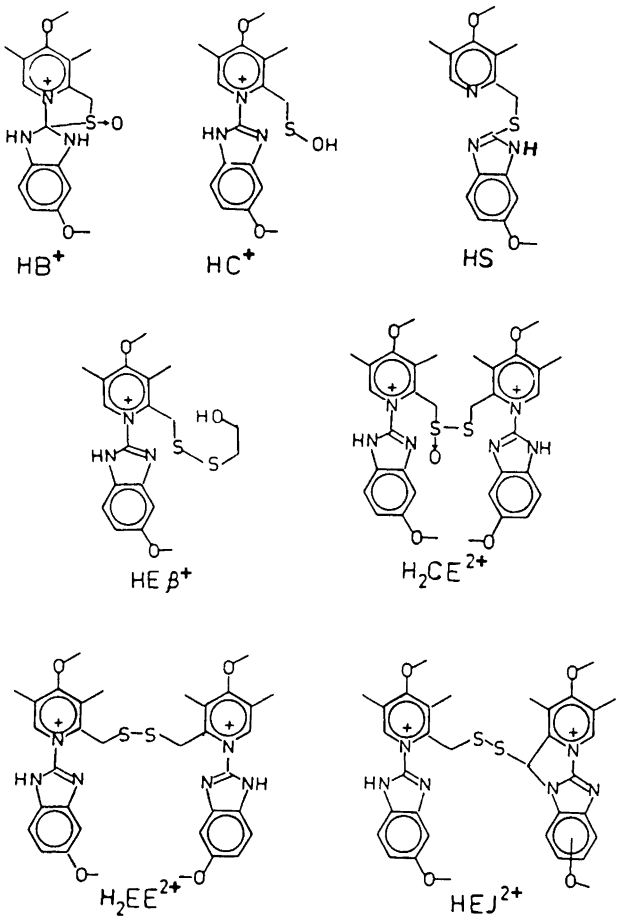


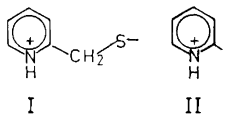
Fig. 2. pK_a values of unconjugated acids of the general type ROH vs. σ^*.[8] The points correspond to the following substituents R (from left to right): CH_3, CCl_3CH_2, CF_3CH_2, HO, I, Br, Cl.



Scheme 4.

HC^+ also contains a sulfenic acid group. Sulfenic acids are known to have a low stability, and a direct determination of the pK_a value is therefore difficult. The only pK_a value reported for a sulfenic acid seems to be that for the dissociation of the first proton in anthraquinonedisulfenic acid. This is estimated to be in the range 6–12.[9] However, an approximate value for the sulfenic acid $C_6H_5CH_2SOH$ can be obtained from a plot of pK_a values of unconjugated acids of the type ROH against the Taft constant σ^* (Fig. 2). Interpolation of this plot gives a pK_a of 11.4 for $C_6H_5CH_2SOH$. To estimate the pK_a value of HC^+ we need an estimate of the corresponding σ^* value. The substituent should have the same σ^* value as I (Scheme 5). The σ^* for this substituent is not known, but we have the relationship $\sigma^*(I) = \sigma^*(II)/2.4^2$.[10] $\sigma^*(II)$ is not known, but $\sigma(II) = 3.21$, and from the relationship $\sigma^* = (\sigma+0.106)/0.217$,[11] we obtain $\sigma^*(II) = 15.3$ and $\sigma^*(I) = 2.65$. The same value is also obtained using other methods of calculation, e.g. from a correlation of $\sigma^*(X)$ with $\sigma^*(X\text{–}S)$. The value $\sigma^* = 2.65$ gives a pK_a value of 8.9 for the sulfenic acid groups of HC^+.

Under normal conditions the sulfenamide D is a non-protolytic compound. However, the protons of the CH_2 group are activated and may be released at a reasonable rate by the attack of a base.



Scheme 5.

The compounds H_2CE^{2+}, H_2EE^{2+} and HEJ^{2+} can be estimated to have pK_a values close to those of $HE\beta^+$ and HC^+ for the release of protons from the NH group, and, like D^+ and HC^+, they have CH_2 groups with activated protons with high pK_a values, but which are able to be released at a reasonable rate by the attack of a base.

Experimental

Apparatus. A standard pH meter (Bergman & Beving PH M62, equipped with a combination electrode (Radiometer, GK 2321 C) was used in the pH measurements. A recorder was used to register the pH change in the pK_a determinations of omeprazole and its analogues. In order to change the position of the curve properly, a 4.5 V battery equipped with a potentiometer was attached between the recorder and the pH meter.

Chemicals. Buffers for calibration purposes were from Radiometer. HCl solutions were made from commercial ampoules (Tritrisol^R, Merck) by dilution with water (milli Q) and titrated. Methanol (HPLC grade) was obtained from Fisons.

Rapid potentiometric method for the determination of the thermodynamic acid-dissociation constant. The pH meter was calibrated at 37 °C using fresh buffer solutions. The pH of 2 ml of a dilute solution (ca. 4×10^{-4} M) of HCl (ionic strength 0.1 M) was measured and then 100 µl of a methanol solution (ca. 1.85×10^{-2} M) of the compound was added and the change in pH was registered on the recorder. A typical experiment is shown in Fig. 3. Owing to the decomposition of omeprazole in acidic solution, a slow increase in pH is observed after the first rapid change due to the neutralization. The asymptote is extended to zero time to give the pH value of the solution of undecomposed omeprazole, which is used in the calculation of the pK_a value.

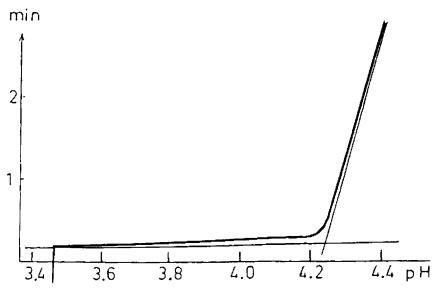


Fig. 3. A typical experiment from the pK_a determination of omeprazole.

The experiment was repeated at three different concentrations of HCl using two different solutions of substrate, thus, in all, 6 measurements.

Calculation of K_a. The experiment starts with V ml of H_0 M HCl. This solution has the pH value pH_0. We then add v ml of the base HA with the molarity A_0 and obtain the pH value pH by extrapolation back to time $t = 0$. We make use of the definition given in eqn. (15).

$$a_{H_3O^+} = 10^{-pH} \tag{15}$$

Since v is small compared with V the ionic strength and hence the activity coefficient of the solution is not changed by the addition of the base. The concentration $[H_3O^+]$ after the addition of the base is thus obtained from eqn. (16). From the total quantities of HA and HCl we obtain eqns. (17) and (18).

$$[H_3O^+] = H_0 \cdot 10^{(-pH + pH_0)} \tag{16}$$

$$v\,H_0 = ([H_3O^+] + [H_2A^+]) \cdot (V + v) \tag{17}$$

$$v\,A_0 = ([HA] + [H_2A^+]) \cdot (V + v) \tag{18}$$

The acidity constant K_a is given by eqn. (19), which is obtained from eqns. (17) and (18) and the assumption that the activity coefficients for H_3O^+ and H_2A^+ are the same.

$$K_a = \frac{\{v\,A_0 + (V+v)[H_3O^+] - V\,H_0\} \cdot [H_3O^+]}{V\,H_0 - (V+v) \cdot [H_3O^+]} \tag{19}$$

The accuracy of the method was tested by measuring the pK_a values for two stable compounds with well-documented pK_a values. We thus obtained pK_a = 3.96 with a standard deviation of 0.013 for 4-chloroaniline at 25 °C compared with the value 3.983 obtained by Bolton and Hall.[12] For imidazole we obtained pK_a = 6.73 ± 0.015 at 37 °C compared with the value 6.744 obtained by interpolation of the values from Datta and Grzybowski.[13]

Calculation of rate constants from the experiments to give the pK_a *value.* The slow increase in pH during the measurements above is due to the reaction of HA and a proton to give one or more quaternary pyridinium compounds, here called D^+. If this is a second-order reaction the rate law is given by eqn. (20).

$$\frac{d[D^+]}{dt} = \frac{-d[HA]}{dt} = k[H_3O^+]\,[HA] \tag{20}$$

From the expressions for the total concentrations given in eqns. (21) and (22) and the protolytic equilibrium, we obtain eqn. (23). This is rearranged to eqn. (24). Differentiating this with respect to t gives eqn. (25). Introduction of eqns. (23) and (25) into (20) gives eqn. (26).

$$\frac{V\,H_0}{V+v} = H_{tot} = [H_3O^+] + [H_2A^+] + [D^+] \tag{21}$$

$$\frac{v\,A_0}{V+v} = A_{tot} = [HA] + [H_2A^+] + [D^+] \tag{22}$$

$$A_{tot} - H_{tot} + [H_3O^+] = [HA] = \frac{K_a}{K_a + [H_3O^+]} \cdot (A_{tot} - [D^+]) \tag{23}$$

$$A_{tot} - [D^+] = (K_a + [H_3O^+]) \cdot ([H_3O^+] + A_{tot} - H_{tot})/K_a \tag{24}$$

$$-\frac{d[D^+]}{dt} = \frac{(K_a + 2[H_3O^+] + A_{tot} - H_{tot})}{K_a} \frac{d[H_3O^+]}{dt} \tag{25}$$

Eqn. (26) can be rearranged to eqn. (27), which is readily integrated to give eqn. (28). Rearrangement of eqn. (28) gives eqn. (29).

$$-(K_a + 2\,[H_3O^+] + A_{tot} - H_{tot}) \frac{d[H_3O^+]}{dt} = kK_a([H_3O^+] + A_{tot} - H_{tot})\,[H_3O^+] \tag{26}$$

$$\frac{d[H_3O^+]}{[H_3O^+]} + \frac{K_a d[H_3O^+]}{([H_3O^+] + A_{tot} - H_{tot})\,[H_3O^+]} + \frac{d[H_3O^+]}{[H_3O^+] + A_{tot} - H_{tot}} = -kK_a dt \tag{27}$$

$$\ln[H_3O^+] - \frac{K_a}{A_{tot} - H_{tot}} \ln\left(\frac{[H_3O^+] + A_{tot} - H_{tot}}{[H_3O^+]}\right) + \ln([H_3O^+] + A_{tot} - H_{tot}) = -kK_a t + const. \tag{28}$$

$$\left(1 + \frac{K_a}{A_{tot} - H_{tot}}\right) \ln [H_3O^+] + \left(1 - \frac{K_a}{A_{tot} - H_{tot}}\right) \ln([H_3O^+] + A_{tot} - H_{tot}) = -kK_a t + const. \tag{29}$$

A plot of the left-hand side of eqn. (29) against t gives a straight line from which k is calculated.

From the values of kK_a and *const.* obtained by the regression, the right-hand side of eqn. (29) is calculated. By comparing this with the value of the left-hand side obtained from the experimental pH value and minimizing the difference obtained by successive additions or subtractions of small ΔpH values to the experimental pH value, we can readily calculate the pH value that satisfies eqn. (29). This is called pH(calc). A typical run for omeprazole is given in Table 5.

In this way a rough value for the constant k is very readily obtained. This is usually good enough for screening

Table 5. Rate constant for the reaction HA → D^+ calculated from pH-registration of the solution. pK_a (measured) = 3.943 $H_{tot} = 5.005 \times 10^{-4}$ mol l^{-1}, $A_{tot} = 9.23 \times 10^{-4}$ mol l^{-1} and $f^{\pm}$ (measured) = 0.749.

t/s	p*H*	
	Exp.	Calc.
0	4.167	4.171
30	4.206	4.207
45	4.225	4.225
60	4.245	4.243
75	4.264	4.261
90	4.281	4.280
105	4.303	4.298
120	4.317	4.316
135	4.334	4.335
150	4.350	4.353
165	4.368	4.371

$k = 33.7 \pm 0.5$ l mol^{-1} s^{-1}.

purposes and can be used as an aid in the design of experiments to obtain a more accurate constant.

In spite of the excellent fit of the points in Table 5 to the 'theoretical' curve, k is about 30 % lower than the value obtained by other methods. The difference is due to the fact that the method given above measures the *net* transformation of HA into quaternary pyridinium compounds. If the reaction HA → D^+ is reversible, or if HS is formed, the constant obtained will be too low. From other measurements we know that both these reactions occur.

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