Spectroscopic Approach to Estimation of Microequilibrium Constants of Prototropic Reactions of Aminobenzoic Acids

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Abstract □ The microequilibrium constants of protolytic dissociation of diprotic acids, dihydric bases, or ampholytes such as the aminobenzoic acids, with dissimilar ionizing groups, can be estimated by spectrophotometric titration and measurement of the molar absorptivity at the long wavelength absorption maximum of simple alkylated derivatives. The method is applicable when the long wavelength absorption spectral bands of the tautomeric species are well resolved. Compared to the traditional method of estimating microequilibrium constants using the dissociation constants of alkylated derivatives, the proposed method is simpler, faster, and more accurate.

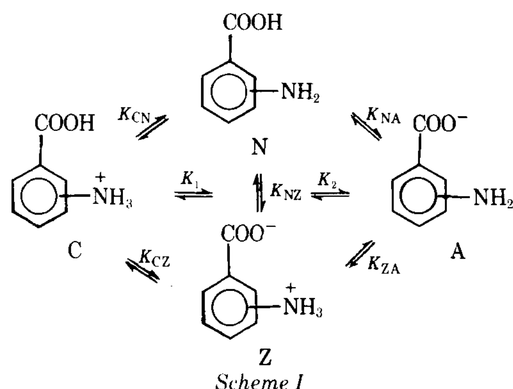
Keyphrases □ Aminobenzoic acids, various—microequilibrium constants of protolytic dissociation estimated spectrophotometrically □ Microequilibrium constants—various aminobenzoic acids, protolytic dissociation, estimated spectrophotometrically □ Spectrophotometry—estimation, microequilibrium constants of protolytic dissociation of various aminobenzoic acids □ Protolytic dissociation—various aminobenzoic acids, microequilibrium constants estimated spectrophotometrically

The purpose of this study was to show that for acids demonstrating tautomeric equilibria and absorbing visible or UV light in such a way that the long wavelength absorption bands of the tautomeric species are well resolved, the tautomeric equilibrium constant and, therefore, the microscopic prototropic equilibrium constants can be determined with greater accuracy than is presently available by using Ebert's method (1). In this approach, it is necessary to determine the molar absorptivity of an alkylated derivative, such as an ester, at its absorption maximum, as well as to determine the macroequilibrium constants of the acid of interest by spectrophotometric titration.

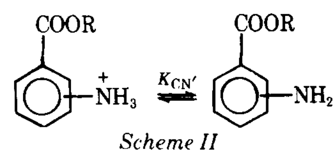
The aminobenzoic acids were chosen as test compounds because their dissociation constants are already well established (2), permitting concentration on the spectroscopic aspects of the study.

BACKGROUND

The aminobenzoic acids undergo prototropic dissociation according to Scheme I. Because of the proximity of the macroequilibrium constants K_1 and K_2, dissociation of the cation, C, may result in formation of a



Scheme I



Scheme II

neutral molecule, N, or a zwitterion, Z (3). The respective microequilibrium constants for these dissociations are K_{CN} and K_{CZ} and are related to K_1 (3) by:

$$K_1 = K_{CN} + K_{CZ} \quad \text{(Eq. 1)}$$

Either uncharged species (N or Z) can then dissociate to form the anion, A. The microequilibrium constants for these processes are K_{NA} and K_{ZA} and are related to K_2 (3) by:

$$K_2^{-1} = K_{NA}^{-1} + K_{ZA}^{-1} \quad \text{(Eq. 2)}$$

The tautomeric ratio K_{NZ} is related to the microequilibrium constants by:

$$K_{NZ} = \frac{K_{CN}}{K_{CZ}} = \frac{K_{ZA}}{K_{NA}} \quad \text{(Eq. 3)}$$

For the aminobenzoic acids, K_1 and K_2 were determined potentiometrically (2). The microequilibrium constants K_{CN}, K_{CZ}, K_{NA}, and K_{ZA} were estimated (1) by determining the dissociation constants K_{CN}' for the dissociations of the cations derived from the methyl or ethyl esters of the aminobenzoic acids (4, 5) to form the neutral esters (Scheme II) and equating K_{CN}' to K_{CN}. This approach enables the estimation of K_{CZ} from:

$$K_{CZ} \approx K_1 - K_{CN}' \quad \text{(Eq. 4)}$$

K_{NZ} from:

$$K_{NZ} \approx \frac{K_{CN}'}{K_{CZ}} \quad \text{(Eq. 5)}$$

and, ultimately, K_{NA} and K_{ZA} from:

$$K_{NA} \approx K_2(1 + K_{NZ}^{-1}) \quad \text{(Eq. 6)}$$

and:

$$K_{ZA} = K_2(1 + K_{NZ}) \quad \text{(Eq. 7)}$$

The accuracy of this approach depends on the accuracy of the assumption that $K_{CN}' = K_{CN}$. This assumption was shown for several *N*-arylglycines to be justifiable to about 0.2 pKa unit (6). This value is an acceptable error for the comparison of pKa's (standard free energies of proton exchange) of related compounds. However, if species distributions are important, an error of 0.2 pKa unit translates into an error of 58% in the estimated value of K_{CN}. Moreover, in compounds in which the proton replaced by an alkyl group is involved in an intramolecular or a strong intermolecular hydrogen bond, the error is far more serious. For example, the pKa of salicylic acid is 3.0 while that of *O*-methoxybenzoic acid is 4.1 (7). The discrepancy of 1.1 pKa units would translate into an error of ~1.2×10^3% if the K_a of *O*-methoxybenzoic acid was used to represent that of salicylic acid.

EXPERIMENTAL

The *o*-, *m*-, and *p*-aminobenzoic acids, methyl *o*-aminobenzoate, methyl *m*-aminobenzoate, and ethyl *p*-aminobenzoate were purchased[1] as the highest quality analytical reagents and were used without further purification. Salicylic acid, *m*-hydroxybenzoic acid, *p*-hydroxybenzoic

[1] Aldrich Chemical Co., Milwaukee, Wis.

Table I—Molar Absorptivities of the Pertinent Species at the Chosen Analytical Wavelengths and Macroequilibrium Constants of the Aminobenzoic Acids and Their Esters

	ϵ_C	$\epsilon_{N'}$	ϵ_A	$K_{CN'}$ [a]	K_1 [b]	K_2 [b]	ϵ_U
o-Aminobenzoic acid (λ = 327 nm)	0	—	1.76×10^3	—	7.77×10^{-3}	1.12×10^{-5}	$1.75 \pm 0.02 \times 10^3$
Methyl ester (λ = 328 nm)	—	3.63×10^3	—	6.90×10^{-3}	—	—	—
m-Aminobenzoic acid (λ = 311 nm)	0	—	1.40×10^3	—	7.60×10^{-4}	1.82×10^5	$5.68 \pm 0.48 \times 10^2$
Methyl ester (λ = 322 nm)	—	2.06×10^3	—	2.75×10^{-4}	—	—	—
p-Aminobenzoic acid (λ = 285 nm)	1.1×10^2	—	8.00×10^3	—	3.90×10^{-3}	1.42×10^5	$1.48 \pm 0.02 \times 10^4$
Ethyl ester (λ = 285 nm)	—	1.60×10^4	—	4.17×10^{-3}	—	—	—

[a] From Refs. 4 and 5. [b] From Ref. 2.

acid, and the methyl ethers and methyl esters of the hydroxybenzoic acids were also purchased[2] and used without further purification.

Absorption spectra were taken on a grating-type spectrophotometer[3] at 25° in 1-cm cells. The solutions whose spectra were taken were ~1×10^{-4} *M* in the *o*- and *m*-aminobenzoic acids and their esters and ~1×10^{-5} *M* in *p*-aminobenzoic acid and its ester. The pH of these solutions was adjusted with perchloric acid[4] using a pH meter[5] with a combination glass silver–silver chloride electrode. The spectrum of each aminobenzoic acid was scanned for 18 values of pH between pH 7.5 and $H_0 - 0.36$. From these absorptiometric titrations, plots of absorbance *versus* pH were constructed in which the absorbance was measured at the longest wavelength absorption maximum observable in each set of spectra.

Absorption spectra of the hydroxybenzoic acids at $H_0 - 0.36$ (neutral molecules), pH 7.0 (singly charged anions), and pH 14.2 (doubly charged anions) were recorded. For salicylic acid, it was necessary to take the spectrum in more concentrated (8.0 *M*) sodium hydroxide ($H_- = 15.8$) to isolate the doubly charged anion. The absorption spectra of the aminobenzoic esters at pH 7.0 (neutral molecules) and 0.2 (singly charged cations) and of the hydroxybenzoic ethers and esters at pH 1.0 (neutral molecules) and pH 12.0 (singly charged anions) were also recorded.

RESULTS AND DISCUSSION

The absorptiometric titrations of the aminobenzoic acids are represented graphically in Figs. 1 and 2. Pertinent long wavelength absorption maxima and macroequilibrium constants, taken from the literature (4, 5), of the aminobenzoic acids and their esters are listed in Table I. Those of the hydroxybenzoic acids and their ethers and esters are listed in Table II. The tautomeric and microequilibrium constants of the aminobenzoic acids are presented in Tables III and IV.

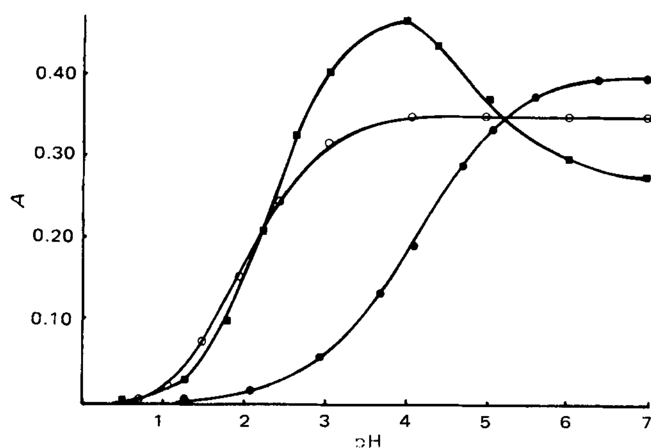


Figure 1—*Variations of absorbance, with pH, of* o*-aminobenzoic acid (○) (λ_{abs} = 327 nm),* m*-aminobenzoic acid (●) (λ_{abs} = 311 nm), and* p*-aminobenzoic acid (■) (λ_{abs} = 285 nm). The analytical wavelength in each case was the absorption maximum of the neutral molecule (longest wavelength absorbing species).*

[2] Pfaltz and Bauer, Flushing, N.Y.
[3] Beckman model DB-GT.
[4] Mallinckrodt Chemical Works, St. Louis, Mo.
[5] Orion model 801.

The protolytic equilibrium constants K_1 and K_2 of a diprotic acid with equivalent ionizing groups (*e.g.*, phthalic acid) may be calculated from the solution of:

$$(a - \epsilon_D C_T l)[H^+]^2 + (a - \epsilon_M C_T l)K_1[H^+] + (a - \epsilon_A C_T l)K_1K_2 = 0 \quad \text{(Eq. 8)}$$

for several different values of a, the absorbance at the analytical wavelength, and the corresponding values of $[H^+]$ in the absorptiometric titration. In Eq. 8, ϵ_D, ϵ_M, and ϵ_A are the molar absorptivities of the diprotic acids, its conjugate base (the monoprotic acid), and the conjugate base of the monoprotic acid, respectively; C_T is the formal concentration of diprotic acid; and l is the optical depth of the sample. If the successive prototropic equilibria appreciably overlap (*i.e.*, if $K_1/K_2 < 1 \times 10^3$), ϵ_M cannot be determined independently because the monoprotic species cannot be isolated. However, ϵ_M can be treated as a unknown parameter along with K_1 and K_2 if Eq. 8 is solved for at least three points in the absorptiometric titration.

Now, consider the spectrophotometric determination of K_1 and K_2 for diprotic acids with dissimilar ionizing groups, such as the aminobenzoic acids. For the latter compounds, K_2 and K_1 are related only to the total proton uptake by anion A and uncharged species U (U represents both the neutral species and zwitterion), respectively, and are independent

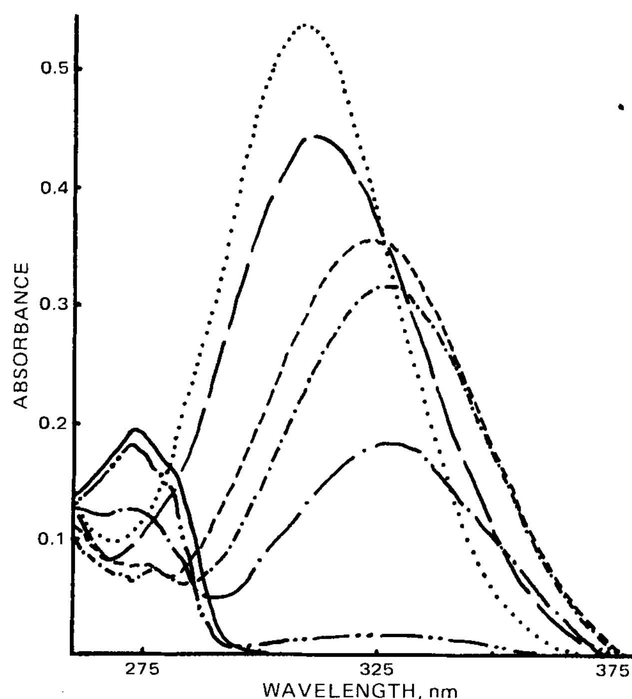


Figure 2—*The pH dependence of the absorption spectrum of* o*-aminobenzoic acid, demonstrating the red shifting and subsequent blue shifting of the spectrum, with decreasing pH as the anion is converted partially to the neutral molecule and then to the cation. Key: . . . , pH 11.04 and 7.03; – – –, pH 5.05; - - - , pH 4.08; ·–·–·, pH 3.05; —·—, pH 2.11; and —··—, pH 1.07.*

Table II—Longest Wavelength Absorption Maxima in Water of the Various Species Derived from the Hydroxybenzoic Acids and Their Ethers and Esters

	Neutral Molecule		Monoanion		Dianion	
	λ_{max}, nm	ϵ_{max}	λ_{max}, nm	ϵ_{max}	λ_{max}, nm	ϵ_{max}
Salicylic acid	302	3.68×10^3	295	3.57×10^3	309	4.09×10^3
Methyl ether	295	3.29×10^3	280	2.03×10^3		
Methyl ester	302	3.12×10^3	333	4.21×10^3		
m-Hydroxybenzoic acid	297	2.60×10^3	287	2.30×10^3	312	2.99×10^3
Methyl ether	301	2.58×10^3	286	2.21×10^3		
Methyl ester	296	2.80×10^3	322	2.90×10^3		
p-Hydroxybenzoic acid	256	1.47×10^4	246	1.25×10^4	281	1.75×10^4
Methyl ether	257	1.46×10^4	250	1.29×10^4		
Methyl ester	256	1.60×10^4	296	2.44×10^4		

of the tautomeric composition of U. Therefore, it is permissible to write Eq. 8 as:

$$(a - \epsilon_C C_T l)[H^+]^2 + (a - \epsilon_U C_T l)K_1[H^+] + (a - \epsilon_A C_T l)K_1 K_2 = 0 \quad \text{(Eq. 9)}$$

where ϵ_C and ϵ_A are the molar absorptivities of the cation and anion, respectively, and ϵ_U *may pragmatically be taken as the molar absorptivity* of the uncharged species. The actual significance of ϵ_U may be explained as follows. At the analytical wavelength:

$$A = \epsilon_C[C]l + \epsilon_N[N]l + \epsilon_Z[Z]l + \epsilon_A[A]l \quad \text{(Eq. 10)}$$

where [C], [N], [Z], and [A] are the equilibrium concentrations of cation, neutral molecule, zwitterion, and anion, respectively, and ϵ_N and ϵ_Z are the molar absorptivities of the neutral molecule and the zwitterion, respectively. If the total absorbance of uncharged species U is given by:

$$\epsilon_U[U]l = \epsilon_N[N]l + \epsilon_Z[Z]l \quad \text{(Eq. 11)}$$

where [U] is the total concentration of uncharged species, then:

$$\epsilon_U = \frac{\epsilon_N[N] + \epsilon_Z[Z]}{[U]} \quad \text{(Eq. 12)}$$

but:

$$[U] = [N] + [Z] \quad \text{(Eq. 13)}$$

so:

$$\epsilon_U = \frac{\epsilon_N[N] + \epsilon_Z[Z]}{[N] + [Z]} \quad \text{(Eq. 14)}$$

Consequently, ϵ_U may be defined as the composite molar absorptivity, at the analytical wavelength, of both uncharged species, weighted for the relative contributions of the neutral and zwitterionic species to this composite. The solution of Eq. 10 for at least three values of $[H^+]$ and the corresponding values of a in the spectrophotometric titration gives the values of K_1, K_1K_2, and ϵ_U satisfying these simultaneous equations (8).

Equation 14 may be rearranged to give:

$$\frac{[N]}{[Z]} = \frac{\epsilon_U - \epsilon_Z}{\epsilon_N - \epsilon_U} = K_{NZ} \quad \text{(Eq. 15)}$$

The value of K_{NZ} obtained in this manner could be used to resolve K_1 and K_2 into the component microequilibrium constants. However, because the uncharged species cannot be isolated, ϵ_N and ϵ_Z are generally unknown. In some cases, notably when one ionizing group is intimately coupled to the π-system of the chromophore and one is not, it is possible to equate ϵ_Z or ϵ_N to ϵ_C and the other to ϵ_A. Since ϵ_C and ϵ_A can be determined directly, K_{NZ} can be evaluated (9, 10).

In molecules like the aminobenzoic acids, however, both ionizing groups are intimately coupled to the chromophoric part of the molecule and this approach is not possible. However, in some molecules such as the aminobenzoic acids, the dissociation of one functional group (*e.g.*, the carboxyl group) produces a blue shift and the dissociation of the other group (*e.g.*, the amino group) produces a red shift of the absorption spectrum. The spectral maxima of the neutral and zwitterionic forms may then be sufficiently separated that an analytical wavelength may be chosen where the molar absorptivity of one uncharged species will be appreciable while that of the other will be negligible.

In the aminobenzoic acids, if the analytical wavelength is chosen as the long wavelength absorption maximum of the neutral molecule, $\epsilon_Z = 0$ in all three isomers. Hence, Eq. 15 reduces to:

$$K_{NZ} = \frac{\epsilon_U}{\epsilon_N - \epsilon_U} \quad \text{(Eq. 16)}$$

The molar absorptivity of a substituted aromatic molecule is determined by the degree of electronic interaction of the substituents with the aromatic π-system. The greater the degree of interaction, the greater is the extent to which the selection rules governing the probability of electronic transition in the unsubstituted aromatic nucleus break down. In the longer wavelength absorptions of benzenoid molecules, the electronic transitions are forbidden by the angular momentum selection rule (11). Hence, the presence of strongly interacting substituents on a benzene ring tends to intensify the long wavelength absorption bands. This action is illustrated in the hydroxybenzoic acids (Table II), where the species having the neutral carboxyl groups and the most highly dissociated hydroxyl groups have the highest absorptivities.

In the aminobenzoic acids, the neutrality of the amino and carboxyl groups results in the strongest coupling of the functional groups with the ring and, hence, the most intense absorption bands. Protonation of the amino group or dissociation of the carboxyl group destroys electronic coupling with the aromatic ring and, therefore, results in weaker absorption bands than in the neutral molecule. For this reason, ϵ_C and ϵ_A would be poor substitutes for ϵ_N in Eq. 16. The esters of the aminobenzoic acids, however, have electronic configurations that should closely approximate those of the neutral aminobenzoic acids. This theory is supported by the fact that the neutral hydroxybenzoic acids have molar absorptivities, at their absorption maxima, similar to those of their uncharged ethers and esters at their absorption maxima (the maximum relative deviation is 15%). Moreover, the singly charged anions of the hydroxybenzoic acids (ionized at the carboxyl groups) have molar absorptivities similar to those of the anions derived from the methoxybenzoic acids (also ionized at the carboxyl groups).

Consequently, it is permissible to equate ϵ_N', the molar absorptivity of the neutral aminobenzoic ester at its absorption maximum, with ϵ_N, the molar absorptivity of the corresponding neutral aminobenzoic acid at its absorption maximum. Equation 16 then becomes:

$$K_{NZ}' = \frac{\epsilon_U}{\epsilon_N' - \epsilon_U} \quad \text{(Eq. 17)}$$

Table III—Microequilibrium Constants for the Protolytic Dissociations of the Aminobenzoic Acids Calculated from the Macroequilibrium Constants K_1 and K_2 and the Spectroscopic Data in Table I

Isomer	K_{NZ}'	K_{CN}	K_{CZ}	K_{NA}	K_{ZA}
ortho	0.93	3.7×10^{-3}	4.0×10^{-3}	2.3×10^{-5}	2.2×10^{-5}
meta	0.38	2.1×10^{-4}	5.5×10^{-4}	6.6×10^{-5}	2.5×10^{-5}
para	12.3	3.60×10^{-3}	3.0×10^{-4}	1.54×10^{-5}	1.89×10^{-4}

Table IV—Microequilibrium Constants for the Protolytic Dissociations of the Aminobenzoic Acids Calculated from the Macroequilibrium Constants K_1 and K_2 and the Dissociation Constants of Their Methyl Esters (K_{CN}')

Isomer	K_{NZ}	K_{CN}'[a]	K_{CZ}	K_{NA}	K_{ZA}
ortho	7.9	6.90×10^{-3}	8.7×10^{-4}	1.3×10^{-5}	1.0×10^{-4}
meta	0.57	2.75×10^{-4}	4.9×10^{-4}	5.0×10^{-5}	2.9×10^{-5}
para	−16	4.17×10^{-3}	-2.7×10^{-4}	-1.5×10^{-5}	-2.3×10^{-4}
	8.5	3.49×10^{-3} (ethyl ester)[b]	4.1×10^{-4}	1.6×10^{-5}	1.3×10^{-4}

[a] From Refs. 4 and 5. [b] Determined spectrophotometrically in this work.

Since the maximum error in substituting ϵ_N' for ϵ_N is ~15% for the hydroxybenzoic acids, it may be assumed that this value is the order of maximum error in substituting ϵ_N' for ϵ_N for the aminobenzoic acids.

In the present study, the literature values of the macroequilibrium constants K_1 and K_2 (2) are used and Eq. 9 is rearranged to solve for ϵ_U for each of the aminobenzoic acids, using the absorptiometric titration data represented in Fig. 1, according to:

$$\epsilon_U = \frac{(a - \epsilon_C C_T l)[H^+]^2 + (a - \epsilon_A C_T l)K_1K_2 + aK_1[H^+]}{C_T l K_1[H^+]} \quad \text{(Eq. 18)}$$

The values of ϵ_U thus obtained are presented in Table I. These values, along with those of ϵ_N' (Table I), are employed in Eq. 17 to calculate the value of K_{NZ}' which approximates the true tautomeric equilibrium ratio K_{NZ} of each aminobenzoic acid. The values of K_{NZ}', calculated in this manner, as well as those calculated from the literature K_1, K_2, and K_{CN}' values, are also presented in Tables III and IV for comparison.

The agreement between the microequilibrium constants calculated by both methods is quite good for the *meta*-isomer. However, in the *ortho*-isomer, the spectroscopic method indicates that the neutral molecule and the zwitterion comprise almost equal fractions of the population of uncharged molecules, while the method using the K_{CN}' of the ester suggests that the neutral molecule is predominant over the zwitterion by about 8:1. Although it is difficult to establish unequivocally which approach is more accurate, the disparity between the results obtained in this case for the *para*-isomer is more definitive. The spectroscopic method indicates that the neutral molecule predominates over the zwitterion in *p*-aminobenzoic acid by 12.3:1. However, the K_{CN}' of the methyl ester yields a negative value for the tautomeric ratio, a result that is physically impossible and is transmitted into the calculations of the remaining microconstants.

The K_{CN}' of the ethyl ester of *p*-aminobenzoic acid was determined. Use of this value to calculate the microconstants of the *para*-isomer gives microconstants in reasonably good agreement with those obtained by the spectroscopic method. Hence, the microconstants obtained by using the K_{CN}' of the ester are substantially dependent on the inductive effect (and other chemical effects) of the esterifying group. The absorptivities of the methyl and ethyl esters of *p*-aminobenzoic acid are, however, virtually identical; therefore, the spectroscopic method is, barring unusual steric interferences, free of uncertainties imposed by the nature of the esterifying group.

It is concluded, therefore, that the spectroscopic method described in this paper for estimating microequilibrium constants of prototropic reactions is, when applicable, simpler, faster, and more accurate than the conventional method, employing the dissociation constant of an alkylated derivative as equivalent to one microequilibrium constant of interest.

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Comparative Pharmacokinetics of Coumarin Anticoagulants XXXIII: Frequency Distribution of Dicumarol Total Clearance in Rats

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Abstract □ The total clearance of dicumarol was determined in 172 adult male Sprague–Dawley rats. Clearance values ranged from 1.46 to 27.0 ml/hr/kg. Statistical analysis of a histogram of the total clearance values indicated a trimodal distribution, with modes at 6.28, 14.8, and 23.7 ml/hr/kg. The percentage of animals in each of these components was 60.5, 33.7, and 5.8. A previous study had shown that the total clearance of dicumarol was proportional to the fraction of nonprotein-bound drug in serum (serum free fraction) and that interindividual differences in total clearance of dicumarol in rats were due almost entirely to corresponding differences in the serum free fraction. Therefore, it is likely that the observed trimodal frequency distribution of total clearance values reflects a similar distribution of serum free fraction values of dicumarol. The frequency distribution curve for dicumarol total clearance is very similar to the trimodal frequency distribution curve for warfarin serum free fraction values in rats. This observation is consistent with the previously demonstrated strong correlation of serum free fraction values of dicumarol and warfarin in individual animals.

Keyphrases □ Dicumarol—total clearance in rats, frequency distribution □ Clearance, total—dicumarol in rats, frequency distribution □ Pharmacokinetics—total clearance of dicumarol in rats, frequency distribution □ Coumarin anticoagulants—dicumarol, total clearance in rats, frequency distribution □ Anticoagulants—dicumarol, total clearance in rats, frequency distribution

Pronounced differences exist in the elimination kinetics of dicumarol in animals and humans. Vesell and Page (1) found that the dicumarol biological half-life ($t_{1/2}$) in 28 healthy adult humans not taking other drugs ranged from 7 to 74 hr and that these values were reproducible upon subsequent administration of a second dose. Studies in this laboratory revealed a $t_{1/2}$ range of 5.1–27.9 hr and a total clearance range of 2.6–24.0 ml/hr/kg in 30 adult male Sprague–Dawley rats (2). Such differences have been found repeatedly and are also well reproducible (2, 3).

The dicumarol $t_{1/2}$ was determined in human subjects after administration of a standard oral dose, and these