

Figure 5—Plot of log bioactivity versus time obtained from computer simulation for various initial concentrations of ampicillin.

the model. The kinetic model seems sufficient to explain presently available results but awaits experimental confirmation, as do the actual values for the rate constants.

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# Molecular Orbital Calculations on Some Nitrogen Derivatives of Conjugated Hydrocarbons: Base Strength of Benzacridines and Their Amino Derivatives

FEDERICO PERADEJORDI, ALFRED N. MARTIN\*▲, ODILON CHALVET, and RAYMOND DAUDEL

**Abstract** □ The relations which exist between the electronic structure and base strength of benzacridines and their amino derivatives were investigated using semiempirical molecular orbital calculations. The calculations are complicated by a number of factors which affect equilibria in solution. The results indicate that the energy to protonate a nitrogen derivative of a conjugated hydrocarbon may be divided into the terms  $\Delta E_\sigma$  and  $\Delta E_\pi$  for changes in localized and delocalized electron energies, respectively, an energy term for solvation, and a term for steric hindrance to protonation. When the term  $\Delta E_\pi$  alone is used to determine the pKa values, it yields a linear relationship within each family of derivatives. The term  $\Delta E_{solv}$  appears to depend primarily on the size of the molecule and may be calculated by the use of a modified Born equation. The combination of  $\Delta E_\pi$  and  $\Delta E_{solv}$ , as a representation of  $\Delta E$ , yields a

single relationship when plotted against pKa for a number of benzacridines and their amino derivatives as well as the derivatives of pyridine, isoquinoline, quinoline, and acridine, which were reported previously. The deviation from this relationship for some of the compounds appears to be due to structural factors which depend on the  $\Delta E_{ster}$  and  $\Delta E_\sigma$  terms.

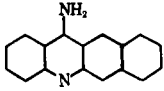
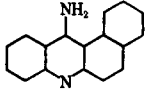
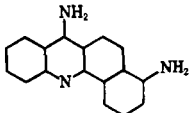
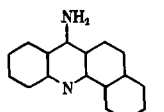
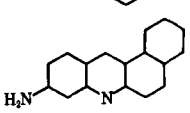
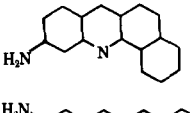
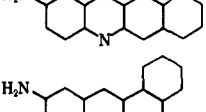
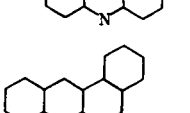
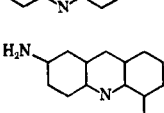
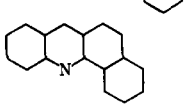
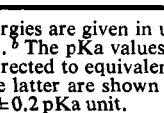
**Keyphrases** □ Benzacridines and amino derivatives—relationship between electronic structure and base strength, molecular orbital calculations □ Base strength of benzacridines and amino derivatives—relationship to electronic structure, molecular orbital calculations □ Molecular orbital calculations—used to determine the relationship between electronic structure and base strength of benzacridines and amino derivatives

The relationships which exist between the electronic structure and the base strength of organic molecules were studied by a number of investigators, and reference to several of their reports was made by Peradejordi (1).

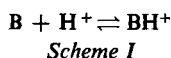
## THEORETICAL

The equilibrium reaction occurring in solution between a neutral organic base B and its positively charged acid BH<sup>+</sup>, which is said to be conjugated to the base, may be written as Scheme I. The con-

**Table I—Base Strength of Benzacridines and Calculated Energies of Protonation<sup>a</sup>**

Benzacridine Derivative	pK <sub>a</sub> (7) <sup>b</sup>	ΔE <sub>π</sub>	ΔE <sub>solv</sub>	ΔE <sub>π</sub> + ΔE <sub>solv</sub>
	(10.4) <sup>b</sup>	1.523	0.432	1.954
	(9.1)	1.471	0.424	1.895
	(9.1)	1.536	0.372	1.908
	(8.8)	1.457	0.432	1.889
	7.4	1.400	0.310	1.710
	6.7	1.382	0.338	1.720
	(6.1)	1.348	0.366	1.715
	(5.7)	1.318	0.370	1.688
	4.7	1.263	0.369	1.263
	(4.7)	1.300	0.401	1.701
	(4.1)	1.237	0.416	1.653

<sup>a</sup> Energies are given in units of β<sub>(carbon-carbon)</sub> as defined in the Huckel method. <sup>b</sup> The pK<sub>a</sub> values were determined in water or in dilute alcohol and corrected to equivalent values in water as described by Albert *et al.* (7). The latter are shown in parentheses and are subject to an error of about ±0.2 pK<sub>a</sub> unit.

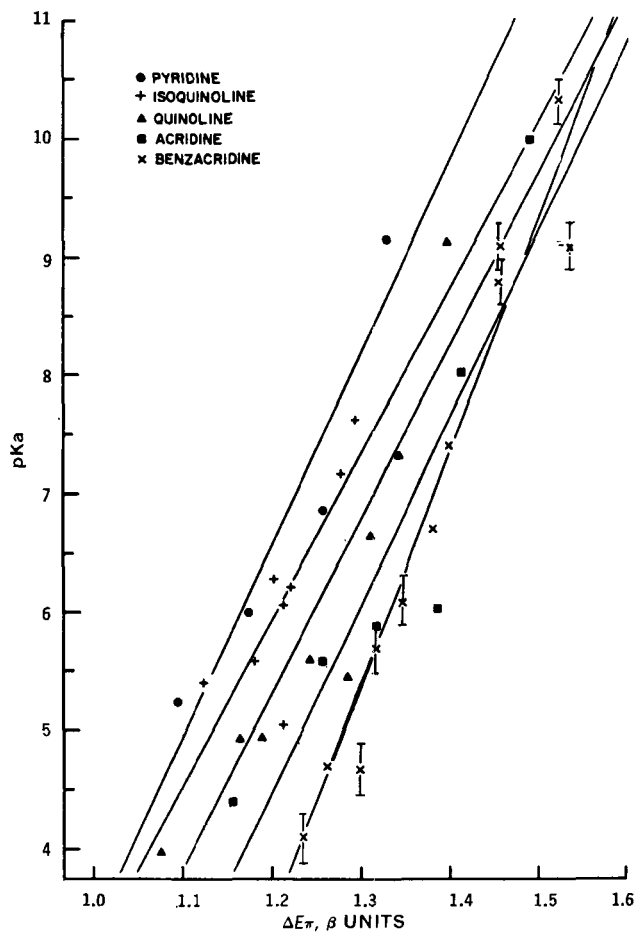


stant *K* characterizing this equilibrium is given, according to the principles of statistical thermodynamics, by the expression:

$$K = \frac{f_{BH^+}}{f_B f_{H^+}} e^{-\Delta\epsilon/RT} \quad (\text{Eq. 1})$$

where Δε = E<sub>BH<sup>+</sup></sub> - (E<sub>B</sub> + E<sub>H<sup>+</sup></sub>) represents the difference in ground-state energy between the acid BH<sup>+</sup> and the reactants B and H<sup>+</sup>, the difference ΔE = E<sub>BH<sup>+</sup></sub> - E<sub>B</sub> being the energy of protonation. The *f* terms represent the several partition functions.

A study of the relations which exist between the electronic structure of organic molecules and their acid or base strengths is complex because of the number of factors that affect the equilibrium and because of the difficulty of evaluating the terms theoretically. In the case of conjugated molecules, it is common to consider that



**Figure 1—pK<sub>a</sub> as a function of ΔE<sub>π</sub>.**

the variation in energy ΔE can be approximated by the sum of terms ΔE ≈ ΔE<sub>σ</sub> + ΔE<sub>π</sub> + ΔE<sub>solv</sub> + ΔE<sub>ster</sub>. ΔE<sub>σ</sub> represents the alteration in energy of the system of localized bonds and pairs of unshared electrons which occur during protonation, and ΔE<sub>π</sub> is the change in energy of the delocalized bonds during protonation. The term ΔE<sub>solv</sub> accounts for the effect of the solvent. This quantity represents the variation of solvation energy which occurs during protonation and is a function of the temperature. Finally, the interactions between nonbonded atoms should be taken into account by introducing an additional term, ΔE<sub>ster</sub>, to express the variation of the energy for steric hindrance to protonation, which can occur in the amino derivatives referred to in the present report.

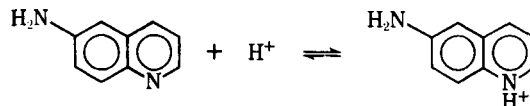
If ΔE, the difference in energy between the ion and the molecule, is considered to be made up of the various energy differences, one can write Eq. 1 in a modified form:

$$K = f(T, solv, ster) \times \exp[-(\Delta E_{\sigma} + \Delta E_{\pi} + \Delta E_{solv} + \Delta E_{ster} + E_{H^+})/RT] \quad (\text{Eq. 2})$$

where *f* stands for the ratio of the partition functions and depend on the temperature, steric effects, and the solvent. The formula can also be written in logarithmic form:

$$pK = -\log K = -\log f(T, solv, ster) + [(\Delta E_{\sigma} + \Delta E_{\pi} + \Delta E_{solv} + \Delta E_{ster} + E_{H^+})/2.3RT] \quad (\text{Eq. 3})$$

and a plot of pK can be made against the ΔE terms, singly or in



**Scheme II**

**Table II**— $pK_a$  versus  $\Delta E_\pi$  Relationships for *N*-Heterocyclic Amino Derivatives

Family of Amino Derivatives	Linear Correlation Equation	Standard Error of Estimate, $pK_a$ Units	Correlation Coefficient	$F(a,b)^a$ Test of Confidence	$p$ Value
All molecules	$pK_a = 11.865\Delta E_\pi - 8.836$	0.987	0.821	(1,35) 72.175	<0.005
Benzacridines	$pK_a = 20.386\Delta E_\pi - 21.228$	0.470	0.978	(1,9) 196.109	<0.005
Acridines	$pK_a = 15.382\Delta E_\pi - 13.908$	0.914	0.914	(1,4) 20.184	<0.025
Quinolines	$pK_a = 14.526\Delta E_\pi - 12.145$	0.663	0.928	(1,6) 37.153	<0.005
Isoquinolines	$pK_a = 13.554\Delta E_\pi - 10.293$	0.534	0.823	(1,6) 12.620	<0.025
Pyridines	$pK_a = 16.057\Delta E_\pi - 12.667$	0.612	0.956	(1,2) 21.351	<0.100

<sup>a</sup>  $a$  is the degrees of freedom for the numerator and  $b$  the degrees of freedom for the denominator. These are found in parentheses immediately before the  $F$  test values in the table.

combination, to evaluate the significance of the various energy factors.

In this way, Elliott and Mason (2) examined the different factors which influence the  $pK_a$  of aromatic amines (bases). The  $pK_a$  is a measure of the strength of an acid or base; the larger the value of  $pK_a$  the less ionized is the positively charged acid conjugate to a neutral base and the greater is the strength of the base. These workers studied, in particular, the effects of  $\Delta E_\pi$  and  $\Delta E_{ster}$  on  $pK_a$  and, in a qualitative manner, treated the role of  $\Delta E_{solv}$  and

the steric effects on the change in entropy of the system during the protonation reaction. The results of Elliott and Mason (2) show that in the case of *N*-heterocyclic amines (Scheme II), one can predict the  $pK_a$  values with a precision of approximately  $\pm 1$  unit from a consideration of  $\Delta E_\pi$  alone.

The method of Longuet-Higgins (3), which was used by Elliott and Mason (2) to calculate  $\Delta E_\pi$ , makes use of the simplest approximations. To obtain a more accurate estimation of the relative importance of the terms of Eq. 3 on the variation of  $pK_a$ , Chalvet *et al.* (4) reinvestigated the role of  $\Delta E_\pi$  in the determination of  $pK_a$  for pyridine, quinoline, isoquinoline, and acridine, using the method of Pariser and Parr (5) and Pople (6). Chalvet *et al.* (4) also estimated the solvation energy terms,  $\Delta E_{solv}$ , and studied the effect that this quantity had on the variation of the entropy,  $\Delta S$ , which accompanies protonation. Peradejordi (1) investigated the effect

**Table III**—Base Strength of Compounds with Steric Hindrance to Protonation

Compound	$pK_a$ (1, 7)	$\Delta E_\pi + \Delta E_{solv}$ [(1) and Table I]
	(9.1) <sup>b</sup>	1.908 <sup>a</sup>
	(8.8)	1.889
	7.62	1.882
	7.34	1.872
	6.86	1.798
	6.7	1.720
	5.05	1.720
	(4.7)	1.701
	4.40	1.628
	(4.1)	1.653
	3.99	1.596

<sup>a, b</sup> See Table I.

**Table IV**—Base Strength of Compounds with Steric Hindrance to  $\pi$ -Electron Delocalization, and Calculated Energies of Protonation

Compound	$pK_a$ (1, 7)	$\Delta E_\pi + \Delta E_{solv}$ [(1) and Table I]
	(10.4) <sup>b</sup>	1.954 <sup>a</sup>
	9.99	1.919
	9.17	1.814
	(9.1)	1.859
	6.28	1.741
	6.06	1.658
	6.04	1.726
	5.59	1.618
	5.46	1.648

<sup>a, b</sup> See Table I.

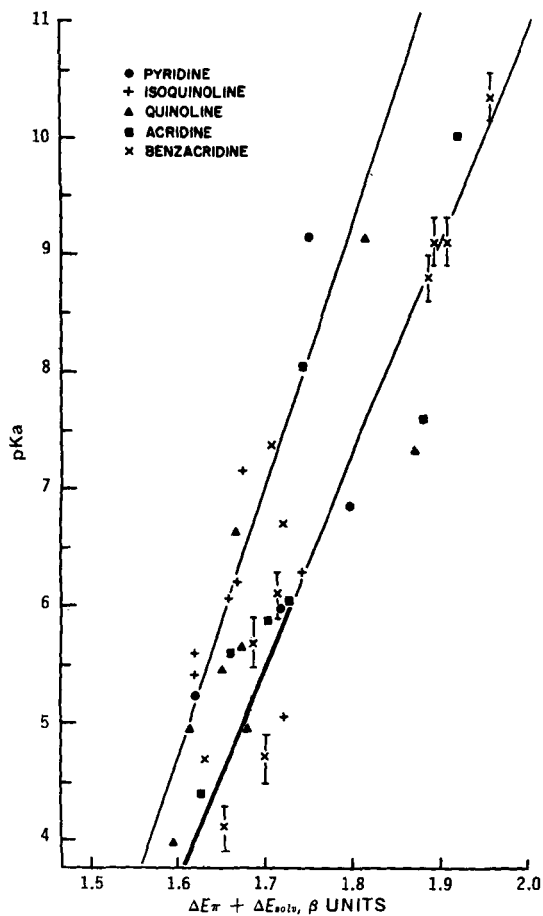
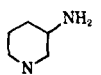
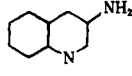
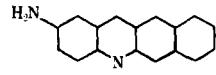
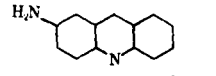
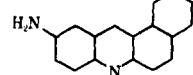
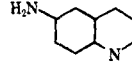


Figure 2— $pK_a$  as a function of  $\Delta E_\pi + \Delta E_{solv}$ .


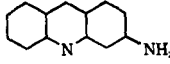
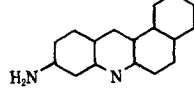
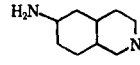
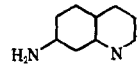
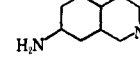
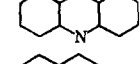
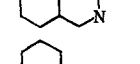

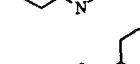
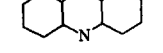
of combining  $\Delta E_\pi$  and  $\Delta E_{solv}$  in the evaluation of  $pK_a$  values for aromatic amino derivatives in the pyridine, isoquinoline, quinoline, and acridine series. The present report extends the last referred

Table V—Base Strength of Compounds with the Amino Substituent in Nonconjugative Position to the Nitrogen, and Calculated Energies of Protonation

Compound	$pK_a$ (1, 7)	$\Delta E_\pi + \Delta E_{solv}$ [(1) and Table I]
<i>meta</i> -Substituted:		
	5.98	1.717 <sup>a</sup>
	4.95	1.680
<i>β</i> -Substituted:		
	(6.1) <sup>b</sup>	1.714
	5.88	1.702
	(5.7)	1.688
	5.63	1.674

<sup>a, b</sup> See Table I.

Table VI—Base Strength of Compounds with the Amino Substituent in Conjugated Position to the Nitrogen which Are Unaffected by the Term  $\Delta E_{ster}$ , and Calculated Energies of Protonation

Compound	$pK_a$ (1, 7)	$\Delta E_\pi + \Delta E_{solv}$ [(1) and Table I]
	9.17	1.750 <sup>a</sup>
	8.04	1.743
	7.4	1.710
	7.17	1.676
	6.65	1.575
	6.20	1.559
	5.60	1.660
	5.40	1.618
	5.23	1.617
	4.94	1.614
	4.7	1.632

<sup>a</sup> See Table I.

work to the study of aminobenzacridines, as found in Table I.

## RESULTS AND DISCUSSION

The molecular wave functions were calculated by the semi-empirical method of Pariser, Parr, and Pople as described in *Reference 1* for amino derivatives of *N*-heterocyclic alternant conjugated hydrocarbon bases. Solvation energies,  $\Delta E_{solv}$ , were calculated by a modified Born equation (8) according to the method of Peradejordi (1). The results in Table I are found to be in good accord with the theory, as summarized in Eq. 3, and with the results previously reported (1).

When  $\Delta E$  is considered to be represented by the term  $\Delta E_\pi$  alone, a plot of  $pK_a$  versus this estimate of  $\Delta E$  results in a family of relationships in which the molecules are grouped according to their basic skeleton and molecular dimensions. The relationship for the benzacridines investigated in the current work is given in Table II and shown in Fig. 1 (line farthest to the right) together with compounds previously investigated (1). The lines for the various series were obtained from least-squares analysis (Table II).

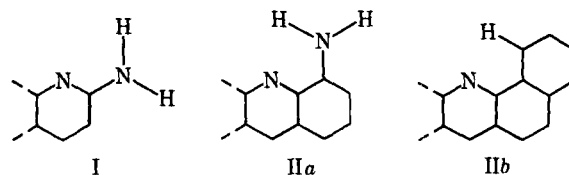


Table VII—pKa versus ( $\Delta E_\pi + \Delta E_{solv}$ ) Relationship for N-Heterocyclic Amino Derivatives

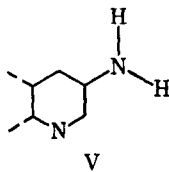
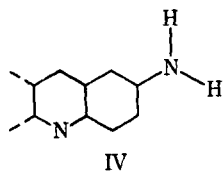
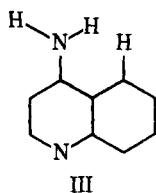
Family of Amino Derivatives	Linear Correlation Equation	Standard Error of Estimate, pKa Units	Correlation Coefficient	$F(a,b)$ Test of Confidence	p Value
All molecules	$pK_a = 14.927 (\Delta E_\pi + \Delta E_{solv}) - 19.229$	0.883	0.859	(1,35) 98.826	0.005
Molecules affected by $\Delta E_\sigma$ terms, unaffected by $\Delta E_{ster}$ terms	$pK_a = 27.808 (\Delta E_\pi + \Delta E_{solv}) - 40.017$	0.453	0.953	(1,9) 98.030	0.005
Molecules affected by $\Delta E_\sigma$ and $\Delta E_{ster}$ terms	$pK_a = 16.717 (\Delta E_\pi + \Delta E_{solv}) - 22.713$	0.713	0.927	(1,23) 140.600	0.005
Molecules with steric hindrance to protonation	$pK_a = 15.628 (\Delta E_\pi + \Delta E_{solv}) - 21.274$	0.627	0.948	(1,9) 80.633	0.005
Molecules with steric hindrance to $\pi$ -electron delocalization	$pK_a = 16.106 (\Delta E_\pi + \Delta E_{solv}) - 20.955$	0.597	0.925	(1,7) 86.669	0.005
Molecules substituted in $\beta$ -position	$pK_a = 11.776 (\Delta E_\pi + \Delta E_{solv}) - 14.124$	0.062	0.942	(1,2) 32.603	0.025

If  $\Delta E_{solv}$  is included together with  $\Delta E_\pi$  in the estimation of  $\Delta E$ , the points are no longer grouped according to their basic molecular skeleton on the graph of pKa versus  $\Delta E(\Delta E_\pi + \Delta E_{solv})$  as seen in Fig. 2. The left-hand curve of Fig. 2 is a composite line for compounds of all series, except those affected by particular structural factors as described here. Deviations are noted for some points on Fig. 2. They are due to factors other than can be accounted for alone by use of the terms  $\Delta E_\pi$  and  $\Delta E_{solv}$ . Steric hindrance and localized bond effects must certainly play an important role in these deviations. The points for *ortho* (I) and *peri* (II) derivatives of the type found in Table III are observed to be shifted to the right in Fig. 2, most probably due to  $\Delta E_{ster}$ , the steric hindrance to protonation.

Compounds with amino substituents of the type shown in Structure III, as listed in Table IV, also result in points that are shifted to the right in Fig. 2. This finding probably results from the steric hindrance to  $\pi$ -electron delocalization. The hydrogen atom in the *peri*-position prevents the amino group from assuming coplanarity with the ring and thus interferes with conjugation between the amino group and the aromatic ring. This hindrance leads to a weakening of basic strength and a decrease of pKa.

The failure to include the change of  $\sigma$ -framework energies,  $\Delta E_\sigma$ , during protonation probably leads to discrepancies in the case of some compounds. The energy of the lone  $\sigma$ -pair of electrons on a ring nitrogen should be much more affected upon protonation if the amino group and the ring nitrogen are in conjugative positions, facilitating the transfer of charge from amino to ring nitrogen. For molecules with Structures IV and V, as summarized in Table V, where the amino substituent is in the  $\beta$ -position or is *meta* to the nitrogen atom on the ring, the  $\Delta E_\sigma$  term will probably have negligible importance. The points for this type of compounds are shifted to the right in Fig. 2. This is not the case for the other amino-substituted compounds, summarized in Table VI, because the change in  $\Delta E_\sigma$  energies presumably is not negligible and should be taken into account for these substances.

The relationships between pKa and  $\Delta E$ , expressed as ( $\Delta E_\pi + \Delta E_{solv}$ ), are summarized in Table VII.



## SUMMARY AND CONCLUSION

This report represents a continuation of previous work (1) designed to investigate the various factors required in determining the strength of a series of nitrogen derivatives of conjugated hydrocarbons. The results on benzacridines and their amino derivatives investigated in this project corroborate the previous findings and show that:

1. The protonation energy  $\Delta E$  of a nitrogen derivative of a conjugated hydrocarbon may be divided into  $\Delta E_\sigma$  and  $\Delta E_\pi$  terms for changes in localized and delocalized electron energy, respectively,  $\Delta E_{solv}$  for solvation, and  $\Delta E_{ster}$  for steric hindrance to protonation.
2. When the term  $\Delta E_\pi$  alone is used to obtain the pKa values, it yields linear relationships within individual families of derivatives.
3. The term  $\Delta E_{solv}$  appears to depend primarily on the size of the molecules.
4. The combination of  $\Delta E_\pi$  and  $\Delta E_{solv}$  as a representation of  $\Delta E$  yields a single relationship when plotted against pKa for a number of compounds, including derivatives of pyridine, isoquinoline, quinoline, acridine, and the benzacridine series currently investigated.
5. The deviation of points from this relationship for some of the compounds appears to be due essentially to structural factors which depend on the  $\Delta E_{ster}$  and  $\Delta E_\sigma$  terms. However, a quantitative estimation of these terms is not attempted in the present report.

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