Applications of Magnetic Circular Dichroism: A Hammett-like Equation for Structural Work. Determination of Protonation Sites in Azaindolizines

John W. Downing,[1a] Jacek W. Waluk,[1a] Branko Stanovnik,[1b] Miha Tisler,[1b] Bojan Vercek,[1b] and Josef Michl*[1a]

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, and the Department of Chemistry and Chemical Technology, University of Ljubljana, 61001 Ljubljana, Yugoslavia

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The MCD *B* terms of the two L transitions in 14 azaindolizines in neutral and protonated forms have been measured. Interpretation was based on the perimeter model and consideration of the effect of the —CH═ → —N═ and —CH═ → —NH⁺═ replacements on the orbital energy double difference ΔHOMO − ΔLUMO. The experimental data were used to derive incremental contributions to the quantity ΔHOMO − ΔLUMO for such replacements in six of the seven ring positions, assuming proportionality between the effect of the —N═ and the stronger effect of the —NH⁺═ groups. In turn, this allowed the determination of the protonation sites in the heterocycles from their measured MCD spectra. The increments derived by fitting experimental data agree qualitatively with those obtained by applying first-order perturbation theory to the results of INDO/S calculations. These calculations, as well as PPP calculations, were also used to calculate the *B* terms in the MCD spectra directly and a good agreement was found. Weak nπ* transitions were noted and assigned in several absorption and MCD spectra of the azaindolizines.

It has become clear in recent years that the magnetic circular dichroism (MCD) of the two to four lowest ππ* transitions in cyclic π-electron systems derived at least remotely from a $(4N + 2)$-electron [*n*]annulene perimeter can be understood qualitatively in terms of the perimeter model approximation. This requires no elaborate calculations and provides simple physical insight into the origin of the observed MCD signs and magnitudes. The four transitions usually are the dominant features of the readily accessible region of the spectra of aromatics. A mathematical description of the application of a modified version of Platt's perimeter model[2] to the MCD of aromatics is given in ref 3 and 4; more qualitative descriptions and discussion are available in ref 5–8.

A quantitative measure of the MCD strength of a transition in a molecule of low symmetry is given by its *B* term, defined by $B = -33.53^{-1}\int d\tilde{\nu}\,[\Theta]_M/\tilde{\nu}$, where $[\Theta]_M$ is molar ellipticity per unit magnetic field strength in units of deg L m^{-1} mol^{-1} G^{-1}, *B* is in units of β_e D^2/cm^{-1}, and $\tilde{\nu}$ is wavenumber. A positive MCD peak thus corresponds to a negative *B* term and vice versa.

Most aromatic molecules of interest in organic applications are derived from $(4N + 2)$-electron perimeters for which $N \neq 0$ and $N \neq (n/2) - 1$ and which carry a net charge of at most ±2. The perimeter model predicts the presence of two weaker transitions at lower energies, referred to as the L transitions, and of two strong transitions at higher energies, referred to as the B transitions. The *B* terms of both L and B transitions can be thought of as being composed of two contributions of distinct physical origin. One of these contributions is proportional to a relatively small magnetic moment μ^-, and the other to a relatively large magnetic moment μ^+. Estimated values of these magnetic moments as functions of *N* and *n* have been tabulated.[3]

The μ^- contribution to the *B* terms of the two L transitions is not only small, but also exhibits little sensitivity to the details of molecular structure. On the other hand, the μ^+ contribution, which usually dominates the *B* terms of the two L transitions, is very sensitive to structural details. The factors which determine its sign and magnitude can be approximated by the orbital energy differences ΔHOMO and ΔLUMO. These are defined as the respective energy splitting of the highest occupied molecular orbitals (HOMO) and lowest unoccupied molecular orbitals (LUMO) which would be degenerate in the idealized perimeter, but usually no longer are after the introduction of the perturbations necessary to convert the ideal perimeter into the molecule at hand. The sign of the double difference ΔHOMO − ΔLUMO controls the sign of the μ^+ contribution to the *B* term. Since the relative magnitudes of ΔHOMO and ΔLUMO can usually be determined by inspection of the molecular structure and application of the principles of Dewar's PMO method,[9] which requires no numerical computations, the perimeter model represents a suitable framework for the application of MCD spectroscopy to problems of electronic and molecular structure of aromatics. The qualitative validity of the perimeter model description of the MCD effect in aromatics has been tested successfully on well over a hundred compounds, and the key role of the μ^+ contributions, i.e., the quantity ΔHOMO − ΔLUMO, is now well established.[8]

Potential applications in aromatic chemistry are legion. Because of its sensitivity to the relative values of ΔHOMO and ΔLUMO, MCD spectroscopy can be used to investigate electronic structure (e.g., presence of transannular[10] and hyperconjugative[11] interactions in bridged annulenes, orbital energy pattern in heterobenzenes,[12] presence of a cyclic 10π-electron aromatic system in an inorganic sulfur

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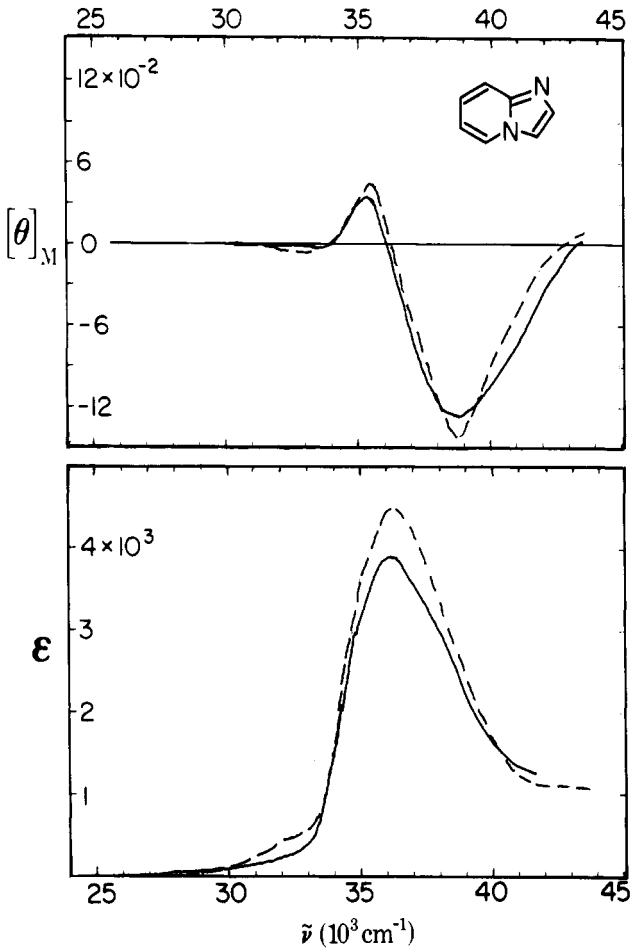


Figure 1. MCD (top) and UV (bottom) spectra in ethanol (—) and 4 N $HClO_4$ in ethanol (- -).

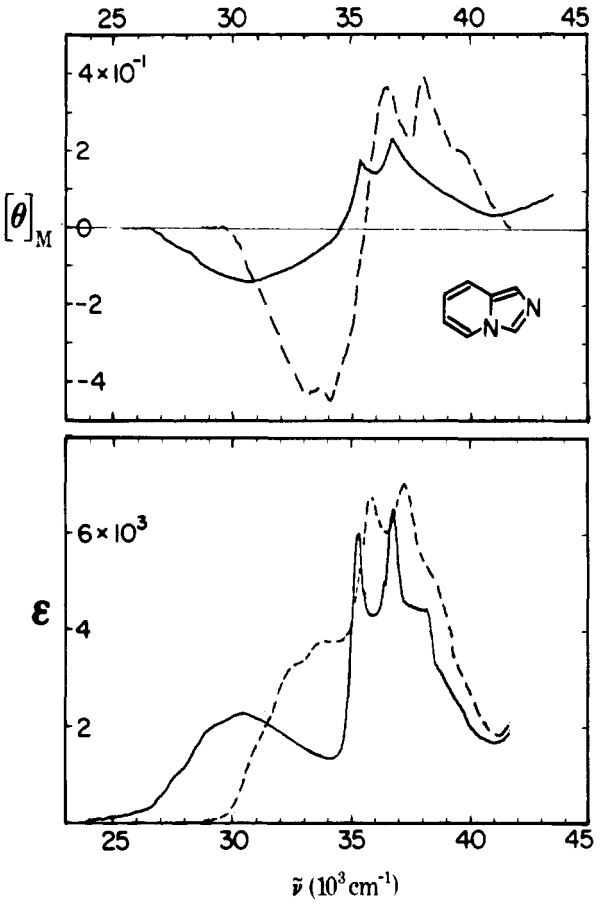
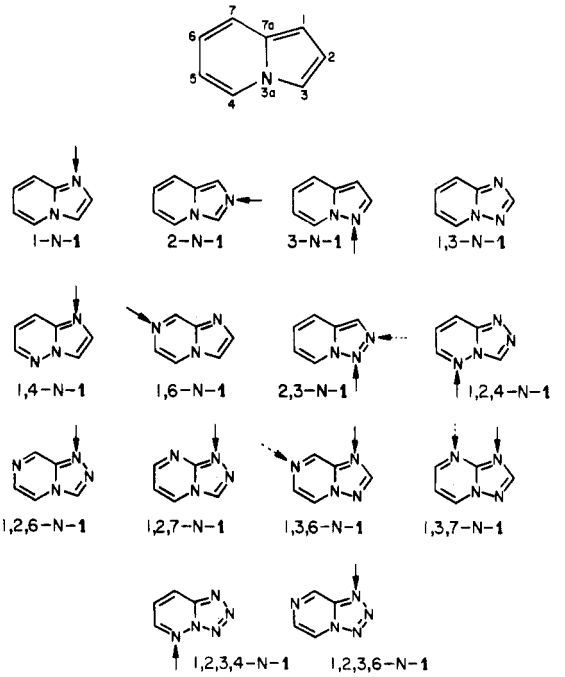


Figure 2. MCD (top) and UV (bottom) spectra in ethanol (-) and 4 N $HClO_4$ in ethanol (- -).

nitrogen heterocycle,[13] π-electron donor and acceptor strength of substituents[14]) as well as molecular structure (e.g., isomerism in substituted polynuclear aromatics[15,16] and porphyrins,[17] tautomerism[18] and protonation sites[6] in heterocycles).

The determination of the position of protonation in heterocycles with several basic sites by MCD spectroscopy is based on the notion that protonation increases the electronegativity of an aza nitrogen and therefore has a predictable effect on ΔHOMO – ΔLUMO and thus on the MCD spectrum. The subject has so far been only briefly touched upon when it was noted that the observed MCD spectra of the protonated forms of the four isomeric *N*-methylpurines and of two *N*-methyladenines were consistent only with certain protonation sites.[6] Since the determination of protonation sites in heterocycles is of considerable interest, and since it is frequently difficult to accomplish by other techniques, we return to this subject in greater depth and more systematically in the present study. We have chosen a group of 14 azaindolizines as model substrates. The ring numbering of indolizine (1) and the structures of the azaindolizines and their abbreviations are shown in Chart I. The indolizine numbering system will be used throughout.

Chart I. Most Probable Protonation Pattern (full arrows) Derived from the MCD Data and Several Alternatives Also Compatible with the Data



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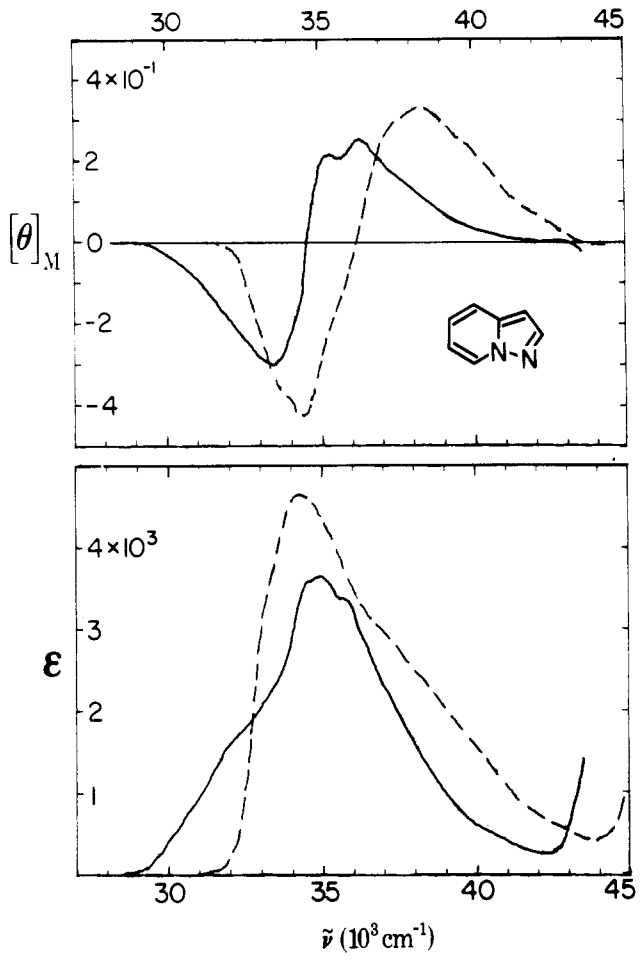

Figure 3. MCD (top) and UV (bottom) spectra in ethanol (—) and 4 N $HClO_4$ in ethanol (- -).

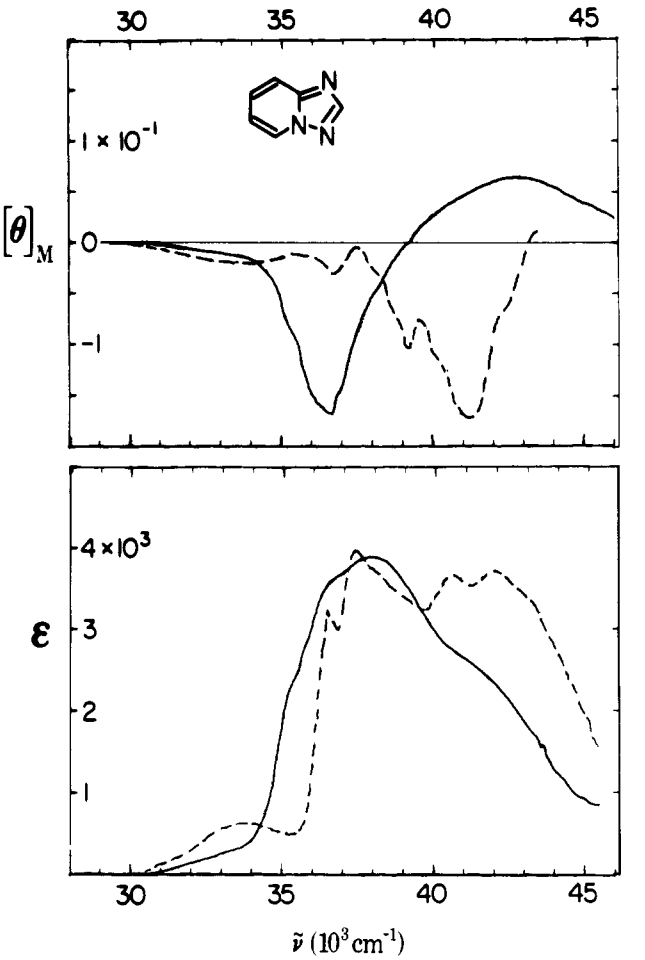

Figure 4. MCD (top) and UV (bottom) spectra in ethanol (-) and 4 N $HClO_4$ in ethanol (- -).

Results and Discussion

Representative MCD and absorption spectra of azaindolizines in their unprotonated and protonated forms are shown in Figures 1–7. Comparisons with the spectra of the regular [9]-annulenide anion perimeter,[19] with the parent indenide anion,[19] with the isoelectronic heterocycles of the indole series,[6] and with previous spectroscopic and theoretical work on indolizine and azaindolizines[20,21] lead one to expect two transitions of the L type in the 25 000 to 40 000 cm^{-1} region. While the two moderately intense bands merge in many of the absorption spectra, the MCD spectra leave no doubt that two transitions are indeed present. In only one case, unprotonated 1,2,3,4-N-1, does the MCD spectrum show only a single broad band. With this single exception, it is possible to estimate the separate *B* terms of both L transitions by integration. The accuracy of the integration procedure is relatively low because of band overlap, particularly when the two L transitions are close in energy. In several cases weaker bands, presumably due to $n\pi^*$ transitions, are present in the absorption spectra at longer wavelengths as illustrated in Figures 1 and 4. They are not seen in the MCD spectra except extremely weakly in one or two cases. This accords with our previous experience concerning the MCD effect associated with $n\pi^*$ transitions.[22] The measured MCD spectra of the unprotonated indolizines are summarized in Figure 8 which also gives the MCD *B* terms calculated by the PPP and INDO/S methods with procedures outlined in ref 23 and 24b, respectively. The excitation energies, intensities, and *B* terms for the unprotonated and protonated indolizines are collected in Table I.

Comparison of Spectra with Semiempirical Calculations. The MCD spectra of both the unprotonated and the protonated azaindolizines show considerable variation in sign and magnitude, and it is natural to ask about the origin of this variability. In the following, we interpret the apparently bewildering variety of sign patterns at two levels. First, we compare the observed spectra with those of PPP and INDO/S calculations. Second, we use the perimeter model to obtain more insight into the origin of the MCD signs. Either procedure can be used to obtain predictions for additional azaindolizines, both neutral and protonated in various positions, and can therefore be used as a guide in the assignment of protonation sites from measured MCD spectra. The MCD spectra of the azaindolizines and their changes upon protonation are reproduced quite well by both the PPP and INDO/S methods

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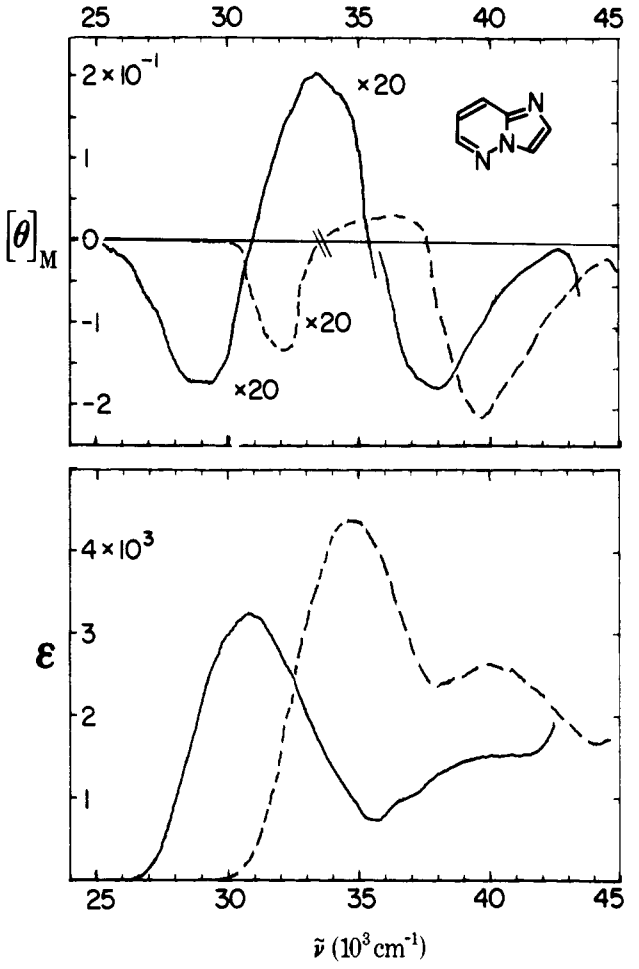

Figure 5. MCD (top) and UV (bottom) spectra in ethanol (–) and 4 N $HClO_4$ in ethanol (- -).

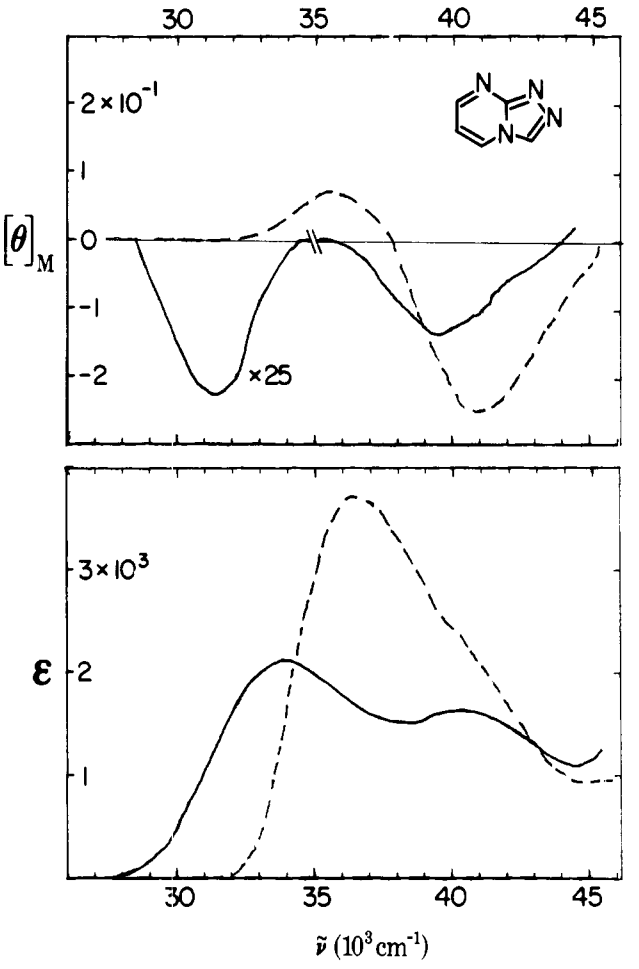

Figure 6. MCD (top) and UV (bottom) spectra in ethanol (–) and 4 N $HClO_4$ in ethanol (- -).

Table I. MCD Spectra of Azaindolizines[a]

free base	$E(L_1)$	$B(L_1)$	$E(L_2)$	$B(L_2)$	$f(L_1) + f(L_2)$
1-N-1	35 000	−0.03	38 500	0.41	0.09
2-N-1	30 500	0.67	36 500	−0.59	0.16
3-N-1	33 500	0.71	36 500	−0.67	0.09
1,3-N-1	36 500	0.36	42 500	−0.21	0.14
1,4-N-1	30 500	0	38 000	0.52	0.10
1,6-N-1	33 500	−0.68	37 000	1.48	0.16
2,3-N-1	34 000	1.07	37 000	−1.17	0.15
1,2,4-N-1	33 000	0.13	40 000	0.32	0.06[b]
1,2,6-N-1	35 000	0.29	42 000	0.11	0.14
1,2,7-N-1	31 500	0.03	39 500	0.45	0.10
1,3,6-N-1	35 000	−0.03	38 500	0.49	0.15
1,3,7-N-1	35 000	−0.44	38 500	1.38	0.12
1,2,3,4-N-1	36 500	*c*	40 000	0.40[c]	0.07
1,2,3,6-N-1	36 500	0.70	40 000	−0.56	0.14
		Protonated			
1-N-1	35 500	−0.044	39 000	0.46	0.10
2-N-1	34 000	1.38	38 000	−1.05	0.19
3-N-1	34 500	0.85	38 000	−1.02	0.12
1,3-N-1	37 000	*c*	40 500	0.39[c]	0.14
1,4-N-1	33 500	−0.07	40 000	0.59	0.15
1,6-N-1	30 500	−1.10	35 500	2.36	0.25
2,3-N-1	35 000	1.29	38 500	−1.42	0.16
1,2,4-N-1	35 500	0.02	41 000	0.66	0.12
1,2,6-N-1	31 500	0.22	38 000	0.28	0.09[b]
1,2,7-N-1	36 000	−0.18	41 000	0.81	0.12
1,3,6-N-1	34 000	−0.36	38 000	1.34	0.19
1,3,7-N-1	37 000	−0.52	41 500	1.76	0.14
1,2,3,4-N-1	38 500	−0.04	42 000	0.46	0.10
1,2,3,6-N-1	33 000	0.20	37 000	0.10	0.10

[a] Wavenumbers of the L_1 and L_2 transitions in cm^{-1}, their B terms in units of $10^{-3}\beta_e$ D^2/cm^{-1}, and their oscillator strengths $f(L_1) + f(L_2)$. [b] L_1 only. [c] $B(L_1) + B(L_2)$.

of calculation (Figures), except that the theory tends to overestimate the absolute values of both the B terms and the oscillator strengths. Not surprisingly, both methods are poor at predicting the signs of those B terms which are nearly equal to zero (Figure 8). The main advantage of the INDO/S method is its ability to predict $n\pi^*$ transitions. It performs only moderately well in suggesting in which cases these will be below the lowest $\pi\pi^*$ transitions and therefore will be easily observable. The main disadvantage of the INDO/S method is the near randomness with which it scatters the calculated $n\pi^*$ transitions; in some instances, a near degeneracy of a $n\pi^*$ and $\pi\pi^*$ transition leads to unrealistically large calculated values of B terms. The predicted intensities and B terms of $n\pi^*$ transitions are very weak in agreement with experiment.

In order to use numerical calculations by the INDO/S or PPP methods for the determination of protonation sites in further heterocycles of this type, a comparison of the measured change of the MCD spectrum upon protonation with that calculated for each possible protonated isomer is necessary. This is not likely to find much favor with organic chemists since it requires considerable computation (49 calculations in the present case) as well as assignment of the calculated states to observed transitions. Also, the application of such calculations only infrequently yields definitive assignments of protonation sites.

While the ability of standard quantum chemical methods to predict correct signs for the B terms by numerical computation is satisfying, further analysis is required in order to obtain insight into the relation of the observed MCD spectra to molecular structure, and in particular, protonation sites. Such insight is provided by analysis in

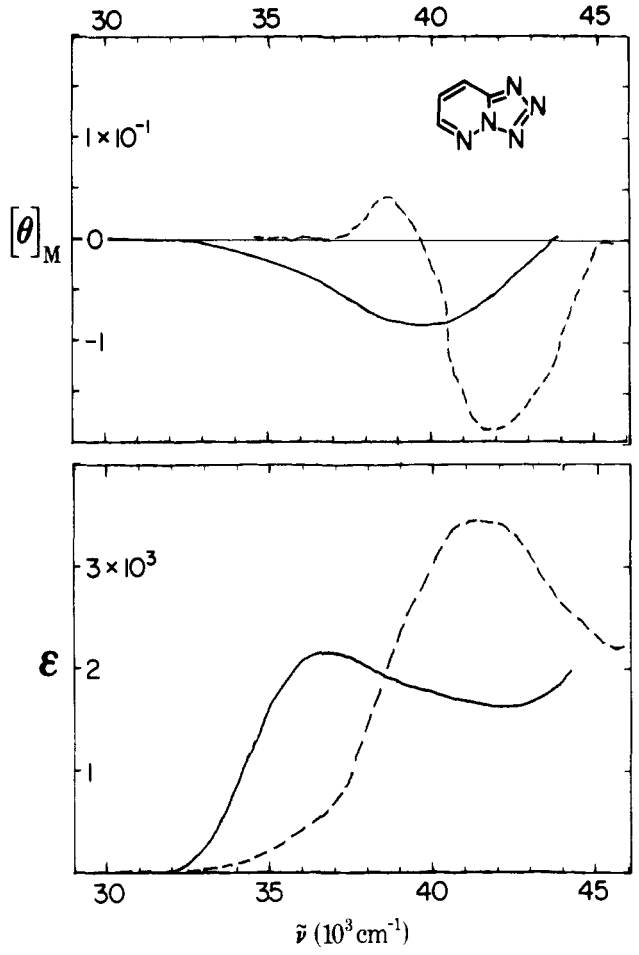

Figure 7. MCD (top) and UV (bottom) spectra in ethanol (–) and 4 N $HClO_4$ in ethanol (- -).

terms of the perimeter model as described briefly in the introduction. This model has already been used to predict the sequence of signs of B terms for 1 itself.[6-8]

Treatment in Terms of the Perimeter Model. The Starting Expression. We shall base our semiquantitative analysis on the expressions for the B terms of the L_1 and L_2 transition derived[4] using the approximate perimeter model:

$$B(L_1) = -2\mu^-(n,N)m^2(n,2N+1)\{[W(L_2)-W(L_1)]^{-1}\sin^2\beta + [W(B_1)-W(L_1)]^{-1}\cos^2\beta\}\sin^2\alpha - \tfrac{1}{2}\mu^+(n,N)m^2(n,2N+1)\{[W(L_2)-W(L_1)]^{-1} - [W(B_1)-W(L_1)]^{-1}\}\sin 2\alpha \sin 2\beta \quad (1)$$

$$B(L_2) = 2\mu^-(n,N)m^2(n,2N+1)\{[W(L_2)-W(L_1)]^{-1}\sin^2\alpha - [W(B_2)-W(L_2)]^{-1}\cos^2\alpha\}\sin^2\beta + \tfrac{1}{2}\mu^+(n,N)m^2(n,2N+1)\{[W(L_2)-W(L_1)]^{-1} + [W(B_2)-W(L_2)]^{-1}\}\sin 2\alpha \sin 2\beta \quad (2)$$

where the negative magnetic dipole moments $\mu^-(n,N)$ and $\mu^+(n,N)$ and the square of the electric dipole moment $m^2(n,2N+1)$ are characteristic of the $C_9H_9^-$ perimeter ($n = 9$, $N = 2$) and will therefore be assumed constant for all indolizines in the following.

$W(i)$ is the energy of state i, α and β are given by

$$\alpha = \tfrac{1}{2}\tan^{-1}\frac{\Delta HOMO + \Delta LUMO}{B-L}$$

$$\beta = \tfrac{1}{2}\tan^{-1}\frac{\Delta HOMO - \Delta LUMO}{B-L}$$

where $B - L$ is the difference in the energies of the perturbed sense-preserving and sense-reversing excited electronic configurations of the perimeter as defined in ref 4, and $\Delta HOMO$ and $\Delta LUMO$ are the already defined fundamental parameters describing the nature of the perturbation which produces the azaindolizine in question from the parent perimeter.

Assumptions and Approximations. We shall now introduce a set of further approximations which simplify eq 1 and 2 to a form useful for the present purpose. First, we note that $B - L$ is a property of the perimeter which shows little sensitivity to perturbations. Therefore, it will be assumed constant in all azaindolizines in the following. Second, we recognize that α and β are small angles, and replace $\sin 2\alpha$ and $\sin 2\beta$ by $\tan 2\alpha$ and $\tan 2\beta$, respectively. Third, since $\mu^-(9,2)$ is more than an order of magnitude smaller[3] than $\mu^+(9,2)$, the μ^- contribution is small relative to the μ^+ contribution unless $\Delta HOMO \approx \Delta LUMO$. We shall neglect its variation with structure and assume that it has the values $B^-(L_1)$ and $B^-(L_2)$ for the L_1 and L_2 transitions, respectively, in indolizine and all neutral or protonated azaindolizines.

With these approximations, expressions 1 and 2 simplify to

$$B(L_1) = B^-(L_1) + K'(\Delta HOMO^2 - \Delta LUMO^2)\{[W(L_2) - W(L_1)]^{-1} - [W(B_1) - W(L_1)]^{-1}\} \quad (3)$$

$$B(L_2) = B^-(L_2) - K'(\Delta HOMO^2 - \Delta LUMO^2)\{[W(L_2) - W(L_1)]^{-1} + [W(B_2) - W(L_2)]^{-1}\} \quad (4)$$

where K' is a positive proportionality constant.

The quantities in the folded brackets are measurable, provided that the energies of both L states, $W(L_1)$ and $W(L_2)$, and of both B states, $W(B_1)$ and $W(B_2)$, can be extracted from the spectra. While this is easy for the L states, it is usually not possible for the B states since the transitions to these states are at high energies and at most one and often neither one is observed in our spectra. However, since the energy differences $W(B_1) - W(L_1)$ and $W(B_2) - W(L_1)$ are considerably larger than the differences $W(L_2) - W(L_1)$, we can further assume that the ratios $R_1 = [W(B_1) - W(L_2)]/[W(B_1) - W(L_1)]$ and $R_2 = [W(B_2) - W(L_2)]/[W(B_2) - W(L_1)]$, both of which are positive and a little smaller than unity, are constant for all azaindolizines. With the definition

$$\Delta E = W(L_2) - W(L_1) \quad (5)$$

we can now write eq 3 and 4 in the form

$$B(L_1)\Delta E = B^-(L_1)\Delta E + K'R_1(\Delta HOMO^2 - \Delta LUMO^2) \quad (6)$$

$$B(L_2)\Delta E = B^-(L_2)\Delta E - (K'/R_2)(\Delta HOMO^2 - \Delta LUMO^2) \quad (7)$$

where $K'R_1$ and K'/R_2 are positive proportionality constants. In the following, they will be treated as adjustable parameters common to all azaindolizines, as will the μ^- contributions $B^-(L_1)$ and $B^-(L_2)$. At the end, we shall check that the adjusted values of these parameters are compatible with their physical significance within the perimeter model.

With a few exceptions noted above, the three quantities $B(L_1)$, $B(L_2)$, and ΔE are available from our measurements for each neutral and protonated azaindolizine, 52 pieces of data altogether. This is enough information to determine the values of the four adjustable parameters and to determine the quantity $\Delta HOMO^2 - \Delta LUMO^2$ for each species for which both $B(L_1)$ and $B(L_2)$ have been measured, but not enough to determine $\Delta HOMO$ and $\Delta LUMO$ separately. What would then still remain to be done is to

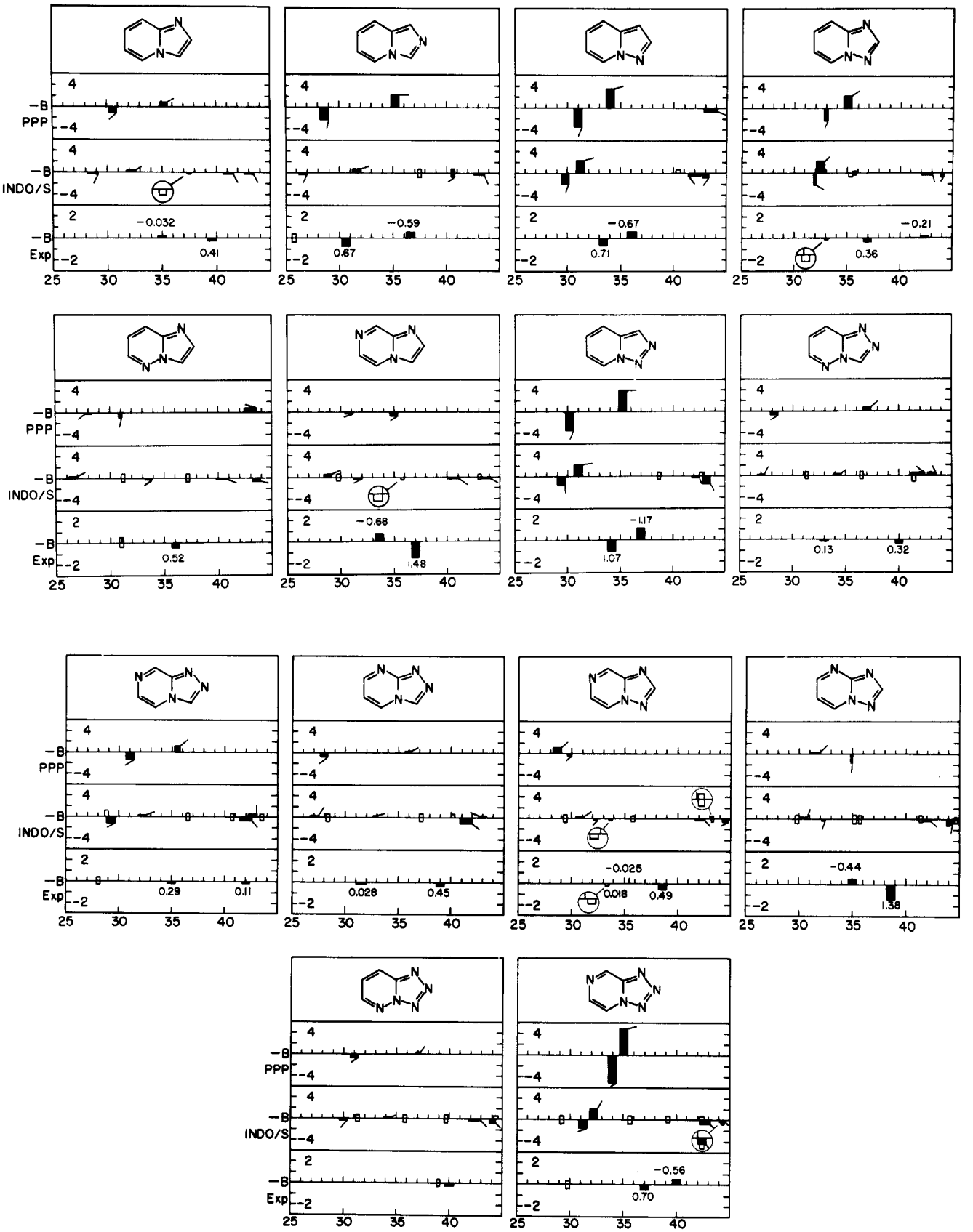

Figure 8. Calculated and experimental MCD and absorption spectra of azaindolizines. Horizontal axis units are 10^3 cm^{-1} and vertical axis units are β_e D^2/10^3 cm^{-1}. Bar widths indicate oscillator strength and heights indicate magnitudes of MCD B terms for each transition. $n\pi^*$ transitions are open bars and $\pi\pi^*$ filled. $n\pi^*$ transitions for which the B term is very small extend both above and below the axis. Transition moment directions with respect to the long axis of the molecule are indicated by flags appended to the bars.

relate the value $\Delta HOMO^2 - \Delta LUMO^2$ to molecular structure and in particular, to the position of protonation.

It is possible that two different positions in the same azaindolizine have nearly identical basicities such that both are present in significant amounts. The observed MCD spectrum would then represent the weighted average of the MCD spectra of the two components and this might lead to misleading conclusions. We shall first assume that

this does not occur and shall subsequently return to the problem.

Use of PMO Theory—Further Simplification. In order to tie the $\Delta HOMO^2 - \Delta LUMO^2$ value to molecular structure in a way that requires a minimum number of parameters, we shall use the PMO theory.[9] While its simplicity is appealing, it may appear to be too crude a tool to use. However, remembering the relatively poor accuracy with which the experimental B terms were determined, and the approximate nature of the perimeter model, we feel that the PMO method is appropriate.

For the parent indolizine 1, $\Delta HOMO$ and $\Delta LUMO$ will have some values which are presently of no great interest in themselves. Introduction of an aza nitrogen in position κ will change both of these values. In the first-order perturbation theory approximation, the change in $\Delta HOMO$, which we shall label $\Delta\Delta HOMO$, will be equal to $(c_{1,\kappa}^2 - c_{2,\kappa}^2)\Delta\alpha_N$ and the change in $\Delta LUMO$, which we shall label $\Delta\Delta LUMO$, will be equal to $(c_{-2,\kappa}^2 - c_{-1,\kappa}^2)\Delta\alpha_N$, where $\Delta\alpha_N$ is the difference of the Coulomb integral of the aza nitrogen p_z AO relative to that of carbon. Introduction of a protonated aza nitrogen (azonia nitrogen) will cause larger changes, $\Delta\Delta HOMO$ and $\Delta\Delta LUMO$, given by similar expressions in which $\Delta\alpha_{NH^+}$ has replaced $\Delta\alpha_N$. Both $\Delta\alpha_N$ and $\Delta\alpha_{NH^+}$ are negative quantities. We neglect changes in the resonance integrals caused by the presence of heteroatoms. The symbol $c_{i,\kappa}$ stands for the LCAO coefficient of the ith molecular orbital in position κ. Occupied orbitals are labeled 1,2,,··· in the order of decreasing energy and unoccupied orbitals are labeled −1, −2,··· in the order of increasing energy. At the PMO level of approximation, the changes $\Delta\Delta HOMO$ and $\Delta\Delta LUMO$ can be taken to be additive for several simultaneous aza replacements.

There are seven possible positions for aza substitution, each characterized by its additive incremental contribution to the $\Delta\Delta HOMO$ value and its additive incremental contribution to the $\Delta\Delta LUMO$ value. If we determine these increments, they could be used for the prediction of $B(L_1)\Delta E$ and $B(L_2)\Delta E$ values for any additional azaindolizine, and they could also be compared with $c_{1,\kappa}^2 - c_{2,\kappa}^2$ and $c_{-2,\kappa}^2 - c_{-1,\kappa}^2$ values obtained from MO calculations. Aza substitution in position 5 is not represented in the group of compounds available to us presently, so that there are twelve unknown increments plus six adjustable parameters, $B^-(L_1)$, $B^-(L_2)$, $K'R_1$, K'/R_2, and the $\Delta HOMO$ and $\Delta LUMO$ values in indolizine itself, to be determined from 26 $B\Delta E$ values measured for free base indolizines (the values for 1,2,3,4-N-1 could not be determined because of band overlap).

The Final Approximation. At this point, we prefer to reduce the number of unknowns by adopting one further simplification in our model. Both the PPP and the INDO/S calculations suggest that the relative variation in $\Delta HOMO + \Delta LUMO$ within the series of azaindolizines is much smaller than that in $\Delta HOMO - \Delta LUMO$, and we shall assume that $\Delta HOMO + \Delta LUMO$ is constant. Then only the $\Delta HOMO - \Delta LUMO$ value, rather than $\Delta HOMO$ and $\Delta LUMO$ separately, remains as an unknown for each azaindolizine, and each position is characterized by the value $\Delta\Delta HOMO - \Delta\Delta LUMO$ which an aza nitrogen atom produces when introduced there. For position κ, this is given by

$$\Delta\Delta HOMO - \Delta\Delta LUMO = (c_{1,\kappa}^2 - c_{2,\kappa}^2 + c_{-1,\kappa}^2 - c_{-2,\kappa}^2)\Delta\alpha_N = \Delta_\kappa\Delta\alpha_N \quad (8)$$

The $\Delta HOMO - \Delta LUMO$ value of the parent indolizine remains to define an adjustable parameter, formulated as $A_0 = KR_1(\Delta HOMO - \Delta LUMO)$, where $K = K'(\Delta HOMO + \Delta LUMO)$.

Table II. Increments for Heteroatom Effects on Indolizine

κ	A_κ(N)	A_κ(N and NH^+)[a]	Δ_κ(PPP)	Δ_κ(INDO/S)
1	−0.762	−0.281	−0.19	−0.24
2	1.693	1.549	0.36	0.35
3	1.657	0.948	0.09	0.01
4	−2.211	−2.629	−0.41	−0.35
5			0.25	0.32
6	−1.480	−2.365	−0.08	−0.17
7	−3.425	−3.889	−0.36	−0.28

[a] $B^-(L_1) = 0.498$, $B^-(L_2) = -0.243$, $A_0 = -0.783$, $C = 1.59$, and $h = 2.64$ for use in eq 11 and 12.

This finally leads us to adopt the following parameterized form for the fitting of the experimental data on the free base azaindolizines:

$$B(L_1)\Delta E = B^-(L_1)\Delta E + A_0 + \sum_\kappa A_\kappa\delta_{\kappa,N} \quad (9)$$

$$B(L_2)\Delta E = B^-(L_2)\Delta E - C(A_0 + \sum_\kappa A_\kappa\delta_{\kappa,N}) \quad (10)$$

where $C = 1/R_1R_2$. Here and in the following, $\delta_{\kappa,N} = 1$ if aza nitrogen is present in position κ and $\delta_{\kappa,N} = 0$ if it is not. The summations run over the seven ring positions, $\kappa = 1$–7. These equations contain the parameters, A_0, C, $B^-(L_1)$, and $B^-(L_2)$, and the six desired increments A_κ ($\kappa = 5$ does not occur among our data), defined within the PMO approximation by $A_\kappa = KR\Delta\alpha_N\Delta_\kappa$.

Heteroatom Increments from MCD of the Free Bases. Optimum values of the ten unknowns have been determined by the least-squares method by using the 26 $B\Delta E$ values available experimentally (linear optimization for A_κ, $B^-(L_1)$, and $B^-(L_2)$, nonlinear for C). The correlation coefficient was 0.979, and the standard deviation on $B\Delta E$ is 0.493. The optimized values of the adjustable parameters are $B^-(L_1) = 0.509$, $B^-(L_2) = -0.325$, $A_0 = -1.171$, and $C = 1.634$. The increments A_κ, which reflect the sensitivity of $B(L_1)$ to substitution by aza nitrogen in position κ, are listed in Table II. The availability of the increments A_κ now permits a prediction of the $B\Delta E$ values for any additional azaindolizine.

Protonated Azaindolizines—Final Working Equations. More important, we can make the assumption that first-order perturbation theory is still adequate for the description of azonia replacement, —CH═ → —NH^+═, and introduce one additional parameter $h = \Delta\alpha_{NH^+}/\Delta\alpha_N$ for the description of the strength of the —NH^+═ perturbation relative to the —N═ perturbation. Thus, we have our final working equations analogous to 9 and 10, but treating both the protonated and unprotonated species:

$$B(L_1)\Delta E = B^-(L_1)\Delta E + A_0 + \sum_\kappa A_\kappa(\delta_{\kappa,N} + h\delta_{\kappa,NH^+}) \quad (11)$$

$$B(L_2)\Delta E = B^-(L_2)\Delta E - C[A_0 + \sum_\kappa A_\kappa(\delta_{\kappa,N} + h\delta_{\kappa,NH^+})] \quad (12)$$

where $\delta_{\kappa,NH^+} = 1$ if azonia nitrogen is present in position κ and $\delta_{\kappa,NH^+} = 0$ otherwise. If a protonation position is assumed for any given azaindolizine, its $B(L_1)\Delta E$ and $B(L_2)\Delta E$ values can be determined if h is known. Since $h > 1$, it is possible to reject many protonation sites out of hand.

The $B\Delta E$ value predicted for protonation at each position of each azaindolizine was calculated for $h = 1.6$, 2.0, and 2.4 by using the C and A_κ determined from the free bases. For each compound, positions which consistently predicted incorrect signs for the larger $B\Delta E$ values or which were of the correct sign but were consistently much different in magnitude from the experimental $B\Delta E$ as compared to other available sites in that compound were

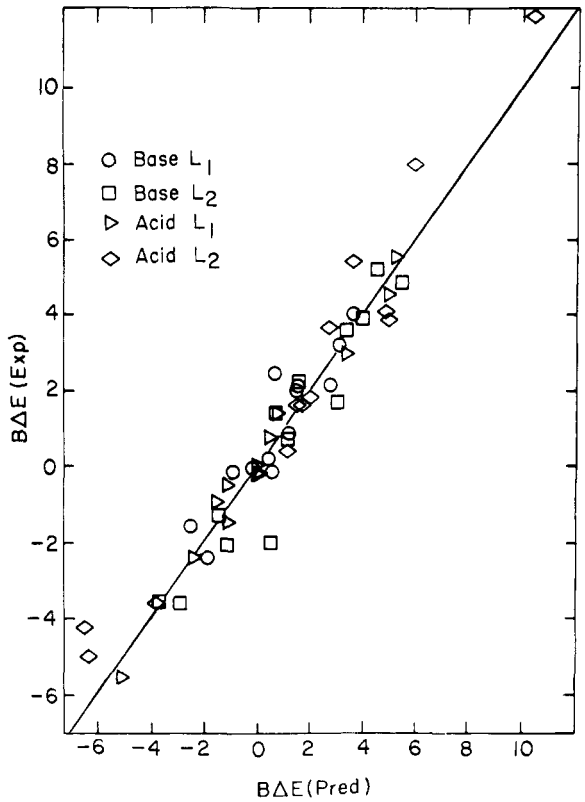

Figure 9. Experimental vs. predicted values of $B\Delta E$ for L_1 and L_2 transitions of azaindolizines (β_e D^2). Prediction is based on the increment and parameter set optimized on both free base and protonated azaindolizines (Table II). Correlation coefficient 0.965, slope 0.999, intercept 0.0058, and standard deviation 0.869.

rejected. This left a total of 128 plausible protonation patterns.

For each of these plausible patterns, eq 11 and 12 were solved by using the 52 experimental $B(L_1)\Delta E$ and $B(L_2)\Delta E$ values available for both protonated and free bases. The equations were solved by determining the values of C and h which maximized the correlation coefficient produced by the linear least-squares solution for $B^-(L_1)$, $B^-(L_2)$, and the A_κ's. The range of resulting values for C, h, and the correlation coefficient were 1.59–1.65, 1.47–2.64, and 0.920–0.965. The protonation patterns which produced the highest correlation coefficients are shown in Chart I, and a plot of the predicted against the experimental values of $B\Delta E$ for the pattern with the highest r, which we consider the most likely one, is shown in Figure 9.

The values for C, h, $B^-(L_1)$, $B^-(L_2)$, and the A_κ obtained for the protonation pattern with the highest r are listed in Table II. The values of the linear unknowns [A_κ, $B^-(L_1)$, $B^-(L_2)$] and of the nonlinear unknown C do not depend strongly on the choice of protonation pattern for the best few patterns, and more significantly, they do not differ greatly from the values determined from the free base data alone. They are all physically reasonable when compared with expectations based on the perimeter model and the increments A_κ follow qualitatively the Δ_κ values obtained from INDO/S and PPP MO's which are also shown in Table II. Also, the value $h = 2.64$ is physically reasonable and fits common notions[24a] concerning the relative magnitudes of $\Delta\alpha_N$ and $\Delta\alpha_{NH^+}$.

Effects of Random and Systematic Errors. To assure that the method used is capable of extracting protonation patterns from imperfect data which are derived from the model but contain random white noise or systematic errors, a protonation pattern and values of the parameters and linear unknowns were assumed and exact data constructed from them. Noise and systematic errors were then added to the exact data and those modified data were used as input to our method.

The correlation coefficient for the fit produced by an assumed protonation pattern correlates very well with the number of mismatches between the assumed pattern and the true one. For all noise levels tested (±0.5%, 1%, 2.5%, 5%, and 6%), the true pattern from which the data were constructed had the highest correlation of any pattern. The noise level which produces a correlation coefficient comparable to that given by the experimental data was about 5–6%.

Systematic multiplicative errors in the B term are absorbed into the A_κ and leave the values of the nonlinear unknowns essentially unchanged. The correlation between the number of mismatches between the true and an assumed protonation pattern and the correlation coefficient of the fit product is unaffected. Systematic additive errors in $W(L_2) - W(L_1)$ cause large errors in the $B^-(L_1)$ and $B^-(L_2)$ parameters but also leave the relation between the number of mismatches and the correlation coefficient unchanged.

The value of C is insensitive to choice of protonation pattern, but the value of h is very sensitive. A wrong protonation pattern leads to values of h smaller than the true value. In fact, the value of h decreases monotonically with the number of mismatches between the true and assumed protonation pattern.

The protonation pattern and parameter values derived from the azaindolizine data have the properties which these numerical experiments suggest should be exhibited by a correct pattern and solution: A noise level of 6% is reasonable for the data, the correlation coefficient is correlated with the number of mismatches between the highest correlation pattern and other patterns, and $B^-(L_1)$ and $B^-(L_2)$ have the signs and relative magnitude expected from the perimeter model. Also, the value of h was largest for the highest correlation pattern and was quite sensitive to choice of pattern.

This occurs because in the solutions for all plausible patterns, A_1 is smaller than the other A_κ, and in the best pattern position 1 is nearly always protonated if it is available. Thus, if the protonation site is incorrectly taken to be other than 1 for a compound, then decreasing h decreases the error for that compound.

Sites of Protonation in Azaindolizines. As shown in Chart I, positions 1, 4, and 6 seem to be generally preferred as protonation sites. Protonation of 2,3-N-1 at position 2 rather than 3 cannot be excluded since the predicted B terms for both choices are strong and positive, just as is observed experimentally. Similarly, protonation of 1,3,6-N-1 and 1,3,7-N-1 at 6 and 7, respectively, cannot be excluded. Protonation sites which are definitely inconsistent are 1,3,6-N-1 at 3, 1,2,4-N-1, 1,2,6-N-1, and 1,2,7-N-1 at 2, and 1,2,3,6-N-1 and 1,2,3,4-N-1 at 2 or 3.

As mentioned above, if the parameters derived from the bases alone are used to attempt to predict protonation site, there are seven compounds for which two sites are plausible, which leads to 128 different alternative overall assignments. These are 2,3-N-1 at 2 or 3, 1,6-N-1 at 1 or 6, 1,3,7-N-1 at 1 or 7, 1,3,6-N-1 at 1 or 6,1,4-N-1 at 1 or 4, 1,2,3,6-N-1 at 1 or 6, and 1,2,3,4-N-1 at 1 or 4. Inclusion of the data from the protonated species and reoptimization of the parameters removed two of these uncertainties (1,2,3,6-N-1 at 6 and 1,6-N-1 at 1) and weighs heavily in favor of 1,3,6-N-1 and 1,3,7-N-1 at 1.

Protonation Sites from Comparison with INDO/S Calculations. Calculations by the INDO/S method of

MCD B terms of all of the series of azaindolizines treated here and of each of them protonated in all possible positions yield inconclusive results and indicate that the method is not sufficiently accurate. This was already suggested by the only qualitative agreement between the trends in the increments A_κ and those in the Δ_κ values produced by INDO/S (Table II).

Rather than compare the actual signs and magnitudes of the B terms as calculated, which are sensitive to choice of parameters and other details of the calculation, we compare the sign of the change in the B term effected by protonation in various sites. This sign of change should be dictated by the form of the molecular orbitals and not particularly sensitive to the method of calculation.

If the experimentally determined change in MCD B term in going from the base to the protonated form is compared with the calculated change, we find them to be inconsistent for 3-N-1 and for 2,3-N-1. Experimental data necessary for this comparison are missing for 1,3-N-1, but the calculated change is the same regardless of protonation site, so even if the missing data were available, they would not allow a prediction. Similarly, experimental data are missing for 1,2,3,4-N-1, but the calculated changes for protonation at 1 and 4 are the same, as are those for protonation at 2 and 3. Thus, at best only two possibilities could be eliminated. The experimental effect for 1,4-N-1 is small and agrees with the calculated effect of protonation in either of the 1 or 4 position. The calculated changes for 1,2,3,6-N-1 are the same for all positions of protonation and agree with the experimental results. For 1,2,4-N-1, 1,2,6-N-1, and 1,2,7-N-1, the INDO/S results exclude protonation at position 2 but leave the other two alternative sites for each compound undecided. Similarly, position 3 in 1,3,7-N-1 is excluded but either of 1 and 7 is consistent with the calculated results. For 1,6-N-1 alone is a clear cut conclusion possible: protonation at the 1 position is the only choice consistent with the calculations. This result disagrees with the conclusion reached using the Hammett-like eq 11 and 12 and shown in Chart I (protonation in position 6). We tend to be somewhat skeptical of the INDO/S result.

Other Experimental Determinations of Protonation Sites. Comparison of the results in Chart I with independently available assignments of protonation sites is possible for 1,4-N-1 and 1,2,4-N-1. Analysis of ^{13}C NMR data[25] has led to the conclusion that the former molecule protonates in position 1 and the latter in positions 1 and 4, in agreement with our results.

Possible Occurrence of Multiple Protonation Sites. As noted above, it is possible that simultaneous competing protonation on two or more alternative sites occurs. If a sample contained a mixture of species corresponding to protonation at two different sites, we would expect to observe shoulders on the absorption and MCD peaks or even separate peaks for the two species present. We actually see little evidence of this in the spectra. However, such evidence would not be observable if either the concentration of one of the species were low or if the splitting were small with respect to the spectral bandwidths.

In the latter case, the observed value of $B\Delta E$ will be a weighted sum of contributions from the different protonated species present. The value of this sum may correspond in our model to no particular site of protonation, and the points for both the L_1 and L_2 bands of the compound will appear far off the correlation line in plots of $B\Delta E$(Pred) vs. $B\Delta E$(Exp) for all choices of parameters and protonation sites. This does not seem to occur to any significant degree, as the points for the protonated heterocycles show a similar scatter as those for the unprotonated ones in Figure 9. Of course, small percentages of protonation occurring on alternative sites may be responsible for some of the scatter and cannot be excluded.

On the other hand, the weighted sum may correspond to protonation at some site which is not actually protonated at all. For example, a sample in which sites p and q are protonated in the ratio f:$(1 - f)$ and site r is unprotonated would have an observed $B\Delta E$ for both the L_1 and L_2 transitions equal to those predicted for protonation at r if $f = (A_r - A_q)/(A_p - A_q)$, which is possible if the value of $B\Delta E$ for site r lies between that for sites p and q. Our model would then produce the best fit by erroneously assigning r as the protonation site for this compound. While this possibility cannot be definitely excluded in the case of the compounds 1,2,6-N-1, 1,2,7-N-1, 1,3,6-N-1, and 1,3,7-N-1, in which the assigned protonation at position 1 could be aliased by mixtures ranging from 1:1 to 3:1 of the other two sites, the spectra give no reason to suppose that such a mixture is present.

Conclusions

The good agreement between the observed B terms of the L band of free base and protonated azaindolizines and the expectations based on a very simple theoretical model suggests that the physical basis for the apparently random variation of the signs and magnitudes of their MCD peaks is now understood. It has been used to derive the pattern of protonation sites displayed in Chart I.

The results suggest that the very easily measured MCD spectrum can be of practical utility as a guide to the determination of protonation sites in other heterocycles as well. A possible complication due to concurrent protonation at more than one site should be kept in mind, and it would appear best to combine several methods to derive this type of information. The fact that no discrepancies have been observed so far in those cases where the protonation sites had been independently determined is encouraging.

Treatments similar to that given here should be possible not only for other heterocycles, but for the effects for other perturbations of a parent structure in general.

Experimental Section

The azaindolizines were synthesized and purified as described in the literature: 1-N-1,[26] 2-N-1,[27] 3-N-1,[28] 1,3-N-1,[29] 1,4-N-1,[30] 1,6-N-1,[31] 2,3-N-1,[28] 1,2,4-N-1,[32] 1,2,6-N-1,[33] 1,2,7-N-1,[34] 1,3,6-N-1,[35] 1,3,7-N-1,[35] 1,2,3,4-N-1,[32] 1,2,3,6-N-1.[36] The solvent was ethanol for the unprotonated species and 4 N $HClO_4$ in ethanol for the protonated species. In each case, it was checked that further increases in acid concentration led to no change in the spectra. UV absorption spectra were measured on a Cary 17 spectrophotometer, and MCD spectra were measured on a JASCO 500C spectropolarimeter equipped with a 15 kG electromagnet by using procedures described previously.[37]

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Registry No. 1-N-1, 274-76-0; 1-N-1·$HClO_4$, 91982-01-3; 2-N-1, 274-47-5; 2-N-1·$HClO_4$, 93966-14-4; 3-N-1, 274-56-6; 3-N-1·$HClO_4$, 93966-15-5; 1,3-N-1, 274-85-1; 1,3-N-1·$HClO_4$, 93966-16-6; 1,4-N-1, 766-55-2; 1,4-N-1·$HClO_4$, 1640-77-3; 1,6-N-1, 274-79-3; 1,6-N-1·$HClO_4$, 1640-75-1; 2,3-N-1, 274-59-9; 2,3-N-1·$HClO_4$, 93966-17-7; 1,2,4-N-1, 274-83-9; 1,2,4-N-1·$HClO_4$, 93966-18-8; 1,2,6-N-1, 274-82-8; 1,2,6-N-1·$HClO_4$, 93966-19-9; 1,2,7-N-1, 274-98-6; 1,2,7-N-1·$HClO_4$, 93966-20-2; 1,3,6-N-1, 399-66-6; 1,3,6-N-1·$HClO_4$, 93966-21-3; 1,3,7-N-1, 275-02-5; 1,3,7-N-1·$HClO_4$, 93966-22-4; 1,2,3,4-N-1, 274-89-5; 1,2,3,4-N-1·$HClO_4$, 93966-23-5; 1,2,3,6-N-1, 13349-87-6; 1,2,3,6-N-1·$HClO_4$, 93966-24-6.

A Theoretical Evaluation of Substituent Effects on the Ionization Potential of Bicyclo[1.1.0]butane

Steven C. Richtsmeier,[1a] Paul G. Gassman,*[1a] and David A. Dixon*[1b,c]

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

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Molecular orbital calculations in the PRDDO approximation have been made for substituted bicyclo[1.1.0]butanes. The substituents are CH_3, NH_2, OH, F, and CN with all possible isomers for one to six substituents. Ionization potentials from Koopmans' theorem are discussed. In most cases, ionization is predicted to occur from the bond between the bridgehead carbons. All ionization potentials are compared to that of the parent hydrocarbon. The CH_3 substituent lowers the ionization potential in all cases with the largest decrease due to substitution at the bridgehead (1) position. The NH_2 substituent, except where ionization occurs from the amino lone pairs, lowers the ionization potential, and the largest effect is for substitution at the bridgehead carbon. For the OH substituent, ionization usually occurs from the hydroxyl lone pairs. Substitution of OH at the bridgehead carbon leads to a decrease in the ionization potential, and ionization usually occurs from the bond between the bridgehead hydrocarbons. Substitution of F at the bridgehead carbons leads to a decrease in the ionization potential while substitution at the exo or endo positions leads to an increase in the ionization potential. Substitution of CN leads to an increase in the ionization potential with substitution at the bridgehead carbon causing the smallest increase. Relative energetics for all isomers with the same number of substituents are presented. The energetics and ionization potentials are discussed in terms of the thermodynamic and kinetic stability of the compounds. It is shown that kinetic and thermodynamic stability do not necessarily follow the same trends.

Introduction

The electronic structure of strained rings has been of interest for a number of years because of the unique reactivity imparted to these molecules by the presence of bent σ bonds.[2a] One of the most interesting species is bicyclo[1.1.0]butane which has two different types of bent bonds and is highly reactive. Due to the small size of this compound, it has been studied in detail using molecular orbital theory.[2b] For example, the charge deformation density[2] has been studied theoretically as has the inversion process in bicyclo[1.1.0]butane.[3] Previous theoretical studies have shown that the HOMO is localized in the C_1–C_3 region and is composed predominantly of 2p orbitals.[4] This can be considered to be the bond connecting the two bridgeheads. An extensive study of methyl substituent effects on the ionization potential of bicyclo[1.1.0]butane determined from Koopmans' theorem has been made in conjunction with an experimental study of the electrochemical oxidation of a number of these compounds.[4] A plot of ionization potential vs. half-wave oxidation potential showed a linear relationship with correlation coefficient of $R = 0.978$; the experiments thus confirmed the prediction of the calculations at the PRDDO level.

In order to better characterize the nature of the bonding in bicyclo[1.1.0]butane, in general, and the effect of substituents on the ionization potential, in particular, we have carried out an extensive study of substituent effects on the energetics and ionization potentials of this structure in the PRDDO approximation. The substituents studied were NH_2, OH, F, and CN in addition to the previously studied CH_3 group with all possible isomers for one to six substituents having been examined.

Calculations

All calculations were performed by using the PRDDO method.[5] PRDDO is an approximate molecular orbital method employing a minimum basis set of STO's that is computationally efficient yet gives results which compare very well with ab initio minimum basis set calculations.[6] Exponents for the heavy atoms were taken from standard compilations[7] while the exponent for the 1s orbital on H

(1) (a) Department of Chemistry, University of Minnesota. (b) Current address: E. I. du Pont de Nemours & Co., Central Research and Development Department, Experimental Station 328, Wilmington, DE 19898. (c) A.P. Sloan Fellow, 1977–1979; Camille and Henry Dreyfus Teacher-Scholar, 1978–1983; Du Pont Young Faculty Grantee, 1978.

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