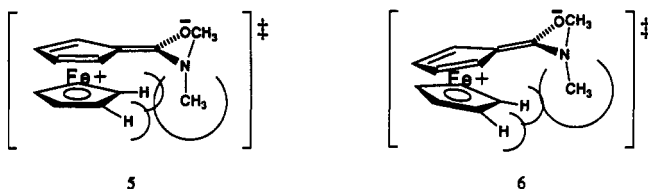


opposite Cp ring (transition state 5). Compounds 3 and 4 are thus complementary to ortho-substituted *N,N*-dimethylbenzamides in which steric strain is relieved upon proceeding to the transition state.²¹ The ferrocene nucleus may relieve steric congestion in the transition state by tilting the offending Cp ring relative to the central axis (transition state 6), which may in turn be accompanied by an interruption of Cp-Cp rotation. If this is so, ferrocenes 3 and 4 serve as examples of dynamic gearing²² in which C-N and Cp-Cp rotations and Cp-Cp angle could all be coupled in a highly ordered activation process. This process is reminiscent of Streitwieser's suggestion²³ that hindered rotation of opposing pair of *tert*-butyl groups in 1,1',3,3'-tetra-*tert*-butylferrocene as they pass each other may account for the observed ΔS^\ddagger of -5 eu for Cp rotation. Jackman et al.²⁴ have discussed the utility of activation entropy as a criterion for correlated rotations.



Experimental Section

General Methods. ¹H NMR spectra were obtained using Bruker AM-300 and AF-300 instruments; chemical shifts are reported relative to internal TMS. IR samples were prepared by spreading a chloroform solution on a NaCl plate and allowing the chloroform to evaporate. Melting points are uncorrected. Dichloromethane was distilled from CaH₂. EtOAc and hexanes for chromatography were both distilled. Flash chromatography²⁵ was performed with Kieselgel 60 SiO₂ (230-400 mesh) from E. Merck. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

***N,N,N,N*-Tetramethylferrocene-1,1'-dicarboxamide (3).** 1,1'-Bis(chlorocarbonyl)ferrocene (0.340 g, 1.09 mmol) was dissolved in 25 mL of dry CH₂Cl₂ containing 0.25 mL of triethylamine. Dimethylamine gas was bubbled through the solution for 15 min, followed by N₂. The reactions mixture was concentrated, and the residue was purified by flash chromatography to give 0.200 g (0.610 mmol, 56% yield) of an orange solid: mp 130 °C; *R*_f 0.12 (4:1 EtOAc/hexanes on SiO₂); ¹H NMR (300 MHz, 16 °C, CDCl₃) δ 4.67 (s, 4 H), 4.37 (s, 4 H), 3.14 (br s, 6 H), 3.03 (br s, 6 H) ppm; ¹³C NMR (75 MHz, 23 °C, CDCl₃) δ 170.0, 80.0, 72.5, 71.5, 39.0 (br), 36.3 (br) ppm; IR (thin film) ν 3088, 2925, 1610 (C=O), 1396, 1107 cm⁻¹; UV (CHCl₃) λ_{max} 243 nm (ϵ 12200); MS (EI) *m/z* 328 (100, M⁺), 284 (15), 257 (21), 241 (16), 192 (42), 121 (52) amu; HRMS *m/z* calcd for C₁₈H₂₀N₂O₂Fe, 328.0874, *m/z* observed 328.0874. Anal. Calcd for C₁₈H₂₀N₂O₂Fe: C, 58.54; H, 6.10; N, 8.54; Fe, 17.07. Found: C, 58.36; H, 6.01, N, 8.36; Fe, 16.66.

***N,N*-Dimethylferrocenecarboxamide (4).** (Chlorocarbonyl)ferrocene (0.270 g, 1.09 mmol) was dissolved in 25 mL of dry CH₂Cl₂ containing 0.25 mL of triethylamine. While cooling the reaction flask, dimethylamine was bubbled through the solution for 30 min. Flushing with N₂, concentration in vacuo, and purification by flash chromatography afforded 0.138 g (0.537 mmol, 49% yield) of an orange solid: mp 108-109 °C; ¹H NMR (300 MHz, 10 °C, CDCl₃) δ 4.62 (s, 2 H), 4.31 (s, 2 H), 4.22 (s, 5 H), 3.23 (br s, 3 H), 3.04 (br s, 3 H) ppm; ¹³C NMR (75 MHz, 23 °C, CDCl₃) δ 170.6, 78.29, 70.51, 69.65, 69.20, 38.53 (br), 36.42 (br) ppm; IR (thin film) ν 3081, 2943, 1613 (C=O), 1391, 1107, 1022

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cm⁻¹; UV (CHCl₃) λ_{max} 242 nm (ϵ 9400); MS (EI) *m/z* 257 (100, M⁺), 213 (43, M⁺ - N(CH₃)₂), 185 (37, M⁺ - CON(CH₃)₂), 121 (35, C₆H₅Fe⁺) amu; HRMS *m/z* calcd for C₁₃H₁₅NOFe, 257.0503, *m/z* observed 257.0504. Anal. Calcd for C₁₃H₁₅NOFe: C, 60.70; H, 5.84; N, 5.45; Fe, 21.79. Found: C, 59.87; H, 5.73; N, 5.20; Fe, 20.96.

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Supplementary Material Available: Data and plots of Arrhenius analysis (3 pages). Ordering information is given on any current masthead page.

A Relationship between Experimentally Determined p*K*_as and Molecular Surface Ionization Energies for Some Azines and Azoles

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Acidities of organic compounds have played a key role in the development and understanding of physical organic chemistry.¹⁻⁸ For example, the Hammett¹⁻³ and Taft^{2,4,5} equations have been based largely on aqueous acidities of substituted benzoic and acetic acids. A working knowledge of relative acidities and basicities is particularly important in organic synthesis; while a considerable amount of this involves nonaqueous media, acidities are nevertheless most often discussed in terms of p*K*_as.^{5,7,8} With the increasing number of organic molecules being designed and prepared, there exists a need to develop methodology for predicting their aqueous acidities.

In this work we present a relationship between the measured p*K*_as of a series of azines (1-4) and azoles (5-10) and the average local ionization energy, $\bar{I}(\mathbf{r})$, on the molecular surface. We will show that this relationship provides a basis for reliable estimates of p*K*_a values within these classes of compounds (Chart I).

$\bar{I}(\mathbf{r})$ has recently been introduced as a useful property for analyzing chemical reactivity;^{9,10} it is rigorously defined within the framework of self-consistent-field molecular orbital (SCF-MO) theory by eq 1.

$$\bar{I}(\mathbf{r}) = \sum_i \frac{\rho_i(\mathbf{r})|\epsilon_i|}{\rho(\mathbf{r})} \quad (1)$$

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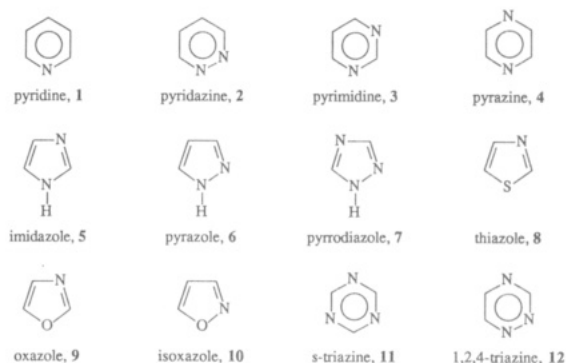
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Chart I



$\rho_i(\mathbf{r})$ is the electronic density of the i th molecular orbital at the point \mathbf{r} , ϵ_i is the orbital energy, and $\rho(\mathbf{r})$ is the total electronic density. $\bar{I}(\mathbf{r})$ can be interpreted as the average energy needed to ionize an electron at any particular point \mathbf{r} in the space of a molecule. We have shown that the surface $\bar{I}(\mathbf{r})$ of monosubstituted benzenes provide both site specific predictions and a quantitative measure of relative reactivities toward electrophilic attack, the latter being indicated by an excellent correlation with the Hammett constants.⁹

Azines and azoles are nitrogen-containing heterocycles widely encountered in nature as building blocks of biologically important molecules.¹¹ They are also prepared synthetically for many purposes, e.g., as components of pharmaceuticals.¹¹ The ring nitrogens in these molecules have differing degrees of basicity, discussed normally in terms of the acidities of the corresponding conjugate acids. In this work we investigate the average local ionization energies on the molecular surfaces of a series of azines and azoles. An excellent correlation is demonstrated between the pK_a s and the surface $\bar{I}(\mathbf{r})$ in the vicinities of the ring nitrogens of these molecules. This relationship provides a means of predicting pK_a s for molecules in these classes whose acidities are not known.

Methods and Procedure

We have used an ab initio SCF-MO approach (GAUSSIAN88¹²) to obtain optimized structures of 1–12 at the STO-3G level. This basis set has been shown to be generally effective for this purpose.^{13,14}

Wave functions for 1–12 were then computed at the 3-12G level, using the STO-3G optimized geometries, and used to compute $\bar{I}(\mathbf{r})$, as given by eq 1, on molecular surfaces defined by the contour of constant electronic density equal to 0.002 electron/bohr³.¹⁵ We have found that there is no significant change in the magnitudes of the surface $\bar{I}(\mathbf{r})$ values (less than 1% decrease) when the surface is defined by the 0.001 electron/bohr³ contour instead of the 0.002. (Preliminary calculations of $\bar{I}(\mathbf{r})$ were also carried out with 6-31G* wave functions. It was found, however, that the 3-21G basis set provided a slightly better corre-

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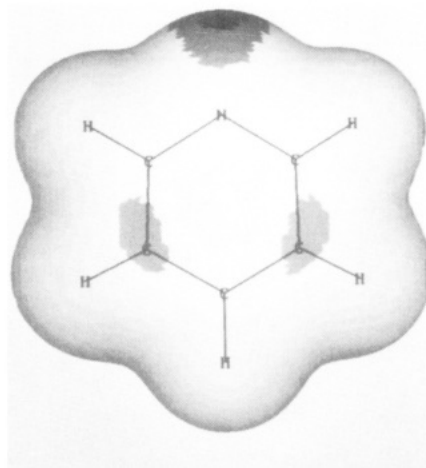


Figure 1. Calculated $\bar{I}(\mathbf{r})$ on the molecular surface of pyridine (1). There are three ranges of $\bar{I}(\mathbf{r})$ represented. Black is for $\bar{I}(\mathbf{r}) < 12.80$ eV; gray is for $12.80 < \bar{I}(\mathbf{r}) < 13.75$ eV; white is for $\bar{I}(\mathbf{r}) > 13.75$ eV.

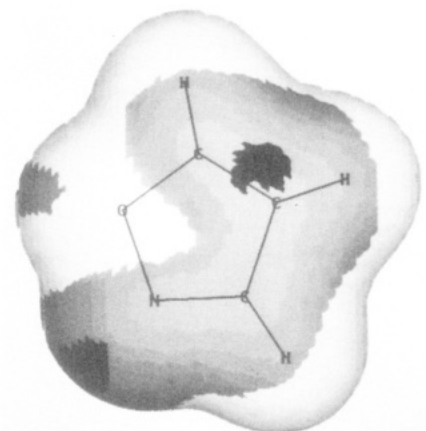


Figure 2. Calculated $\bar{I}(\mathbf{r})$ on the molecular surface of isoxazole (10). There are three ranges of $\bar{I}(\mathbf{r})$ represented. Black is for $\bar{I}(\mathbf{r}) < 13.80$ eV; gray is for $13.80 < \bar{I}(\mathbf{r}) < 17.10$ eV; white is for $\bar{I}(\mathbf{r}) > 17.10$ eV.

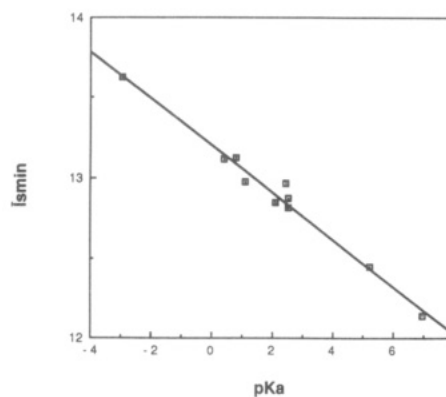














Figure 3. Correlation between experimentally determined pK_a s and ring nitrogens $\bar{I}_{s,\min}$ of ten azines and azoles (1–10). The least-squares equation of the line is $y = 13.2004 - 0.1468x$, with a correlation coefficient of 0.99.

lation with pK_a s and was therefore better suited for our purposes in this study.)

Results and Discussion

Figures 1 and 2 show $\bar{I}(\mathbf{r})$ plotted on the molecular surfaces of pyridine (1) and isoxazole (10), respectively. For pyridine, the lowest average local ionization energies are found above the ring nitrogen and the C₃ and C₅

Table I. Aqueous pK_a s and Calculated $I_{S,\min}$

molecule	pK_a^a	$I_{S,\min}^b$ (eV)
	5.2	N: 12.45 C ₃ : 13.62 C ₆ : 13.62
1		
	2.1	N: 12.85 C ₄ -C ₅ : 14.51
2		
	1.1	N: 12.97 C ₅ : 14.12
3		
	0.4	N: 13.11 C ₂ -C ₃ : 14.35 C ₅ -C ₆ : 14.35
4		
	6.95	N ₃ : 12.14 C ₄ -C ₅ : 12.32
5		
	2.52	N ₂ : 12.87 C ₄ -C ₅ : 12.68
6		
	2.45	N ₂ : 12.96 N ₄ : 13.52
7		
	2.53	N: 12.81 S: 13.05 C ₄ -C ₅ : 13.43
8		
	0.8	N: 13.12 C ₄ -C ₅ : 13.27 O: 17.24
9		
	-2.97	N: 13.63 C ₄ -C ₅ : 13.65 O: 16.89
10		
	(-2.31) ^c	N: 13.54
11		
	(-1.77) ^c	N ₂ : 13.46 N ₁ : 13.62 N ₄ : 13.81 C ₆ : 15.18 C ₃ : 15.51
12		

^aThe pK_a values were determined experimentally and are taken from ref 16. ^bThe locations of the $I_{S,\min}$ are indicated by designating the atom or bond above which they are found, e.g., N, C₃, C₄-C₅. When the $I_{S,\min}$ is closer to atom A in a bond than atom B, the atom closer to $I_{S,\min}$ is italic, e.g., C₄-C₅. ^cEstimated pK_a , using correlation presented in Figure 3.

positions, while, for isoxazole, they are observed above the ring nitrogen and above the C₄-C₅ bond, closer to C₄.

In Table I are listed experimentally determined pK_a values¹⁶ for 1-10 and the locations and magnitudes of the lowest surface $I(r)$ for molecules 1-12; these will be designated as $I_{S,\min}$. The locations of the $I_{S,\min}$ are the points at which, on the average, the least amount of energy is required to remove an electron from the surface of the molecule; thus these sites are expected to be the most reactive toward electrophiles.

Looking first at the $I_{S,\min}$ values of the ring nitrogens, it is seen in Figure 3 that these correlate very well with the pK_a s of 1-10. The linear correlation coefficient is 0.99. The basicities of the ring nitrogens of the azines and azoles increase (as indicated by the corresponding increase in pK_a) as $I_{S,\min}$ decreases. Thus, the magnitude of the ring nitrogen $I_{S,\min}$ provides an index of its relative basicity. It

is particularly noteworthy that there exists such a good correlation between a gaseous phase and a solution phase property.

The locations of the $I_{S,\min}$ associated with the ring carbons or carbon-carbon bonds are also indicative of favored sites for electrophilic attack. For example, the carbon $I_{S,\min}$ of pyridine (Figure 1) are above the β positions (C₃ and C₅), consistent with its known greater susceptibility to electrophilic attack at these carbons.^{11,16} The $I_{S,\min}$ above the C₄-C₅ double bond in isoxazole is closer to C₄ (Figure 2), in agreement with the observation that the carbon β to the nitrogen is the preferred site for electrophilic attack.¹⁶

The relationship between experimentally determined pK_a values and ring nitrogen $I_{S,\min}$ presented in Figure 3 allows us to estimate pK_a values that have not yet been determined for members of the azine and azole families. For example, we predict the pK_a s of *s*-triazine (11) and 1,2,4-triazine (12) to be -2.31 and -1.77, respectively. Thus, both triazines are expected to be much less basic than even the least basic diazine, pyrazine (4), which has a pK_a of 0.4.

Summary

We have computed average local ionization energies, $I(r)$, on the molecular surfaces of a series of azines and azoles. The locations of the lowest values of $I(r)$ on the surface ($I_{S,\min}$) indicate sites that are favored for electrophilic attack. The magnitudes of the ring nitrogen $I_{S,\min}$ correlate linearly with measured pK_a s; the correlation coefficient is 0.99. This relationship provides a predictive capability for determining the aqueous acidities of molecules within the azine and azole classes. Possible extensions of this approach to other types of compounds are being investigated.

Acknowledgment. We greatly appreciate the partial support of this work, by the Office of Naval Research, through contract #N00014-85-K-0217. T.B. thanks Professor Peter Stilbs for arranging the use of computer facilities at the Royal Institute of Technology (Stockholm).

An Efficient Synthesis of 2-Methyl-5,6,7,8-tetrahydro-4H-furo[2,3-d]azepines

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In the course of developing novel agents for the treatment of central nervous system disorders, we required an efficient synthesis of 2-methyl-5,6,7,8-tetrahydro-4H-furo[2,3-d]azepine. A survey of the literature revealed very few references to this fused ring system, and the only known synthesis¹ was impractical due to a very low overall yield.

We have developed an efficient synthesis of this fused azepine system. The key reaction is based on a Claisen

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