Photoelectron Spectroscopy of *N*-Aryl Cyclic Amines. Variable Conformations and Relationships to Gas- and Solution-Phase Basicities

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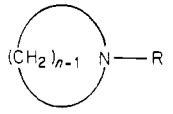
Abstract: The photoelectron spectra of a series of *N*-aryl cyclic amines indicate that the conformation of the aryl group with respect to the amine lone pair varies as the ring size of the amine varies and as ortho methyl substituents are placed on the aryl group. Values of ionization potentials and line shapes are both indicative of conformation. *N*-Phenyl-, *N*-(*o*-methylphenyl)-, *N*-(*o*,*p*-dimethylphenyl)-, and *N*-(*o*,*o*'-dimethylphenyl)aziridines all have the "coplanar" (conjugated) conformation in the gas phase. *N*-Phenyl- and *N*-(*o*-phenyl)azetidine are coplanar, while the *o*,*o*'-dimethyl derivative has the phenyl significantly rotated away from coplanarity. *N*-Phenylpyrrolidine is coplanar, while the *o*-methyl and *o*,*o*'-dimethyl derivatives are noncoplanar. *N*-Phenylpiperidine and the *o*-methyl derivatives are all noncoplanar. The gas-phase basicities of these compounds were predicted from IP's using Aue's correlations. Solution basicity differences from PA's are attributed to solvation effects.

Introduction

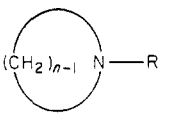
The influence of *N*-aryl substitution upon the solution basicities of cyclic amines has been studied in the laboratories of one of our groups.[4] The basicities of aziridine and *N*-methylaziridine (**3-H** and **3-Me**) are ~3 pK_a units lower than those of the four-, five-, and six-membered analogues (azetidine, pyrrolidine, and piperidine).[2] This is attributed to the relatively high s character of the aziridine lone pair. The *N*-phenyl derivatives, however, are curiously anomalous.[3] *N*-Phenylpiperidine (**6-Ph**) is ~2 pK_a units less basic than **5-Ph** and **4-Ph**. Similarly nonregular behavior is observed for *o*-methylphenyl and dimethylphenyl derivatives, as summarized in Table I. This behavior may result from a complex interplay of hybridization, conformation, aryl π, N lone-pair conjugation, and solvation differences for the different ring sizes and substitution patterns. In order to isolate some of these factors, we have carried out photoelectron (PE) spectroscopic investigations of the series of arylazacycloalkanes shown below, where **R** is phenyl or substituted phenyl.



n	
3	3-R
4	4-R
5	5-R
6	6-R

PE spectroscopy is a sensitive probe for lone-pair, aryl π-conjugation, and thus of conformation.[5] Lone-pair ionization potentials are known to correlate with gas-phase proton affinities (PA).[6] Furthermore, Aue has reported a determination of lone-pair hybridization from determination of PE band shapes.[6a,7] Thus, in principle, PE spectroscopy can isolate all of the important inherent conformational and electronic factors related to gas-phase basicities, and, by comparison of these effects to solution data, it should be possible to determine the role of solvation on pK_a's, as well.

Table I. Experimental Measures of Proton-Accepting Properties of Azacycloalkanes[a]



n	R	pK_a (±0.02)	PA (kcal/mol)[d]
3	H	8.04	215.7
4	H	11.29	222.7
5	H	11.27	224.3
6	H	11.22	225.4
3	Me	7.86	221.5
4	Me	10.40	
5	Me	10.46	227.8
6	Me	10.08	228.8
3	Ph	1-2	
4	Ph	3.62	
5	Ph	3.57	
6	Ph	5.22	
3	*o*-MePh		
4	*o*-MePh	3.97	
5	*o*-MePh	5.01	
6	*o* MePh	4.68	
3	*o*,*p*-Me_2Ph	2	
4	*o*,*p*-Me_2Ph	4.31	
5	*o*,*p*-Me_2Ph	5.28	
6	*o*,*p*-Me_2Ph	5.02	
3	*o*,*o*'-Me_2Ph	3.48	
4	*o*,*o*'-Me_2Ph	4.64	
5	*o*,*o*'-Me_2Ph	4.81	
6	*o*,*o*'-Me_2Ph	3.44	
	dimethylamine	10.64[b]	220.5
	trimethylamine	9.76[b]	224.3
	N,*N*-dimethylaniline	4.26 (5.16)[c]	223.8
	N,*N*,*o*-trimethylaniline	5.07	
	N,*N*,*o*,*p*-tetramethylaniline	5.28	
	N,*N*,*o*,*o*'-tetramethylaniline	4.70	
	ammonia	9.21[b]	205.0
	aniline	4.6[b]	211.5
	methylamine	10.62[b]	214.1

[a] Reference 4, unless otherwise noted. [b] Arnett, E. M. *Prog. Phys. Org. Chem.* 1963, *1*, 223. [c] Reference 9b. [d] Reference 8.

Azacycloalkane Basicities. Table I shows the aqueous basicities (pK_a) and gas-phase PA's all both much smaller for **3-H** and **3-Me**

(1) (a) Louisiana State University. (b) Address correspondence to this author at the University of Pittsburgh. (c) University of Missouri.
(2) Searles, S.; Tamres, M.; Black, F.; Quarterman, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 4917.
(3) Bottini, A. T.; Nash, C. P. *J. Am. Chem. Soc.* **1962**, *84*, 734.
(4) Seyedrezai, S. E. Ph.D. Dissertation, University of Missouri, Columbia, Mo. 65211; *Dissertation Abstracts* **1981**, *41*, 4129-B and manuscript in preparation.
(5) Klessinger, M.; Rademacher, P. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 826, and references therein.
(6) (a) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1975**, *97*, 4137. (b) *Ibid.* **1979**, *98*, 311, 318.
(7) Aue, D. A.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1975**, *97*, 4136.

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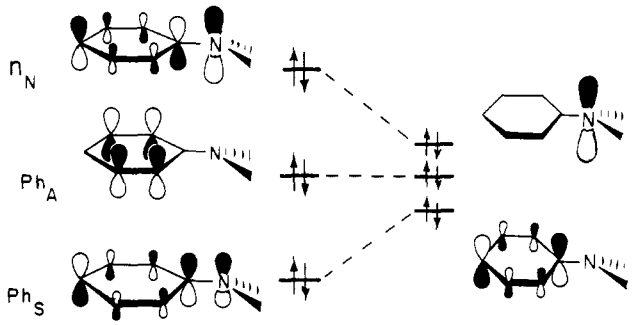


Figure 1. The three highest occupied MO's of *N*-arylanilines in "planar" and "perpendicular" conformations.

than for the larger ring-size amines. Similar behavior is found for the shifts in the frequency of the MeOD stretch in the IR spectrum upon addition of these amines.[4] This has been attributed to the better donor ability of the sp^3-type lone pairs in the larger rings, as compared to the sp^2-type lone pair in aziridine.[4] The pK_a's of the four-, five-, and six-membered compounds are nearly constant, while the PA's increase along this series, indicating better stabilization of ammonium cations by larger alkyl groups.[6] The leveling of basicities for these compounds in solution must arise from differences in solvation, the larger ammonium cation being solvated more poorly.[6-8]

The *N*-aryl compounds show a smaller difference in pK_a's between the three- and four-membered ring compounds, and an increase in pK_a's between the five- and six-membered compounds for the *N*-phenyl series, but a decrease at this point for the methylphenyl compounds.

Previous Photoelectron Spectra of Arylamines. The PE spectra of dimethylaniline and various ring-substituted anilines have been analyzed in detail by Maier and Turner.[9] For *N,N*-dimethylaniline, three ionization potentials are observed in the 7–11-eV region of the spectrum. All three arise from π orbitals which are formally derived from the nitrogen lone-pair orbital and the degenerate HOMO's of benzene.[10] These are shown in Figure 1.

The mixing which occurs when the amine lone pair and aromatic π orbitals are coplanar precludes the designation of any orbital of aniline as a pure "nitrogen lone pair". For simplicity, however, we will refer to the HOMO as a "nitrogen lone pair" (n_N) orbital. The other two orbitals are described as Ph_A and Ph_S, respectively. These are the π orbitals primarily localized on the phenyl group and are antisymmetric and symmetric, respectively, with respect to a plane of symmetry perpendicular to the benzene ring.[10] Methyl substituent(s) on the phenyl ring or rotation about the phenyl–N bond destroy the planar symmetry and allow additional orbitals to mix with each other, making these orbital descriptions more qualitative, but still useful. As the N lone pair is rotated toward a perpendicular orientation, relative to the π orbital, the contribution of Ph_S to n_N, and vice versa, will be less than when the orbitals are coplanar.[11]

Whereas the spectrum of *N,N*-dimethylaniline gives three bands at 7.45, 9.60, and 9.85 eV,[9] indicative of coplanarity, the spectrum of *N,N,o*-trimethylaniline reveals some deviation from coplanarity. Although three low-energy IP's are observed, the first band is noticably broadened, the second band has a slightly increased relative intensity, and the separation between the second and third bands is decreased. The spectrum of *N,N,o,o'*-tetramethylaniline reveals only two low-energy bands with a further intensity increase for the second band.

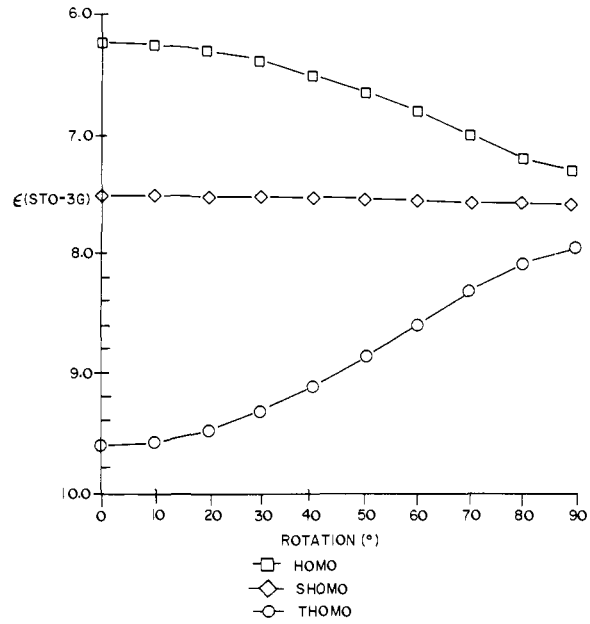


Figure 2. STO-3G orbital energies of *N,N*-dimethylaniline as a function of rotational angle.

Maier and Turner[9] estimated the degree of rotation in *N,N*-dimethylanilines from the splitting between the first and third IP's. Coplanarity was assumed for *N,N*-dimethylaniline; the difference in IP's between the "lone-pair" orbital and Ph_S orbital (2.40 eV) defined the maximum splitting possible for a planar, fully conjugated species. The IP of trimethylamine (8.54 eV) and the second IP of toluene (9.0 eV) were used to define the minimum splittings expected for nonconjugated amine and aromatic orbitals. The use of these parameters led to the estimation of a 50–55° dihedral angle between the lone pair and the phenyl π orbital for *N,N,o*-trimethylaniline and a 68–69° dihedral angle for *N,N,o,p'*-tetramethylaniline,[12] in reasonable agreement with other estimates.[9]

We have applied similar techniques to the series of *N*-arylazacycloalkanes and have approximated the degree of noncoplanarity induced by the various rings and methyl substituents.

Experimental Section

Photoelectron spectra were recorded on a Perkin-Elmer PS-18 photoelectron spectrometer using an He I source with argon and xenon as internal calibrants. Resolution was 20–30 meV at 15.76 eV in all cases. Band maxima are taken as vertical IP's, and the reported values are the average of at least five determinations. All samples were prepared as described earlier.[4]

Calculations on the Influence of Noncoplanarity on IP's. As an aid to interpretation of the PE spectra, ab initio STO-3G[13] calculations were performed on *N,N*-dimethylaniline. A standard geometry was assumed, and the dihedral angle between the nitrogen lone pair and the phenyl π orbitals was varied from 0° (planar) to 90° (perpendicular) in 10° increments. The results are shown in Figure 2. The calculations indicate the orbital order to be Ph_S, Ph_A, n_N.[14] That is, the HOMO is mainly Ph_S, admixed with a small amount of n_N, while the third HOMO is mainly n_N. We believe that the relative contribution of Ph_S and n_N to these two orbitals is incorrectly predicted, but the trends observed for the energies of the three highest occupied orbitals upon rotation remain relevant. The HOMO energy is highest for the planar conformation and decreases in energy for the perpendicular conformation. The second

(8) Aus, D. H.; Bowers, M. T. In "Gas Phase Ion Chemistry"; Academic Press: New York, 1979; Vol. II, Chapter 9.

(9) Maier, J. P.; Turner, D. W. *J. Chem. Soc., Faraday Trans. 2* **1973**, *69*, 521, and references therein.

(10) Benzene orbitals: (a) Rabalais, J. W. "Principles of Ultraviolet Photoelectron Spectroscopy"; Wiley-Interscience: New York, 1977. (b) Turner, D. W.; Baker, C.; Baker, A. D.; Brundle, C. R. "Molecular Photoelectron Spectroscopy"; Wiley: London, 1970.

(11) Ph_A has a node at the site of substitution and does not mix with the lone pair. As the phenyl rotates, lower lying σ orbitals can mix weakly with Ph_A to lower the IP slightly.

(12) The Ph_S IP was indicated by a shoulder on the high-energy side of the second band. The reported value (8.85 eV) may be too high. This error would give rise to a larger dihedral angle since ΔIP is then decreased.

(13) The program GAUSSIAN 70 (Hehre, W. J.; Lathan, W. A.; Ditchfield, R.; Newton, M. D.; Pople, J. A. *QCPE* **1973**, 236) was used for these calculations. Standard bond lengths and angles were used. The methyl groups were oriented in staggered conformations.

(14) The calculated order agrees with that of Cowling, S. A.; Johnstone, R. A. W. *J. Electron Spectrosc. Relat. Phenom.* **1973**, *2*, 161, but we believe this order to be incorrect based on our results, ref 9, and Schafer, W.; Schweig, A. *Angew. Chem., Int. Ed., Engl.* **1972**, *11*, 836, and references therein.

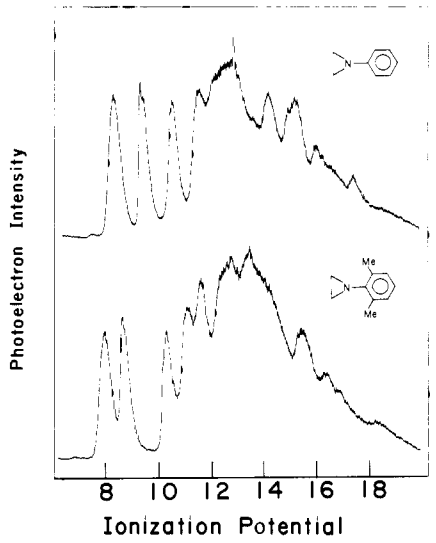


Figure 3. PE spectra of *N*-phenylaziridine (**3-Ph**) and *N*-(2,6-dimethylphenyl)aziridine (**3-*o*,*o*'-Me$_2$Ph**).

highest occupied MO (SHOMO) energy changes only slightly as the dihedral angle increases, since the nitrogen is attached to a nodal site in Ph_A. The third highest occupied MO (THOMO) energy increases in the perpendicular conformation relative to the coplanar conformation. Even though we believe the Ph_S and n_N orbital order to be reversed, the same trends should result. Ph_S and n_S mixing is maximized in the coplanar conformation and disappears in the perpendicular conformation.

Results

Photoelectron Spectra. *N*-Phenylaziridines. The spectra of *N*-phenylaziridine (**3-Ph**) and *N*-(2,6-dimethylphenyl)aziridine (**3-*o*,*o*'-Me$_2$Ph**) are shown in Figure 3, and the IP's are tabulated in Table II, along with those of other compounds studied here and those of appropriate models.[15-17] The spectrum of **3-*o*,*p*-Me$_2$Ph** is not shown, but is very similar to those shown in Figure 3. Three well-separated bands are observed in the 7–11-eV region and are assigned to the n_N, Ph_A, and Ph_S orbitals, respectively. The n_N band shape is narrower in the arizidines than in the larger ring-size amines, as described later, and is indicative of relatively minor geometry changes upon ionization. However, the first IP is broadest and similar in shape to those of other amine lone-pair IP's.[6]

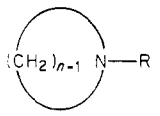
The IP changes observed for all the low-energy π orbitals as the methyl groups are added to the phenyl ring are readily explained by the coefficient sizes in the benzene orbitals. The para coefficients are largest in n_N and Ph_S, while the ortho coefficients are greatest in Ph_A for the planar species. For the perpendicular species, the aromatic coefficients are zero in n_N.

The n_N IP decreases 0.39 eV upon conversion of **3-Ph** (8.19 eV) to **3-*o*,*p*-Me$_2$Ph** (7.80 eV). The ortho methyl group is at a site of small coefficient, while the methyl at the para position is at a large coefficient site. The n_N IP in **3-*o*,*o*'-Me$_2$Ph** (7.88 eV) is decreased 0.31 eV compared to **3-Ph**, an increase of 0.08 eV relative to **3-*o*,*p*-Me$_2$Ph**. Both methyl groups are at sites of small coefficients in **3-*o*,*o*'-Me$_2$Ph**.

The Ph_A orbital experiences a 0.46-eV decrease in IP upon conversion of **3-Ph** (9.16 eV) to **3-*o*,*p*-Me$_2$Ph** (8.70 eV), and experiences an additional 0.13 eV decrease in **3-*o*,*o*'-Me$_2$Ph** (8.57 eV). In **3-*o*,*o*'-Me$_2$Ph**, both methyls are at "large" coefficient sites, whereas the *p*-methyl in **3-*o*,*p*-Me$_2$Ph** is located at a node.

The shifts in the Ph_S orbital are in the same direction and slightly magnified compared to the shifts in n_N, providing support to the assignment of the HOMO to n_N and the THOMO to Ph_S.

Table II. Ionization Potentials (eV, ±0.06 eV) of Azacycloalkanes



n	R	IP$_1$	IP$_2$	IP$_3$	higher IP's
3	H	9.80[a] (9.85)[b]			11.90[b]
4	H	9.04[a]			11.50[b]
5	H	8.77[b]			11.49[b]
6	H	8.66[a] (8.64)[b]			10.75[b]
3	Me	9.26[a]			
4	Me				
5	Me	8.41[a,b]			11.19[b]
6	Me	8.29[a,b]			10.59[b]
3	Ph	8.19	9.16	10.37	11.35, 11.83
4	Ph	7.61	9.08	9.95	11.22, 11.63
5	Ph	7.23	8.89	9.76	
6	Ph	7.72	9.09	9.72	
3	*o*-MePh				
4	*o*-MePh	7.67	8.78	9.80	11.45
5	*o*-MePh	7.73	8.80	9.52	11.52
6	*o*-MePh	7.84	8.81	9.28	11.58
3	*o*,*p*-Me$_2$Ph	7.80	8.70	9.93	10.98, 11.46
4	*o*,*p*-Me$_2$Ph	7.48	8.66	9.56	11.34
5	*o*,*p*-Me$_2$Ph	7.60	8.66	9.21	11.29
6	*o*,*p*-Me$_2$Ph	7.70	8.72	9.02	
3	*o*,*o*'-Me$_2$Ph	7.88	8.57	10.17	10.95, 11.44
4	*o*,*o*'-Me$_2$Ph	7.76	8.56	9.75	11.26
5	*o*,*o*'-Me$_2$Ph	7.67	8.51[c]	8.51	
6	*o*,*o*'-Me$_2$Ph	7.78	8.64[c]	8.64	
4	*o*,*o*'-Et$_2$Ph	7.82	8.52	9.67	11.21
5	*o*,*o*'-Et$_2$Ph	7.60	8.52[c]	8.52	
	N,*N*-dimethylaniline	7.37[d]	8.96	9.80	
		7.48[e]	9.06	9.80	
		7.45[f]	9.60	9.85	
	N,*N*,2,4-tetramethylaniline	7.79	8.74	9.10	11.16
	N,*N*,2,6-tetramethylaniline	7.83	8.61	8.93	11.21
		7.85[f]	8.60	8.85	11.20
	N-ethylaniline	7.67	9.10	10.20	
	2,6-diethylaniline	7.77	8.58	10.56	11.17
	N,*N*,*o*,*o*'-tetraethylaniline	7.77	8.51[c]	8.51	

[a] Reference 6. [b] Reference 15. [c] Only one band is observed, resulting from both Ph_A and Ph_S. [d] Reference 16. [e] Reference 17. [f] Reference 9.

A 0.44-eV decrease in the Ph_S IP is observed upon conversion of **3-Ph** (10.37 eV) to **3-*o*,*p*-Me$_2$Ph** (9.93 eV), while a decrease of only 0.20 eV, relative to **3-Ph**, is observed for **3-*o*,*o*'-Me$_2$Ph** (10.17 eV), since both methyls are at small coefficient sites.

The trends in these aziridine n_N and Ph_S orbital IP's do not follow the trends observed for the substituted *N*,*N*-dimethylanilines, acyclic analogues of the aziridines, also listed in Table II. The ortho methyls cause a rotation about the phenyl–nitrogen bond in the anilines. The smaller aziridine C–N–C bond angle decreases the steric requirement, so that rotation does not occur. The band shapes remain sharp and the Ph_A and Ph_S bands are well separated, a result in contrast to the ortho methylanilines previously reported.[9]

***N*-Phenylazetidines.** The spectra of *N*-phenylazetidine (**4-Ph**) *N*-(2-methylphenyl)azetidine (**4-*o*-MePh**), and *N*,*N*-(2,6-dimethylphenyl)azetidine (**4-*o*,*o*'-Me$_2$Ph**) are shown in Figure 4, and the IP's are tabulated in Table II, along with those of **4-*o*,*p*-Me$_2$Ph**, and **4-*o*,*o*'-Et$_2$Ph**.

Three bands are still observed in all cases, and the assignments are the same as for the aziridines: n_N, Ph_A, and Ph_S. The relative intensities and band widths are noticeably altered in two cases, **4-*o*,*o*'-Me$_2$Ph** and **4-*o*,*o*'-Et$_2$Ph**. The increased intensity and band width of the middle band, the increased width of the first band, and the reduced intensity of the third band, due to Ph_S, all indicate that several conformations are populated in these species. A coplanar conformation gives rise to three bands, as in **4-Ph** and the aziridines, while the rotated noncoplanar conformations of

(15) Yoshikawa, K.; Hashimoto, M.; Morishima, I. *J. Am. Chem. Soc.* **1974**, *96*, 228.
(16) Kobayashi, T.; Nagakura, S. *Bull. Chem. Soc., Jpn.* **1974**, *47*, 2563.
(17) Egdell, R.; Green, J. C.; Rao, C. N. R. *Chem. Phys. Lett.* **1975**, *33*, 600.

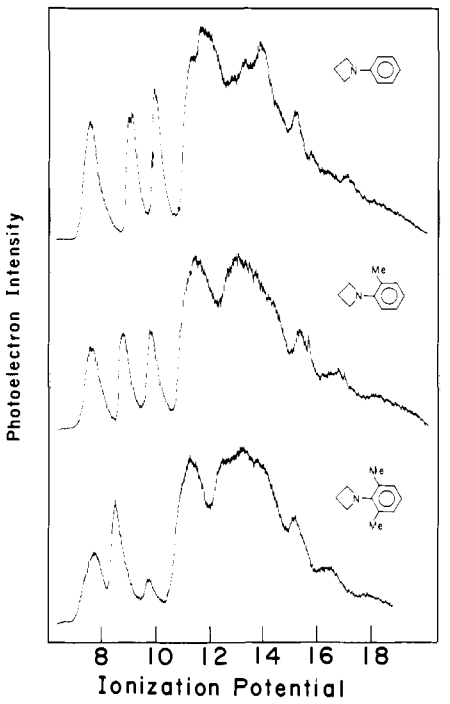


Figure 4. PE spectra of *N*-phenylazetidine (**4-Ph**), *N*-(2-methylphenyl)azetidine (**4-*o*-MePh**), and *N*-(2,6-dimethylphenyl)azetidine (**4-*o*,*o*′-Me_2Ph**).

4-*o*,*o*′-Me_2Ph and **4-*o*,*o*′-Et_2Ph** display overlapping Ph_A and Ph_S bands.

The n_N IP's of conformations with different rotational angles vary due to differing contributions from the Ph_S orbital. Slight changes in the nitrogen lone-pair hybridizations are also possible, especially upon rotation. Both of these effects could contribute to the broad n_N band.

Introduction of an *o*-methyl group in **4-Ph** raises the n_N IP by 0.06 eV (**4-Ph**, 7.61 eV; ***o*-MePh**, 7.67 eV), an effect opposite to that anticipated based on the aziridine results. This apparent anomaly is the result of a small lowering of the IP by the methyl on the phenyl ring, counteracted by rotation to minimize the steric interaction between the azetidine ring and *o*-methyl hydrogens. Addition of a second methyl to give **4-*o*,*p*-Me_2Ph** (IP = 7.48 eV), does not affect the slight rotation, but does increase electron donation to the phenyl orbitals on the n_N IP, thus lowering the IP by 0.13 eV.

When two ortho methyls are introduced, to form **4-*o*,*o*′-Me_2Ph**, the n_N orbital has a higher IP than that for **4-Ph** or **4-*o*-MePh**. This must arise from an even greater degree of rotation about the phenyl–nitrogen bond, since *o*-methyls would otherwise decrease the n_N IP. The n_N IP of **4-*o*,*o*-Et_2Ph** is 0.06 eV lower than that of **4-*o*,*o*′-Me_2Ph**, due to the greater electron donation by ethyl than by methyl. Both compounds are significantly noncoplanar.

The trends in Ph_S IP's are the same as for the aziridines, and the magnitudes of substituent effects very similar. An ortho methyl group causes a 0.15-eV IP decrease; addition of a para methyl to form **4-*o*,*p*-Me_2Ph** decreases the IP an additional 0.24 eV; moving the para methyl to the ortho position raises the IP by 0.19 eV. Here, rotation of the aryl group is expected to decrease the IP of the Ph_S orbital, but no large effect is seen.

***N*-Phenylpyrrolidines.** The spectra of *N*-phenylpyrrolidine (**5-Ph**), *N*-(2-methylphenyl)pyrrolidine (**5-*o*-MePh**), and *N*-(2,6-dimethylphenyl)pyrrolidine (**5-*o*,*o*′-Me_2Ph**), are shown in Figure 5. The spectrum of **5-Ph** is very similar to those of the arizidines and **4-Ph** discussed previously, indicative of coplanarity. The spectrum of **5-*o*-MePh** is similar to that of **4-*o*,*o*′-Me_2Ph**, indicating noncoplanarity and multiple conformations of similar energy. In **5-*o*,*o*′-Me_2Ph**, only two bands are resolved, indicative of further rotation about the phenyl–nitrogen bond. The n_N IP has increased 0.07 eV while Ph_A and Ph_S have merged. The expected increase in the Ph_S IP as the methyl group is moved to the ortho′ position is strongly counteracted by the loss of conjugation with the nitrogen lone pair.

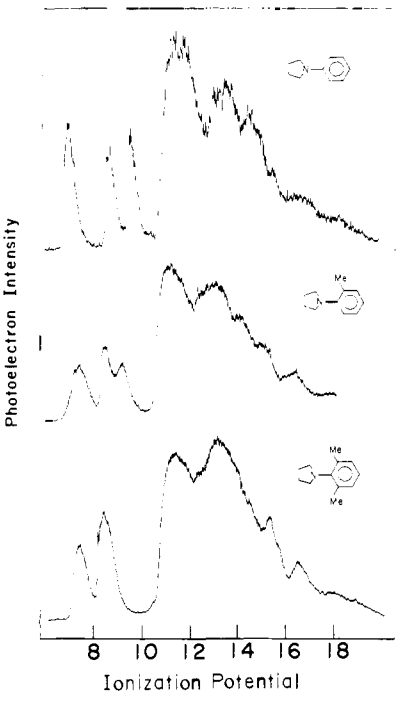


Figure 5. PE spectra of *N*-phenylpyrrolidine (**5-Ph**), *N*-(2-methylphenyl)pyrrolidine (**5-*o*-MePh**), and *N*-(2,6-dimethylphenyl)pyrrolidine (**5-*o*,*o*′-Me_2Ph**).

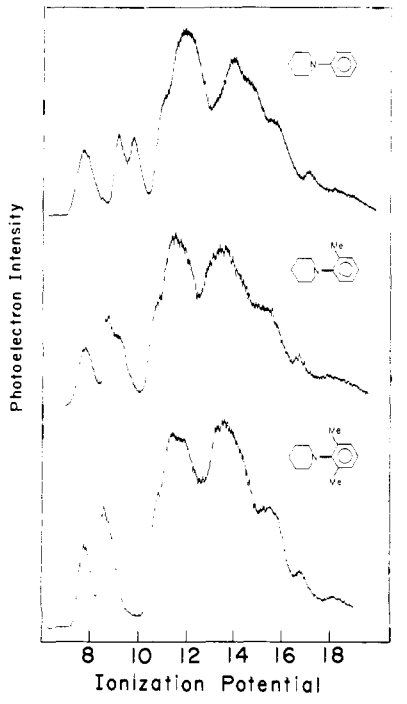


Figure 6. PE spectra of *N*-phenylpiperidine (**6-Ph**), *N*-(2-methylphenyl)piperidine (**6-*o*-MePh**), and *N*-(2,6-dimethylphenyl)piperidine (**6-*o*,*o*′-Me_2Ph**).

***N*-Phenylpiperidines.** The spectra of *N*-phenylpiperidine (**6-Ph**), *N*-(2-methylphenyl)piperidine (**6-*o*-MePh**), and *N*-(2,6-dimethylphenyl)piperidine (**6-*o*,*o*′-Me_2Ph**) are shown in Figure 6. The spectrum of **6-Ph** has three low-energy IP's with the same assignment order as before. The n_N band is broadened relative to the n_N band of the planar amines shown previously. The Ph_A and Ph_S are overlapping slightly and are also definitely less sharp than previously. Thus, even **6-Ph** appears to be noncoplanar.

A comparison of the n_N IP's of all these N-substituted piperidines shows that the n_N IP is relatively insensitive to the presence of methyl substituents on the phenyl ring. Using the data pre-

Table III. Conformations of *N*-Arylazacycloalkanes[a]

substituent	ring size 3	4	5	6
Ph	coplanar (0°)	coplanar (0°)	coplanar (0°)	noncoplanar (48°)
o-MePh	coplanar (0°)	coplanar (28°)	noncoplanar (52°)	noncoplanar (68°)
o,p-Me_2Ph	coplanar (0°)	coplanar (30°)	noncoplanar (58°)	noncoplanar (72°)
o,o'-Me_2Ph	coplanar (0°)	noncoplanar (34°)	noncoplanar (83°)	noncoplanar (86°)

[a] "Coplanar" or "noncoplanar" were determined from band shapes and substituent effects, as discussed in the text. Degrees given in parentheses were determined from the $IP(n_N) - IP(Ph_S)$, as discussed in the text.

viously presented, this fact appears consistent only with a rotation from coplanarity, even in **6-Ph**. A methyl substituent ortho to the amine causes further N–Ar rotation, reducing the interaction between n_N and Ph_S, and the n_N IP increases 0.12 eV. The second *o'*-methyl substituent forces the amine to rotate still further, and the IP again increases as a result of the decreased interaction. The continual decrease in both the Ph_A and Ph_S IP's upon methylation also indicate a decreasing interaction with the lone pair.

Discussion

Conformations of *N*-Arylazacycloalkanes. The band shapes and ionization potentials observed in the photoelectron spectra lead to the qualitative conclusions about conformations summarized in Table III, by the indications "coplanar" and "noncoplanar". In order to provide a more quantitative estimate of the degree of noncoplanarity, we have used a technique similar to that of Maier and Turner.[9] The maximum splits between n_N and Ph_S were taken as 2.34, 2.53, and 2.64 eV for **4-Ph**, **5-Ph**, and **6-Ph**, respectively; the last value is estimated. The minimum splits, expected for the perpendicular conformations, were taken as the differences between the IP's of the *N*-Me cyclic amines (where $n = 4$, 5, or 6) and the IP of toluene, 9.0 eV. Assuming a cos θ relationship between ΔIP and the angle, θ, between the lone pair and the aromatic orbitals, the values given in parentheses in Table III were found. Although these are very approximate, they do give a qualitative idea of the preferred angle of rotation for the noncoplanar species. The only difference between these values and those deduced on the basis of line shape are for **4-*o*-MePh** and **4-*o,p*-Me_2Ph**.

The origin of the conformation changes upon ring-size changes of ortho-methylation can be qualitatively understood from the ORTEP drawings of standard models for these compounds prepared on the PROPHET computer system.[18] Figure 7 shows the planar and perpendicular *N*-phenyl compounds. Since the α-methylenes of the three- and four-membered rings are tied back from the amine by the short carbon chain, there is no steric interaction between the hydrogens on C-2 of the azacycloalkane and the ortho hydrogens of the phenyl group. However, these hydrogens are quite close in the five- and 6-membered analogues, and rotation of the phenyl relieves H–H repulsion.

In the dimethyl compounds (Figure 8), only the three-membered compound avoids severe *o*-methyl hydrogen, C-2 hydrogen repulsion. This compound is coplanar, while in the larger ring sizes, even one methyl is sufficient to induce noncoplanarity.

Estimates of PA's of *N*-Arylazacycloalkanes and Comparison to Solution pK_a's. Finally, we can use the n_N IP's determined here to estimate the gas-phase PA's of these compounds. For the parent cyclic amines and *N*-methyl derivatives included in Tables I and II, there is a reasonable ($r = 0.996$) linear correlation between PA and IP: PA (kcal/mol) = 296.1 − 8.13IP (eV). However, the predicted PA for dimethylaniline (255.5 kcal/mol) is 11.7 kcal/mol too high. In classical terms, this anomalously low PA is due to the resonance stabilization which is interrupted upon protonation. In MO terms, the HOMO is not localized on nitrogen in aniline as it is in alkylamines, so that the PA is not as high for an aniline as it is for a saturated amine having the same IP. In fact, there is also some indication that anilines are protonated on the aromatic ring, not nitrogen, in solution, if not the gas phase.[20]

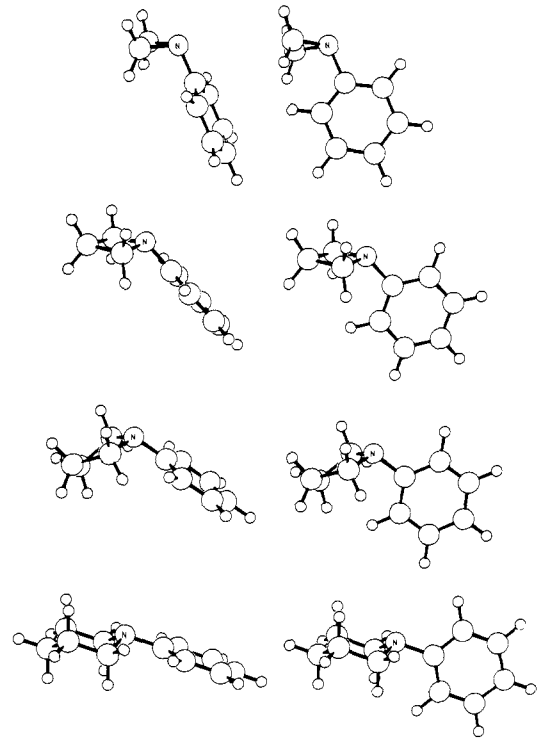


Figure 7. Molecular models of coplanar and perpendicular *N*-phenylazacycloalkanes.[18]

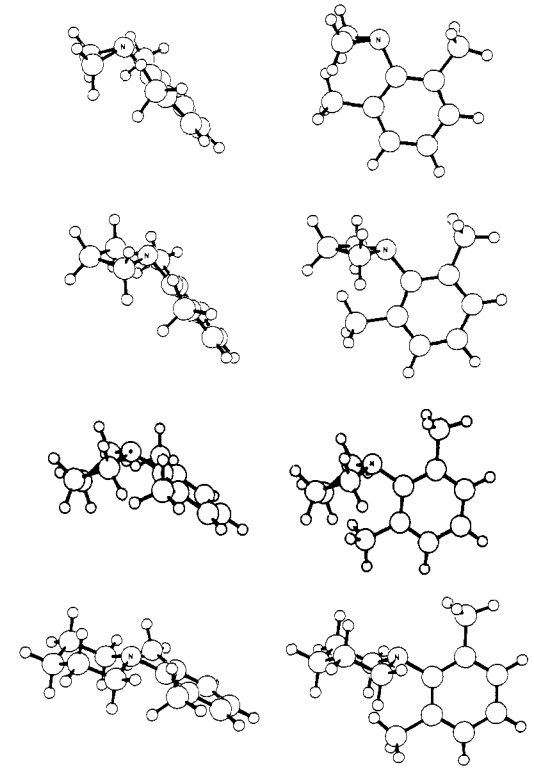


Figure 8. Molecular models of coplanar and perpendicular *N*-(2,6-dimethylphenyl)azacycloalkanes.[18]

(18) PROPHET is an NIH computer system for the study of chemical-biological interactions, sponsored by the National Institutes of Health, Division of Research Resources.

(19) (a) Wepster, B. M. *Prog. Stereochem.* **1958**, *2*, 99. (b) Hoefnagel, A. J.; Hoefnagel, M. A.; Wepster, B. M. *J. Org. Chem.* **1981**, *46*, 4209.

Table IV. Estimated PA's (kcal/mol) of *N*-Arylazacycloalkanes[a]

substituent	ring size 3	4	5	6
Ph	218	222	226	226
o-MePh		223	226	228
o,p-Me_2Ph	221	225	228	230
o,o'-Me_2Ph	220	223	232	232

[a] Estimated from the equation: PA (kcal/mol) = 296 − 8.13IP (eV) − 11.7 cos θ.

For perpendicular *N*-arylazacycloalkanes, we can use the correlation given above to estimate PA's, while for planar species, the PA's are expected to be ~11.7 kcal/mol lower for a given IP. In order to provide a single estimate of PA as a function of IP and rotational angle, we have defined the following equation:

$$PA(est) = 296 - 8.13IP_1 - 11.7 \cos \theta$$

where IP_1 is the first IP of the *N*-aryl azacycloalkane, and θ is the angle of rotation ($\theta = 0°$ for a "planar" species). Using the values of θ listed in Table III, the PA's listed in Table IV are predicted.

These predicted PA's qualitatively follow the order of measured solution pK_a's (±1 pK_a unit) except for three notable exceptions, **5-Ph**, **4-*o,p*-Me_2Ph**, and **6-*o,o'*-Me_2Ph**, all of which have pK_a's ≈ 2 pK_a units too low. The remaining compounds seem to have maximum pK_a's of about 5.5, even when the estimated PA's are quite high, which we attribute to steric hindrance to solvation of the ammonium cations.[19b] Of the three compounds noted above with especially low pK_a's, only the last would seem to provide especially high steric hindrance to solvation.

(20) Pollack, S. K.; Devlin, J. L., III; Summerhays, K. D.; Taft, R. W.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 4583. See also Ellenberger, M. R.; Dixon, D. A.; Farneth, W. E. *Ibid.* **1981**, *103*, 5377.

Conclusion

The PES studies have shown that the conformations of *N*-arylazacycloalkanes may be quite different for different amine ring sizes. Furthermore, the conformations of the aryl group with respect to the amine influences not only the IP, but are predicted to influence gas-phase proton affinities as well. Solution pK_a's are influenced by aryl conformations through the effect on IP's and variations in steric hindrance to the solvation of ammonium cations.

Acknowledgment. We are grateful to National Science Foundation and National Institute on Drug Abuse grants to K.N.H. for financial support of this work.

Registry No. **3**-Ph, 696-18-4; **3-*o,p*-Me_2Ph**, 78376-89-3; **3-*o,o'*-Me_2Ph**, 78376-90-6; **4**-Ph, 3334-89-2; **4-*o*-MePh**, 19198-94-8; **4-*o,p*-Me_2Ph**, 81506-10-7; **4-*o,o'*-Me_2Ph**, 19199-06-5; **4-*o,o'*-Et_2Ph**, 81506-11-8; **5**-Ph, 4096-21-3; **5-*o*-MePh**, 41378-30-7; **5-*o,p*-Me_2Ph**, 81506-12-9; **5-*o,o*-Me_2Ph**, 64175-53-7; **5-*o,o'*-Et_2Ph**, 81506-13-0; **6**-Ph, 4096-20-2; **6-*o*-MePh**, 7250-70-6; **6-*o,p*-Me_2Ph**, 81506-14-1; **6-*o,o'*-Me_2Ph**, 81506-15-2; *N,N*-dimethylaniline, 121-69-7; *N,N*,2,4-tetramethylaniline, 769-53-9; *N,N*,2,6-tetramethylaniline, 769-06-2; *N*-ethylaniline, 103-69-5; 2,6-diethylaniline, 579-66-8; *N,N-O,O'*-tetraethylaniline, 81506-16-3.

Stereochemistry of the Antitumor Agent 4,4′-(1,2-Propanediyl)bis(4-piperazine-2,6-dione): Crystal and Molecular Structures of the Racemate (ICRF-159) and a Soluble Enantiomer (ICRF-187)

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Abstract: Crystal structure elucidations of racemic 4,4′-(1,2-propanediyl)bis(4-piperazine-2,6-dione) (ICRF-159) and the *S*-(+) enantiomer (ICRF-187) have shown that both the cis and trans arrangements of the heterocyclic rings within the molecules represent stable conformations. In addition, analysis of the crystal packing in the two compounds has led to a plausible explanation for their very different solubilities. Crystals of ICRF-159 are triclinic, space group $P\bar{1}$, $a = 6.931$, $b = 11.930$, $c = 8.581$ Å, $\alpha = 101.06$, $\beta = 108.40$, $\gamma = 97.40°$, with two molecules per cell; those of ICRF-187 are monoclinic, $P2_1$, with $a = 10.578$, $b = 9.459$, $c = 6.594$ Å, $\beta = 95.02°$, with two molecules per cell.

Introduction

ICRF-159 [(±)-4,4'-(1,2-propanediyl)bis(4-piperazine-2,6-dione)] (NSC 129943) is a cytostatic agent[2] which has demonstrated significant in vitro and in vivo antitumor activity against a number of tumor types. Its effects appear to be antimetastatic, rather than cytotoxic, with a mechanism of action probably involving changes in tumor vasculature and inhibition of release of tumor cells into the circulation.[3,4] Antitumor activity varies markedly with chemical modification,[2] indicating that specific stereochemical and conformational characteristics are required for interactions with cell components.

Pharmacokinetic studies[5] have shown that orally administered ICRF-159 is poorly absorbed, especially at high doses; this is probably due to the compound's low solubility. In order to increase the bioavailability of the drug, use was made of the observations that the enantiomers of ICRF-159 are biologically active[2] and are more soluble than the racemate[6,7] to perform a systematic study

(1) (a) University of Toronto. (b) University of Washington.
(2) Creighton, A. M.; Hellmann, K; Whitecross, S. *Nature (London)* **1969**, *222*, 384–385.
(3) Salsbury, A. J.; Burrage, K.; Hellmann, K. *Brit. Med. J.* **1970**, *4*, 344–346.
(4) James, S. E.; Salsbury, A. J. *Cancer Res.* **1974**, *34*, 839–842.
(5) Creaven, P. J.; Allen, L. M.; Alford, D. A. *J. Pharm. Pharmacol.* **1975**, *27*, 914–918.
(6) Creighton, A. M. Canadian Patent 941 378, 1974.
(7) Repta, A. J.; Baltezor, M. J.; Bansal, P. C. *J. Pharm. Sci.* **1976**, *65*, 238–242.

0002-7863/82/1504-3453$01.25/0