

Hetaryne Intermediates

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Abstract: The electronic structures of all of the possible 1,2-, 1,3-, and 1,4-didehydroaromatic intermediates derived from pyridine and the diazines (hetaryne intermediates) have been calculated using the extended Hückel theory (EHT). For the didehydropyridines, it is found that of the six possible isomers, the 3,4-didehydropyridine is the most stable, and the 2,6-didehydropyridine the least stable. Great relative stability is also predicted for 4,5-didehydropyrazine and 4,6-didehydropyrimidine. The complex computational trends in the hetaryne stabilities can be rationalized very well by simple molecular orbital considerations of the orbital interactions among nonbonding radical lobes and lone pair orbitals. A dominant effect is shown to be a nitrogen lone pair destabilization of nearby radical lobes. The calculated stability sequences and total electron distributions provide an excellent correlation of the available experimental data on relative stability and orientation effects in the hetaryne intermediates.

The chemistry of dehydroaromatic intermediates derived from heterocyclic molecules has been actively investigated during the last decade. Numerous papers have been published on this subject, together with extensive reviews by den Hertog and van der Plas,³ by Kauffmann,⁴ and by Hoffmann.⁵ Principal attention has been focused on the 1,2-dehydroaromatics derived from nitrogen heterocyclics such as pyridine, quinoline, isoquinoline, and the various diazines. These intermediates are usually formed by the dehydrohalogenation of the corresponding halogenated heterocycle on treatment with a strong base. The two adjacent radical lobes in the 1,2 intermediates are thought to overlap appreciably, forming a partial triple bond in the heterocyclic ring. These species have been designated as hetarynes. The possibility exists, in principle, of forming 1,3 and 1,4 dehydroaromatics, in which the radical lobes are respectively in *meta* and *para* orientations. However, no such intermediates appear to have been reported to date. The only member of the 1,3 series that has received some attention is 2,6-didehydropyridine.⁶ Here it has been postulated that conjugation through the nitrogen lone pair, which is flanked by the two radical lobes, should provide the necessary stabilization for the formation of such an intermediate.

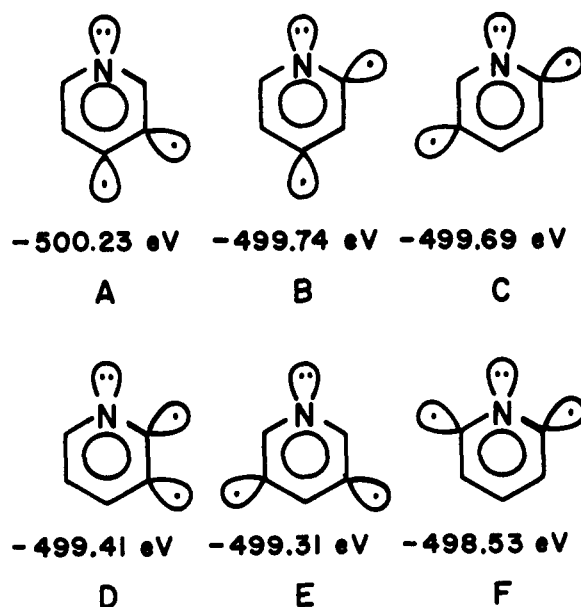
In comparison to the dehydrobenzenes, the hetarynes are considerably more complex. While benzene can only form one 1,2-dehydro intermediate, pyridine can form either 2,3-dehydropyridine or 3,4-dehydropyridine. Of these two possible hetarynes, 3,4-dehydropyridine is formed preferentially in the dehydrohalogenation of 3-halopyridine.⁷ It has only been possible to prepare 2,3-dehydropyridine by blocking the 4 position by substitution.⁸ While the symmetric dehydrobenzene inter-

mediate gives a single product on reaction with a nucleophile, the unsymmetric 3,4-dehydropyridine can form two products, by substitution at either the 3 position or the 4 position. The preferential attack at the 4 position in 3,4-dehydropyridine provides some evidence for an important orientation effect.³⁻⁵ Very little theoretical work seems to be available on these interesting hetaryne intermediates.⁶ For this reason, we decided to examine a number of dehydroheteroaromatic molecules, using all-valence-electron calculations of the extended Hückel type (EHT).⁹

Theoretical Analysis

Extended Hückel calculations⁹ on the six possible didehydropyridines result in the stability order shown in Chart I. In contrast to a previous simple Hückel calcu-

Chart I



lation, which indicated the 2,3-dehydropyridine (D) as the most stable,⁶ the 3,4-dehydropyridine (A) clearly emerges

(1) Cornell University, Ithaca, N. Y.

(2) The Puerto Rico Nuclear Center is operated by the University of Puerto Rico for the U. S. Atomic Energy Commission under Contract No. AT (40-1)1833.

(3) H. J. den Hertog and H. C. van der Plas, *Advan. Heterocyclic Chem.*, **4**, 121 (1965).

(4) T. Kauffmann, *Angew. Chem.*, **77**, 557 (1965).

(5) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967.

(6) H. L. Jones and D. L. Beveridge, *Tetrahedron Letters*, 1577 (1964).

(7) (a) N. Y. Pieterse and H. J. den Hertog, *Rec. Trav. Chim.*, **80**, 1376 (1961); (b) T. Kauffmann and F. B. Boettcher, *Angew. Chem.*, **73**, 65 (1961); *Chem. Ber.*, **95**, 1528 (1962).

(8) H. J. den Hertog, M. J. Pieterse, and D. J. Buurman, *Rec. Trav. Chim.*, **83**, 1173 (1963).

(9) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963), and subsequent papers.

as the most stable isomer. The 2,3-dehydro isomer in fact is so destabilized that it appears in our calculations with a higher energy than some *m*- and *p*-hetarynes.

This agreement with one of the few experimental facts known about the hetarynes is gratifying. However, the above ordering of stabilities is initially puzzling. An explanation of this stability sequence must begin with a review of what is known of the electronic structure of the dehydrobenzenes themselves.¹⁰ When two hydrogen atoms are removed from the aromatic ring, two orbitals may be pictured as remaining. These orbitals each formally contain one electron, and they are termed the radical lobes n_1 and n_2 . The radical lobes can be combined to form wave functions $n_1 + n_2$ and $n_1 - n_2$, which are respectively symmetric (S) and antisymmetric (A) with respect to the twofold rotation which interchanges n_1 and n_2 . In the absence of any interaction, $n_1 + n_2$ and $n_1 - n_2$ are degenerate. Direct overlap between n_1 and n_2 (through-space) and indirect interaction with other σ and σ^* orbitals (through-bond) remove the degeneracy of the S and A molecular orbitals. The magnitude of the energy splitting between S and A is a direct measure of the quantum-mechanical interaction. It is of controlling influence as to whether the ground state of the dehydrobenzene should be a singlet or a triplet state.

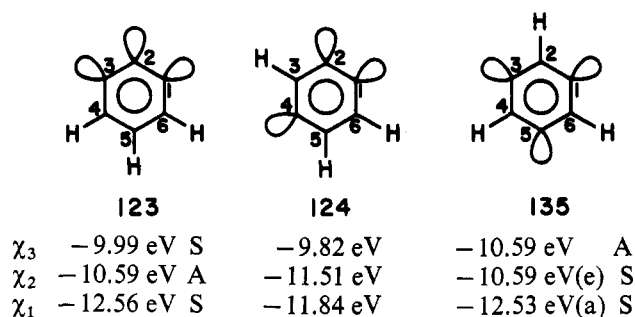
The magnitude and direction of the calculated splittings were surprising.¹⁰ Thus for *o*- and *m*-benzyne we found S below A by 1.52 and 0.92 eV, respectively, while for *p*-benzyne A was below S by 1.44 eV.¹¹ These results together with other unexpected splitting patterns led us to an interpretation of each splitting as a superposition of a direct through-space coupling and an indirect through-bond coupling. The through-space coupling always puts the positive overlap combination at a lower energy. This may be S or A depending on whether the radical lobes are in a *cis* or a *trans* arrangement. The through-bond coupling leads to a lower A level when the radical lobes are separated by an odd number of σ bonds, and to a lower S level when they are separated by an even number of σ bonds.¹⁰

We will construct two models for the analysis of the energy level patterns of the dehydroazines and dehydrodiazines. In the first model the energy levels of trihydro- and tetrahydrobenzenes are considered initially, and the subsequent introduction of nitrogen atoms is treated as a small perturbation. The second model takes the stability ordering of the monodehydropyridine intermediates, and treats the subsequent dehydrogenation as a small perturbation.

There are three tridehydrobenzenes, each having three nearly nonbonding molecular orbitals. The tridehydrobenzenes can be labeled 123, 124, and 135 in an obvious notation, and the nonbonding orbitals designated as χ_1 , χ_2 , and χ_3 in order of increasing energy, as shown in Chart II.

The wave functions, χ , can be classified as S or A under the twofold rotation interchanging orbitals 1 and

Chart II



3 in 123 and 135.¹² For 124 there is no twofold axis, so that the orbitals χ are simply σ orbitals.

We would anticipate that the molecular orbitals formed from the radical lobes n_1 , n_2 , and n_3 in 123 should fall into a typical allylic pattern

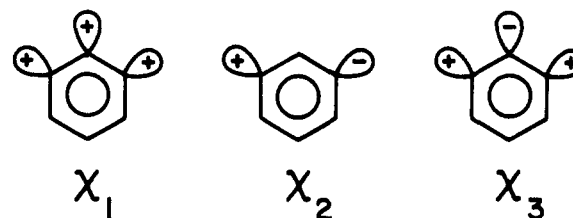
$$\begin{aligned} \chi_3 &\sim n_1 - cn_2 + n_3 & S \\ \chi_2 &\sim n_1 - n_3 & A \\ \chi_1 &\sim n_1 + c'n_2 + n_3 & S \end{aligned}$$

and this they do. For instance, χ_1 is about 94% localized on atoms 1, 2, and 3, and has the following coefficients (z axis normal to the molecular plane and y axis along C_2C_5).

$c_1(2p_x)$	0.4205	$c_2(2p_x)$	0.0000	$c_3(2p_x)$	-0.4205
$c_1(2p_y)$	0.2000	$c_2(2p_y)$	0.5499	$c_3(2p_y)$	0.2000
$c_1(2s)$	0.1262	$c_2(2s)$	0.0474	$c_3(2s)$	0.1262

The molecular orbitals χ_1 , χ_2 , and χ_3 of 123 can therefore be sketched as shown in Chart III. The splitting pat-

Chart III



terns found for the benzyne¹⁰ indicated that for an *ortho* interaction of two radical lobes the S combination was stabilized with respect to the A combination, for a *meta* interaction the S combination was also favored, whereas for a *para* interaction the A combination was favored. From the above diagram we see that χ_1 has two favorable (S) *ortho* interactions ($n_1:n_2$ and $n_2:n_3$) and one favorable (S) *meta* interaction ($n_1:n_3$). χ_2 has one unfavorable (A) *meta* interaction, while χ_3 has two unfavorable (A) *ortho* interactions and one favorable (S) *meta* interaction. By using the symbols (+) and (-) for favorable and unfavorable interactions, we can summarize the energetics of the above interactions as shown in Table I.

(12) The species 135 has threefold symmetry, so that the wave functions fall into an (a) and (e) group classification. A basis can still be chosen for the degenerate representations which is consistent with the lower symmetry of the twofold axis.

(10) R. Hoffmann, A. Imamura, and W. J. Hehre, *J. Am. Chem. Soc.*, **90**, 1499 (1968).

(11) A similar ordering is observed for pyrazine in recently published *ab initio* calculations in a Gaussian basis: E. Clementi, *J. Chem. Phys.*, **46**, 4737 (1967); J. D. Petke, J. L. Whitten, and J. A. Ryan, *ibid.*, **48**, 953 (1968).

Table I

	<i>ortho</i>	<i>meta</i>	<i>para</i>
χ_3	--	+	0
χ_2	0	-	0
χ_1	++	+	0

Table II

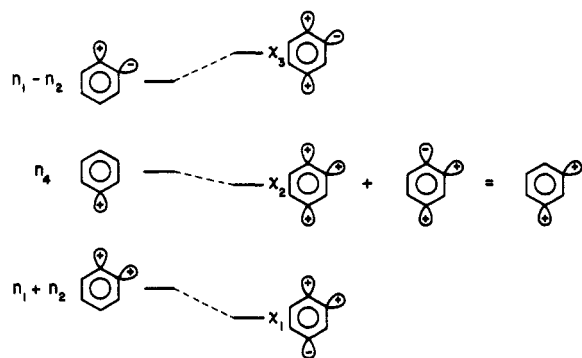
	<i>ortho</i>	<i>meta</i>	<i>para</i>
χ_3	-	-	-
χ_2	0	+	0
χ_1	+	-	+

Table III

	<i>ortho</i>	<i>meta</i>	<i>para</i>
χ_3	0	-(- - +)	0
χ_2	0	-	0
χ_1	0	+++	0

For the molecule 124 the orbitals χ_1 , χ_2 , and χ_3 are less straightforward to construct. A logical approach is to generate the orbitals by allowing the combinations $n_1 + n_2$ to interact with n_4 . The primary interaction is taken as a through-bond coupling of n_1 and n_4 which places a combination $n_1 - n_4$ (A) below $n_1 + n_4$. This corresponds to the stabilization of the A combination by the *para* interaction in the benzenes, and the fact that the *meta* interaction between n_2 and n_4 should be much weaker. The usual interaction rule, derived from perturbation theory, is invoked—namely if two orbitals interact, the lower mixes into itself the upper in a bonding way, but the upper mixes in the lower in an antibonding manner. This is shown in Chart IV. The actual

Chart IV



molecular orbitals have the predicted composition

$$\chi_3 = c(n_1 - n_2) + n_4$$

$$\chi_2 = (c(n_1 + n_2) + n_4) + (n_4 - c(n_1 - n_2)) = cn_2 + n_4$$

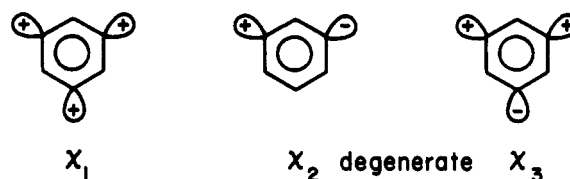
$$\chi_1 = c(n_1 + n_2) - n_4$$

The interactions may now be enumerated as was done above for the 123 system (see Table II).

The orbitals for 135 follow directly from symmetry. Three equivalent symmetrically disposed orbitals must interact to yield a totally symmetric combination and a

degenerate orbital pair.¹³ The degenerate orbitals may be chosen arbitrarily, and the particular combination illustrated in Chart V is picked to reflect symmetry on

Chart V

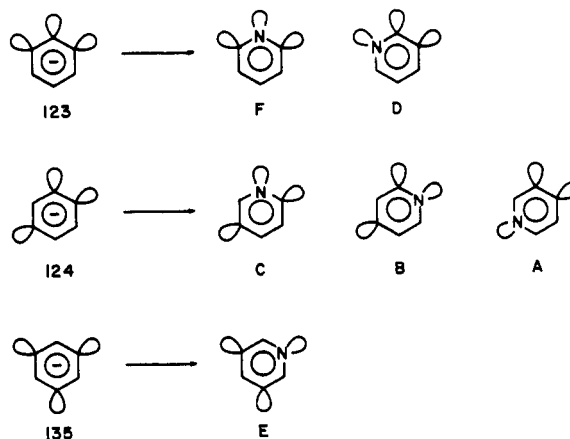


rotation around the C_1 - C_4 axis. The energetics of the interactions in this case are shown in Table III.

Referring back to the extent of the stabilization produced by the *ortho*, *meta*, and *para* interactions in the benzenes¹⁰ in terms of the energy splitting gives E (*ortho*) = 1.52 eV, E (*meta*) = 0.92 eV and E (*para*) = 1.44 eV. The use of these values, and the previous interaction schemes, predicts the following energy ordering for the nine orbitals of 123, 124, and 135: $\chi_1(123) < \chi_1(135) < \chi_1(124) < \chi_2(124) < \chi_2(123) \sim \chi_2, \chi_3(135) < \chi_3(123) < \chi_3(124)$. The actual calculated energy values have been given earlier. They are in exact agreement with the above sequence, supporting the analysis of the interactions.

In the tridehydrobenzene radicals, the radical lobes are each formally occupied by one electron. Of greater significance to the present analysis are the tridehydrobenzene cations, with two electrons in the nonbonding levels, and, more importantly, the anions, with four electrons. The total computed energies for the tridehydrobenzene cations are: 123, -462.81 eV; 124, -461.48 eV; 135, -462.06 eV. The stability ordering of these total energies is clearly in qualitative agreement with the ordering of the one-electron χ_1 energies. The total energies of the tridehydrobenzene anions can be obtained from the cation energy values by adding twice the one-electron energy of the appropriate χ_2 orbital. χ_2 of 124 is of much lower energy than the other χ_2 orbitals, so that the final anion energies are as follows: 123, -483.99 eV; 124, -484.50 eV; 135, -483.24 eV. The importance of the tridehydrobenzene anions is that we now

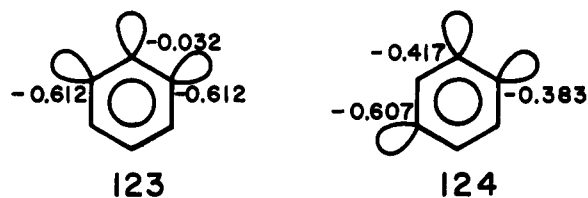
Chart VI



(13) F. A. Cotton, "Chemical Applications of Group Theory," Interscience Publishers, New York, N. Y., 1963, p 163.

suppose that the stability order is approximately preserved if the isoelectronic substitution is made of a N for a C⁻, to form the didehydropyridines (Chart VI). One of the radical lobes is now formally occupied by a nitrogen lone pair. The stability ordering $E(124) < E(123) < E(135)$ for the tridehydrobenzene anions thus implies the following grouping of the didehydropyridines, under the above assumption (A, B, C) < (D, F) < E. A further ordering in each group can be made by simply assuming that the nitrogen preferentially enters the position of highest electron density in the tridehydrobenzene anion. For 123 and 124 these charge densities are shown in Chart VII; this would predict the ordering $A < C <$

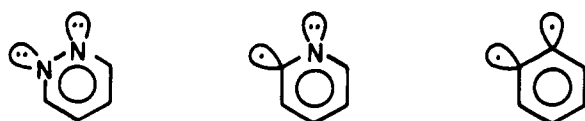
Chart VII



$B < D < F < E$. This is quite close to the actual alphabetical ordering obtained by the direct calculation.

We now turn to the second model for the stability sequence of the dehydropyridines. Table IV compares the energies of the $n_1 + n_2$ (S) and $n_1 - n_2$ (A) molecular orbitals calculated for the benzyne, monodehydropyridines, and diazines. In the benzyne the radical lobes are each formally occupied by one electron, in the monodehydropyridines three electrons are shared between the radical lobes, and in the diazines the "radical lobes" are fully occupied with four electrons. For example, the *ortho* series is shown in Chart VIII. It

Chart VIII



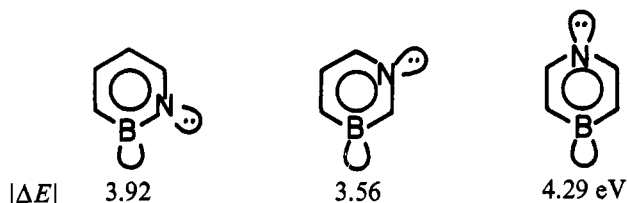
should be noted that whereas symmetry requires the relation $c_1 = \pm c_2$ in the molecular orbital $c_1n_1 \pm c_2n_2$ in the benzyne and diazines, there is no such restraint for the pyridinyl radicals. If n_1 is on N and n_2 is on C, then invariably the lower energy orbital has $|c_1| > |c_2|$ (considerable localization on N), and the higher energy orbital has $|c_1| < |c_2|$. However, the molecular orbitals are such that they can be identified as approximately "S" (c_1 same sign as c_2) and "A" (c_1 opposite sign to c_2).

In all cases the *ortho* and *para* interactions are greater than the *meta* interactions. The specific trends are not completely understood by us, though it is clear that the relative efficiency of through-space vs. through-bond interaction must be involved. Particularly interesting is the greater magnitude of the splitting in the "heteronuclear" pyridinyl case over the "homonuclear" benzyne and diazine splittings. This can be attributed to the separation of the C and N orbital energies before the interaction is "turned on." In confirmation of this, we obtain large splittings in the molecules shown in Chart IX which are isoelectronic with the benzyne.

Table IV. Energies (in eV) of Nonbonding Orbitals in *o*-, *m*-, and *p*-Benzyne, Monodehydropyridines, and Diazines

	Benzyne		Monodehydropyridine		Diazine	
<i>ortho</i>	-10.19	A	-11.00	"A"	-12.40	A
	-11.71	S	-12.96	"S"	-13.39	S
	ΔE		1.96		0.99	
<i>meta</i>	-10.59	A	-11.16	"A"	-12.58	A
	-11.51	S	-12.78	"S"	-13.39	S
	ΔE		1.62		0.81	
<i>para</i>	-10.37	S	-10.83	"S"	-12.58	S
	-11.81	A	-13.24	"A"	-13.85	A
	ΔE		2.41		1.67	

Chart IX



The smaller interaction of *meta*-oriented orbitals in the benzyne, pyridinyl, and diazine systems results in the upper molecular orbital (A in this case) being destabilized less than the upper molecular orbitals for *ortho*- (A) and *para*-oriented (S) lobes. The consequence is that when two electrons occupy the nonbonding molecular orbitals, as in benzyne, monodehydropyridinyl cation, and diazine dication the *ortho* isomer (benzyne) or the *para* isomer (pyridinyl, diazine) is the most stable. However, the *meta* isomer becomes progressively stabilized relative to the other isomers by the addition of one and two further electrons. The actual energetics are summarized in Table V.

Our primary conclusions are based on the results for the neutral pyridinyl (three-electron) and neutral diazine (four-electron) systems. The pyridinyl results imply that a lone pair *para* to a radical lobe is more stable than the

Table V. Total Energies (in eV) of Benzyne, Monodehydropyridines, and Diazines as a Function of the Number of Nonbonding Electrons

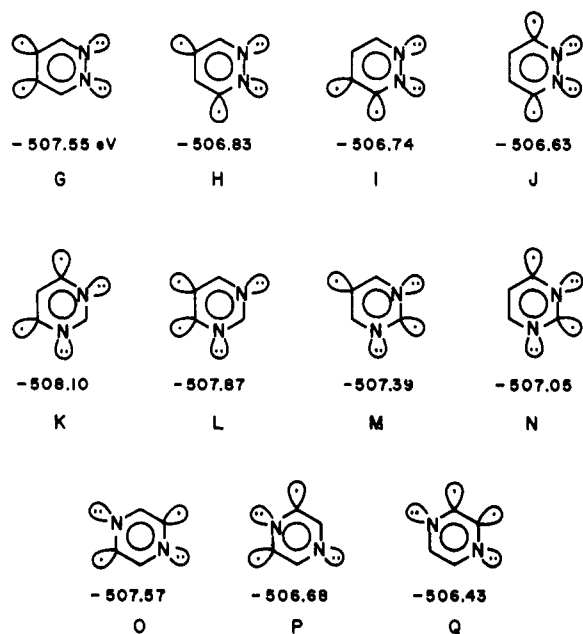
	Two-Electron Case		
	Benzyne	Pyridinyl ⁺	Diazine ²⁺
<i>ortho</i>	-492.58	-507.76	-520.75
<i>meta</i>	-491.99	-507.68	-521.45
<i>para</i>	-492.37	-508.17	-521.88
	Three-Electron Case		
	Benzyne ⁻	Pyridinyl	Diazine ⁺
<i>ortho</i>	-502.77	-518.75	-533.15
<i>meta</i>	-502.58	-518.84	-534.03
<i>para</i>	-502.74	-519.00	-534.06
	Four-Electron Case		
	Benzyne ²⁻	Pyridinyl ⁻	Diazine
<i>ortho</i>	-512.96	-529.75	-545.55
<i>meta</i>	-513.17	-530.00	-546.61
<i>para</i>	-513.11	-529.83	-546.24

meta orientation, which is more stable than the *ortho* orientation. The diazine results further suggest a strong destabilization of two adjacent nitrogens (lone pair repulsion?) and a stabilization of a *meta* interaction of two lone pair orbitals.

We can now examine the didehydropyridine results in the light of the above considerations on lone pair-radical lobe interactions. The number and type of N-radical interactions in the various didehydropyridines are listed in Table VI. Taking the stabilizing effect shown in Table V *para* > *ortho* > *meta* gives the energy sequence $A < B < E < C, D < F$. Only the order of E and C, D is inconsistent. This can be explained by the presence of a stabilizing *ortho* radical-radical lobe interaction of the benzyne type present in C and D, but absent in E.

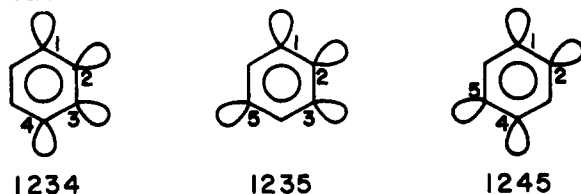
We now turn to the dehydrodiazines. Using idealized geometries, the possible dehydrodiazines exhibit the stability sequence shown in Chart X. Once again the

Chart X



analysis is twofold. We begin by considering the three tetrahydrobenzene shown in Chart XI. The molec-

Chart XI



ular orbitals of 1234 and 1245 are essentially determined by symmetry. We write them as $\phi_1, \phi_2, \phi_3,$ and ϕ_4 in an arbitrary order, since their final energy ordering is not obvious in every case. For 1234 the symbols S and A refer to the symmetry operation interchanging n_1 and $n_4,$ and n_2 and $n_3.$ For 1245 the symbols SS, AA, AS, and SA refer first to the symmetry operation interchanging n_1 and $n_5,$ and n_2 and $n_4,$ then to the symmetry opera-

Table VI

Structure	<i>ortho</i>	<i>meta</i>	<i>para</i>
A	0	1	1
B	1	0	1
C	1	1	0
D	1	1	0
E	0	2	0
F	2	0	0

Table VII

		<i>ortho</i>	<i>meta</i>	<i>para</i>
1234	(A) ϕ_4	---	++	+
	(S) ϕ_3	-(- - +)	--	-
1235	(A) ϕ_2	+(+ + -)	--	+
	(S) ϕ_1	+++	++	-
1245	(S) ϕ_4	--	-(- - +)	-
	(A) ϕ_3	0	-	0
	(S) ϕ_2	0	0	+
	(S) ϕ_1	++	+++	-
1245	(AA) ϕ_4	--	--	--
	(SA) ϕ_3	--	++	++
	(AS) ϕ_2	++	--	++
	(SS) ϕ_1	++	++	--

Table VIII

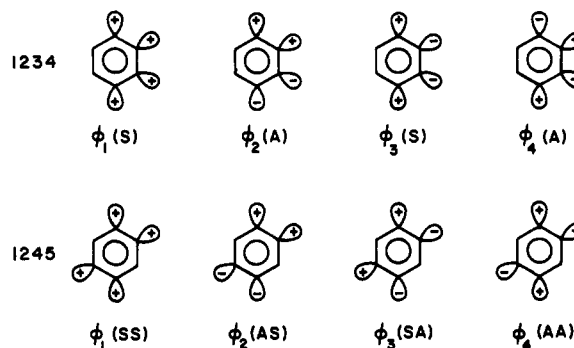
1234	1235	1245
-9.78 (S)	-9.58 (S)	-9.29 (AA)
-10.04 (A)	-10.59 (A)	-11.49 (SS)
-11.83 (A)	-11.78 (S)	-11.55 (SA)
-12.72 (S)	-12.76 (S)	-11.97 (AS)

Table IX

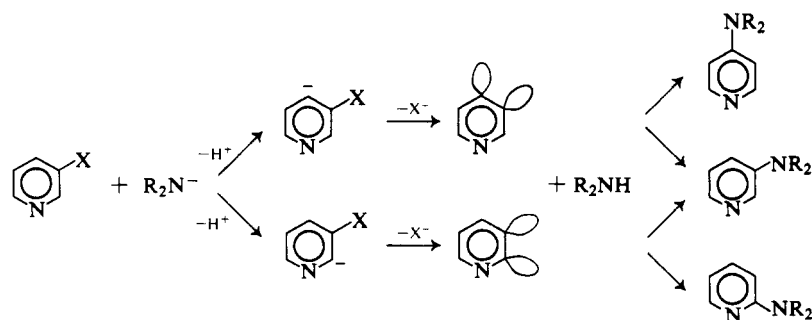
Structure	Nitrogen radical interactions		
	<i>ortho</i>	<i>meta</i>	<i>para</i>
G	0	2	2
H	1	2	1
I	1	2	1
J	2	2	0
K	2	0	2
L	1	2	1
M	2	2	0
N	3	0	1

tion interchanging n_1 and $n_2,$ and n_4 and $n_5.$ Note the obvious and not accidental resemblance of the orbitals of 1234 and 1245 to the π orbitals of a butadiene (see Chart XII). The composition of the 1235 molecular

Chart XII

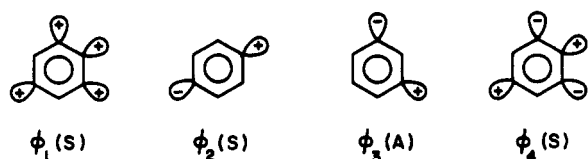


Scheme I



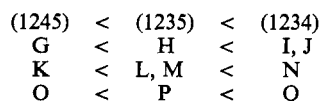
orbitals is not easily predicted. They emerge from the calculation resembling a set of cyclobutadiene orbitals (see Chart XIII).

Chart XIII



We now estimate the favorable and unfavorable interactions for each of these molecular orbitals as was done for the tridehydrobenzenes (Table VII). Recalling that an *ortho* or *para* interaction is more stabilizing than a *meta* interaction, we would predict for 1234 the energy ordering $\phi_1 < \phi_2 < \phi_4 < \phi_3$, for 1235 $\phi_1 < \phi_2 < \phi_3 < \phi_4$, and for 1245 $\phi_2 < \phi_1 \sim \phi_3 < \phi_4$. These conclusions are confirmed by the calculated energy level orderings (in electron volts) shown in Table VIII. The calculated total energies for the six electron systems which correspond to the tetrahydrobenzene dianions are: (1234) dianion, -475.39 eV; (1235) dianion, -476.00 eV; (1245) dianion, -476.54 eV. The stabilization of 1245 is essentially due to the relatively low energy of its highest occupied molecular orbital. In fact, the total energy order $1245 < 1235 < 1234$ is paralleled by the highest occupied level energies $-11.49 < -10.59 < -10.04$, respectively.

To obtain the didehydrodiazines, we proceed to replace two carbon atoms by nitrogen atoms in the tetrahydrobenzene dianions. For each type of diazine the stability sequence presented earlier is completely predicted by the above considerations, that is



Placing all 11 isomers on a single energy scale is difficult, since relative weights would have to be assigned to the effects of radical lobe interactions and lone-pair lobe interactions.

The second analysis, starting from the stabilities of the pyridinyl radicals, is quite successful in rationalizing the observed trends for the dehydropyridazines and pyrimidines (G to N), as illustrated in Table IX. However, it fails to distinguish among the dehydropyrazines where each isomer has two *ortho* and two *meta* interactions.

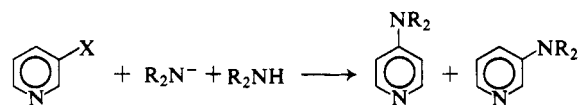
We have gone into great detail in the qualitative analysis shown in Table IX to illustrate how the com-

plex computational trends we have observed are understandable in terms of qualitative molecular orbital arguments. In addition to the molecules already mentioned, our actual calculations covered a number of other dehydroheterocyclics. The results are summarized in Tables X–XII, where the hetarynes are grouped as 1–2, 1–3, or 1–4 diradicals.

Clearly the position of the nitrogen lone pairs has an effect on the energy splitting ΔE between S and A molecular orbitals. Of great interest is the fact that there is a consistent correlation between stability and the magnitude of this one-electron energy splitting. Compare, for example, the dehydropyridines in Tables X–XII. The largest splittings are associated with molecules for which we predict great relative stability. These are 3,4-dehydropyridine, 4,5-dehydropyrazine, and 4,6-dehydropyrimidine, which probably have singlet ground states.

Interpretation of Experimental Data

We first turn to the experimental evidence available on the stability of the 1,2-hetarynes. Treatment of a 3-halopyridine with a strong base (usually an alkylated amide ion) leads to the 3- and 4-amino-substituted pyridines.⁷



No 2-aminopyridine is observed in these reactions, unless the 4 position is blocked by an alkyl group.⁸ A 3,4-didehydropyridine must be the preferred intermediate in this reaction, rather than the 2,3 isomer. Naively, the 2,3 isomer would be expected to be more stable, since two electrons from the radical lobes, together with the nitrogen lone pair, can be delocalized over three atoms. This suggestion has been forwarded, resting on the basis of a Hückel molecular orbital calculation.⁶ As pointed out in the theoretical analysis, our extended Hückel calculations, which are in agreement with the experimental data, argue against the utility of simple delocalization over the three adjacent atoms. On the contrary, whenever the nitrogen lone pair is adjacent to the radical lobes, we have seen that the intermediate experiences a pronounced destabilization.

If the accepted mechanism of dehydrohalogenation of 3-halopyridines is considered,^{3–5} two reasons emerge for the formation of 3- and 4-aminopyridines, rather than 2-aminopyridine. The mechanism is shown in Scheme I. First of all, the formation of the 1,2-hetaryne

Table X. 1,2-Didehydroaromatics










Molecule	E_{total} , eV	Splitting ΔE , eV	Total electron densities	
			q_{α}	q_{β}
	-492.58	1.52	4.20	4.20
	-499.77	0.86	3.77	4.25
	-500.60	1.63	4.35	3.97
	-505.95	1.11	3.94	4.10
	-506.60	1.54	4.29	3.94
	-506.74	0.89	3.98	3.91
	-507.55	1.57	4.11	4.11
	-507.87	1.04	3.55	4.44
	-505.43	0.04	3.81	3.81

Table XI. 1,4-Didehydroaromatics


















Molecule	E_{total} , eV	Splitting ΔE , eV	Overlap population $P_{\alpha\beta}$	Total electron densities	
				q_{α}	q_{β}
	-492.37	1.44	-0.119	4.30	4.30
	-500.05	1.43	-0.108	3.89	4.39
	-500.99	1.28	-0.110	3.97	4.24
	-506.63	1.22	-0.098	3.87	3.87
	-507.39	1.37	-0.096	3.62	4.26
	-507.57	1.52	-0.097	3.99	3.99

Table XII. 1,3-Didehydroaromatics

Molecule	E_{total} , eV	Splitting ΔE , eV	Overlap population $P_{\alpha\beta}$	Total electron densities q_{α}	q_{β}
	-491.99	0.92	0.041	4.21	4.21
	-500.13	1.33	0.034	3.97	4.07
	-498.88	0.04	-0.008	3.85	3.85
	-499.72	0.69	0.047	4.18	4.18
	-505.93	1.11	0.047	4.01	3.89
	-505.29	0.59	0.001	3.87	3.87
	-505.89	0.94	0.046	4.18	4.18
	-506.83	1.15	0.039	3.90	4.02
	-507.05	0.70	-0.037	3.96	3.41
	-508.10	1.70	0.037	3.81	3.81
	-506.68	0.23	-0.173	4.06	4.06

necessitates the removal of a proton by the amide ion to form a carbanion. Two carbanions are possible, the 2-pyridinyl anion and the 4-pyridinyl anion. We have calculated the relative stability of these carbanions in the case where X is hydrogen. The results are shown in Table XIII and indicate that the 4-carbanion is 0.08 eV (1.9 kcal) more stable than the 2-carbanion. Fortunately, recent experimental data confirm this stability ordering, since base-catalyzed deuterium exchange studies on pyridine and 3-chloropyridine indicate that exchange predominates at the 4 position over the 2 position in both cases.¹⁴ The carbanions subsequently eliminate halide ion to form the 1,2-hetaryne. The combination of the preferred formation of the 4-carbanion, which is the precursor of the 3,4-didehydropyridine, together with the greater stability (0.83 eV or 19 kcal/mol, Table X) of this hetaryne over the 2,3-didehydropyridine, accounts for the facts. It is worth reiterating that the predominant factor against the 2,3-hetaryne is the nitrogen lone-pair destabilization of the radical lobes.

(14) J. A. Zoltewicz and C. L. Smith, *J. Am. Chem. Soc.*, **88**, 4766 (1966); **89**, 3358 (1967).

This destabilizing effect of the nitrogen lone pair on the 2-pyridinyl anion and 2,3-pyridyne has been independently recognized by Abramovitch, Singer, and Vinutha.¹⁵ They have shown that 3-methylpyridine methiodide, 3-cyanopyridine methiodide, 3-chloropyridine 1-oxide, and pyridine N-oxide all undergo preferential base-catalyzed hydrogen-deuterium exchange at the 2 position. For example, the exchange rates for 3-chloropyridine 1-oxide are in the order $2 > 6 > 4 \gg 5$, which is in opposite direction to the order $4 \gg 2,6$ established by Zoltewicz and coworkers¹⁴ for 3-chloropyridine. Similar experimental data have recently been forwarded on the base-catalyzed hydrogen-deuterium exchange of pyridine N-oxide and the N-methylpyridinium ion by Zoltewicz, Kauffmann, and Smith.¹⁶

Clearly the removal of the nitrogen lone pair by protonation, N-methylation, or N-oxide formation promotes

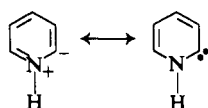
(15) R. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967).

(16) (a) J. A. Zoltewicz and G. M. Kauffman, *Tetrahedron Letters*, 337 (1967); (b) J. A. Zoltewicz, G. M. Kauffman, and C. L. Smith, *J. Am. Chem. Soc.*, **90**, 5939 (1968).

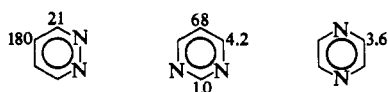
Table XIII. Heteroaromatic Carbanions

Parent	Position	E_{total} , eV	$E(\text{parent}) - E(\text{anion})$
	2	-529.75	...
	3	-530.00	...
	4	-529.83	...
	2	-536.04	...
	3	-536.18	...
	4	-536.06	...
	3	-536.78	8.77
	4	-536.85	8.70
	2	-537.60	9.01
	4	-537.67	8.94
	5	-538.07	8.54
	2	-537.45	8.81

preferential exchange at the 2 position over the 3 and 4 positions. The EHT total energies of Table XIII suggest that for the pyridinium ion exchange at the 2 position should become more competitive with the 3 position compared to the unprotonated pyridine. However, our extended Hückel calculations do not reproduce the several thousandfold enhanced rate of exchange at the 2 position relative to the 3 or 4 positions. In fact, the total energies reveal that in pyridine as well as in the pyridinium ion the rate of exchange should be greatest at the 3 position. We have no explanation for this artifact of the EHT results, unless ylide-carbene resonance stabilization in the pyridinium ion is inadequately accounted for by our calculations.

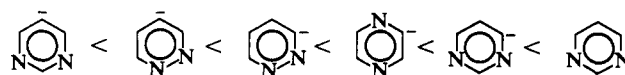


Although little information is available on the 1,2-didehydro intermediates derived from the diazines, some experimental work has recently been reported on base-catalyzed deuterium exchange in these molecules.¹⁷ The relative rates obtained for the sodium methoxide catalyzed exchange in O-deuteriomethanol at 164.6° are



Inspection of Table XIII shows again that within each diazine the relative order of exchange half-lives is correctly predicted by the carbanion stabilities. The comparison of the total energies of carbanions from different diazines cannot be made, since the total energies are dominated by the relative disposition of the nitrogens. To obtain a crude estimate of such a stability sequence the anion energies are subtracted from the parent energies in Table XIII. This gives the energy ordering

(17) J. A. Zoltewicz and G. Grahe, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April, 1968, P128.



Although the general trend is reproduced, our calculations reverse the sequence for the 4-pyridazinyl anion and 5-pyrimidinyl anion and for the 4-pyrimidinyl anion and 2-pyrazinyl anion (where the experimental half-lives are very close). Considering the neglect of solvent effects and the possibility of competitive exchange mechanisms, a perfect agreement is unlikely.

Some experimental data are available on the orientation effects in the addition of nucleophiles to the 1,2-didehydro intermediates. Whereas only one final product is possible from 1,2-didehydrobenzene, 3,4-didehydro-pyridine could undergo nucleophilic attack at the 3 or 4 positions to give different products. The addition of ammonia or piperidine to 3,4-didehydropyridine indicates a preference for nucleophilic addition at the 4 position.³⁻⁵ Previously we have shown that EHT electron densities and total energies of the reaction intermediates successfully correlate orientation effects in nucleophilic substitution.¹⁸ The total electron densities of Table X suggest that for 3,4-didehydropyridine preferential nucleophilic attack should occur at the 4 position, as a consequence of its lower total electron density (3.97 against 4.35 electrons). In addition, the total energies of the pyridinyl anions confirm this preference. Localizing a hydride ion, chosen as a model for the amine nucleophile, at the 3- or 4-radical lobes of 3,4-didehydropyridine produces respectively the 4- or 3-pyridinyl anion. Since the 3-pyridinyl anion is 0.17 eV more stable than the 4 isomer (Table V), nucleophilic attack should be preferred at the 4 position. As we have indicated,¹⁸ when both orientation criteria lead to the same conclusion, we can be confident that they provide a reasonable account of the observed effects. In this case, the preferred nucleophilic attack occurs at the 4 position. In 3,4-didehydroquinoline the preferred addition also takes place at the 4 position and is reproduced by our calculations.¹⁹

The EHT results furthermore suggest preferential nucleophilic attack at the 4 position in the 3,4-didehydro-

(18) W. Adam and A. Grimison, *Tetrahedron*, **21**, 3417 (1965).

(19) (a) W. Adam, A. Grimison, and R. Hoffmann, unpublished results; (b) T. Kauffmann, F. P. Boettcher, and J. Hansen, *Ann.*, **659**, 102 (1962).

pyridinium ion. Although no experimental data are available on the pyridinium ion or N-methylpyridinium ion to confirm this point, orientation effects in the related pyridine N-oxides have been studied. Dehydrobromination of 3-bromo-2,5-dimethylpyridine N-oxide with potassium amide in ammonia gave the 4-amino and 3-amino isomers in a ratio of 5:1.²⁰ Presumably the 3,4-hetaryne has intervened in this reaction as evidenced by the large orientation effect.

Of some interest is the exclusive formation of 4-substituted products in the reaction of 5-bromopyrimidine with piperidine.²¹ This suggests that the 4,5-didehydropyrimidine intermediate undergoes preferential nucleophilic attack at the 4 rather than the 5 position. Again, total electron densities and the total energies of the pyrimidinyl anions are both in agreement with this orientational effect. On the basis of this experimental result, it can be seriously questioned whether the 2,3-didehydropyridine is not formed during the dehydrohalogenation of 2-halopyridines.²² As a result of this reaction, the 2-substituted product is formed exclusively, and it was therefore argued that 2,3-didehydropyridine would have led to the formation of some 3-substituted product. In fact, it was concluded that if the 2,3-hetaryne intervenes, the 3 isomer should be the predominant product, as a consequence of the electron withdrawal by nitrogen. Objections have been raised to this interpretation, since a strong orientation effect, similar to that found in 4,5-didehydropyrimidine, may be operative.²³ Our calculations provide evidence in favor of this objection. Both total electron densities and total energies of the pyridinyl anions predict preferential nucleophilic attack at the 2 position, rather than the 3 position. On the basis of our calculations, deprotonation of pyridine at the 3 position is energetically favored over the 2 and 4 positions. This renders it rather likely that the 2,3-didehydropyridine may indeed be the intermediate in this reaction, and a more detailed experimental study of this point seems advisable.

In the dehydrohalogenation of 4-halopyridazine, two 1,2-didehydro intermediates could be formed, the 3,4- and 4,5-didehydropyridazines. Our calculations indicate that the 4,5 isomer should be more stable, again due to the dominant effect of the lone-pair destabilization. Because of the symmetry of the 4,5 isomer, no orientation effects are possible. In the unsymmetric 3,4 isomer, nucleophilic attack could lead to either a 3- or a 4-substituted product. However, the differences in the total electron densities and in the anion energies are exceedingly small, and predict opposite orientations. This suggests that very little, if any, orientation effect is expected

for the intermediates from 4-halopyridazine. Unfortunately, no experimental data are available.

The lack of experimental data on the 1,3- and 1,4-didehydroaromatics prevents us from confirming some of the interesting conclusions reached in these calculations.²⁴ However, there has been some speculation on the 2,6-didehydropyridine as a reaction intermediate.⁶ Again, Hückel molecular orbital calculations predict this 1,3-dehydro system to be stabilized by conjugation with the nitrogen lone pair. In our EHT calculations, and the attendant theoretical analysis, the 2,6 isomer clearly emerges as the least stable of the six possible hetarynes formed from pyridine (A-F). Once again, we attribute this finding to destabilization by the nitrogen lone pair, since even the 3,5 isomer (E) in which the lone pair is furthest from the radical lobes is energetically favored by 0.84 eV over the 2,6 isomer. This provides an explanation of the failure of all reported attempts to generate this species.²⁵

The effect of the nitrogen lone pair is also revealed in an interesting way in the 1,3-overlap populations. Except in those instances where the lone pair is flanked by the radical lobes, the 1,3-overlap populations are all small but positive, and close to that of 1,3-benzynes. In 2,6-didehydropyridine, 2,4-didehydropyrimidine, and 2,6-didehydropyrazine, where the nitrogen flanks the radical lobes, the overlap populations are still small, but more significantly of negative sign. Clearly the nitrogen lone pair inhibits a direct bonding interaction of the 1,3-radical lobes. It is interesting to find that protonation of the nitrogen lone pair in 2,6-didehydropyridine again results in a slightly positive 1,3-overlap population, therefore restoring the direct, through-space interaction found in 1,3-didehydrobenzene.

Recently we have noted a preliminary account of semiempirical SCF calculations on the hetarynes by Yonezawa, Konishi, and Kato,²⁶ which we would like to bring to the reader's attention. These calculations are able to decide if the ground state of the molecule is in fact a singlet, something which our calculations are not able to do.

Acknowledgment. We wish to thank M. Gheorghiu and Gladys Rodriguez for assistance in some of the computations. This work was generously supported by the University of Puerto Rico (W. A. and A. G.), and by the National Institutes of Health, the National Science Foundation, the Sloan Foundation, and the Chevron Research Company (R. H.). It was completed during the residence of R. H. at Rio Piedras, and he would like to express his gratitude to the Department of Chemistry of the University of Puerto Rico for their hospitality during that stay.

(20) R. J. Martens and H. T. den Hertog, *Rec. Trav. Chim.*, **86**, 655 (1967).

(21) T. Kauffmann, J. Hansen, K. Udluft, and R. Wirthwein, *Angew. Chem.*, **76**, 590 (1964).

(22) R. Wirthwein, Ph.D. Thesis, Darmstadt Institute of Technology, 1966.

(23) H. J. den Hertog and H. C. Van der Plas, *Advan. Heterocyclic Chem.*, **4**, 121 (1965); see especially p 133.

(24) R. S. Berry, J. Clardy, and M. E. Schafer, *Tetrahedron Letters*, 1003, 1011 (1965).

(25) T. Kauffmann, *Angew. Chem.*, **77**, 557 (1965); see especially p 571; ref 5, p 311.

(26) T. Yonezawa, H. Konishi, and H. Kato, *Bull. Chem. Soc. Japan*, **41**, 1031 (1968).