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MNDO Molecular Orbital Study of Nitrenium Ions Derived from Carcinogenic Aromatic Amines and Amides[1]

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Abstract: Semiempirical molecular orbital calculations at the MNDO level predict that the aryl- and *N*-acetyl-*N*-arylnitrenium ions exist as ground-state singlets resulting from the preferential stabilization of this state relative to the triplet (the ground state of NH_2^+ and the aliphatic nitrenium ions) by electron transfer from the phenyl substituent to the formally electron-deficient nitrogen atom. Simple nucleophiles add to these ions, leading to stable σ adducts with relative exothermicities which correctly reproduce the nucleophilic order $OH^- > NH_3 > Cl^- > H_2O$ only if the effects of ion hydration are specifically accounted for. The aryl- and *N*-acetyl-*N*-arylnitrenium ions are predicted to be stable to unimolecular rearrangement.

The class of aromatic amines includes a relatively high proportion of compounds which are carcinogenic in experimental animals,[2a] some of which are known to cause bladder tumors in man.[2b] Studies on the binding of the carcinogen *N*-methyl-4-(aminoazo)benzene to rat liver protein[3] led to the concept of an electron-deficient species as the final reactive consequence of metabolic activation of this compound. Further studies revealed that hydroxamic acids are metabolic intermediates in the activation of several carcinogenic aromatic amides[4] and led to the proposal[5] that a nitrenium ion is the electron-deficient species which ultimately leads to the products found in animals fed aromatic amines. The concept of electrophilic attack by some activated intermediate has proven to be useful for most, if not all, classes of organic compounds which are carcinogenic.[6] The bewildering variety of products formed between nucleic acid bases and carcinogens complicates the understanding of the genetic consequences of any one reaction and demonstrates the inadequacy of traditional means of prediction reaction products. In this respect, even the use of "reactivity indexes" derived from molecular orbital calculations (e.g., frontier orbitals, atomic charges, etc.) fails, for such indexes applied either to the electrophile or nucleophile in isolation must neglect the properties of the reaction partner and reaction medium. Thus, understanding of these reactions and their prediction depends on determining the actual energy changes in the reaction or, at least, developing an approximate methodology which will acceptably reflect them. The work described below is a first step toward the determination of a methodology sufficient to enable reliable predictions of the preferred products from reactions between nitrenium ions and nucleosides or nucleic acids. Future work will deal directly with such predictions and extensions to other classes of carcinogens.

Procedure

All computations reported here were carried out on a Harris S123 computer system consisting of a SLASH 6 central processor unit with 96K 24-bit words of MOS memory with virtual memory on hard disk (10.8 Mbyte) running under the VULCAN operating system. For the MO calculations, all operations involving real quantities were carried out in double precision with an associated accuracy of at least 11 significant figures.

The calculations were carried out using the MNDO procedure described by Dewar and Thiel[7,8] with the standard parameters derived and extensively tested by them.[9] Except where noted, the geometries of all stable species studies were completely optimized with respect to all geometrical variables using the modified[10] Davidon–Fletcher–Powell[11] algorithm incorporated in the program. The efficiency of the DFP procedure is due in part to

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[1] Presented in part at the Second Chemical Congress of the North American Continent, Las Vegas, NV, 1980.

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[3] Scribner, J. D.; Miller, J. A.; Miller, E. C. *Biochem. Biophys. Res. Commun.* **1965**, *20*, 560.

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[11] Fletcher, R.; Powell, M. J. D. *Comput. J.* **1963**, *6*, 163. Davidon, W. C. *Ibid.* **1968**, *10*, 406.

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the fact that the MNDO wave function is variationally optimized and the bond order matrix therefore invariant to small changes in the geometry. Thus the derivatives of the energy with respect to each of the geometrical variables can be obtained from a single SCF calculation at very little additional computational expense. Unfortunately, difficulties arise in the case of open shell (e.g., triplets) or biradical-like molecules. The latter class of molecules may be dealt with by including limited configuration interaction (CI), on the basis of the eigenvectors of the first excited singlet[12] which, like the triplet species, are conveniently treated by using Dewar's "half-electron" formalism.[13] However, in both cases the invariance of the bond order matrix is lost, and geometry optimization becomes extremely time consuming for large molecules. This difficulty is avoided in the spin-unrestricted Hartree–Fock (UHF) version of MNDO (UMNDO[14]). Here different spatial orbitals are assigned to electrons with different spins. Due to the overcompensation for electron correlation and the contamination of the ground state by higher spin states the energies given by this method are too negative. However, the geometries seem to be calculated quite well. Therefore we used this method to carry out a preliminary optimization of the geometries of larger molecules (≥14 atoms) for which we wanted to carry out half-electron triplet or CI calculations. Usually only a single DFP cycle with the more costly methods was required to reduce the gradients to acceptable levels (<10 kcal mol^{-1} Å^{-1}).

Absolute entropies were estimated from standard formulas[15] and moments of inertia from the calculated geometries as before.[16] Here we ignored vibrational contributions to the entropy but included the effect of a freely rotating top via eq 1.[17]

$$S_{\mathrm{ir}} = 3.035 + 4.576 \log [(I_{\mathrm{m}} \times 10^{38})T\sigma^{-1}] \qquad (1)$$

The symmetry number σ is the number of identical configurations into which the molecule can be transformed, and I_{m} is the reduced moment of inertia of the top in g cm^2. The rather complex formulas[17] for I_{m} in the general case reduce approximately to the moment of inertia of the top about its rotational axis in systems like those studies here where the moments of inertia of the rotating top are small compared with those of the molecule to which they are attached. This approximation was therefore made here.

Free energies of hydration for neutral species were estimated by using a group additivity scheme devised by Hine and Mookerjee.[18] For the ions we used an extension of this method which includes an electrostatic contribution based on the Born eq 2,[19] to be described in detail elsewhere.[20] When the bulk dielectric

$$\Delta G_{\mathrm{el}}^{\mathrm{g} \to \mathrm{H_2O}} = -q^2(1 - \epsilon^{-1})/2r \qquad (2)$$

constant for water for a univalent ion is used, eq 2 reduces to $\Delta G_{\mathrm{el}} = -163.9/r$ where r is the radius of the ion. The value chosen for r was that of the sphere having the same volume as the ion, including one molecule of water for each polar O^+–H or N^+–H bond. This volume in turn is calculated from the optimized geometry and the set of van de Waals radii suggested by Alliger.[21] The total volumes calculated in this way are realtively insensitive to the placement of the water molecules at hydrogen bonded distances; for OH–OH$_2$ we chose 1.7 Å and for NH–OH$_2$ 1.9 Å.[22]

Table I. MNDO Heats of Formation (ΔH_f) and Approximate Stabilization Energies (ΔE)[a] of the Singlet and Triplet States of the Nitrenium Ions 6–17

	ΔH_f, kcal mol^{-1}		S_0–T_1,[b] kcal mol^{-1}	ΔE, kcal mol^{-1}	
compd	S_0	T_1		S_0	T_1
6	313.4	292.2	21.2	0	0
7	277.9	271.7	6.2	−37	−22
8	259.1	251.1	8.0	−57	−44
9	231.5	224.5	7.0	$\sim -64^{c}$	$\sim -50^{c}$
10	240.4	250.9	−10.5	−70	−38
11	234.1	238.6	−4.5	−72	−46
12a	241.5	267.6	−26.1	−106	−59
12b	203.0	228.3	−25.3	$\sim -130^{d}$	$\sim -84^{d}$
13a	244.6	273.5	−28.9	−120	−70
13b	206.3	235.3	−29.0	$\sim -144^{d}$	$\sim -94^{d}$
14a	247.0	269.6	−22.6	−118	−74
14b	208.7	230.6	−21.9	-141^{d}	~ -98
15a	249.0	282.3	−33.3	−122	−68
15b	210.4	253.1	−42.7	$\sim -146^{d}$	$\sim -82^{d}$
16a	261.9	280.8	−18.9	−120	−80
16b	223.4	241.5	−18.1	$\sim -144^{d}$	$\sim -105^{d}$
17a	264.4	290.6	−26.2	−122	−75
17b	225.4	251.4	−26.0	$\sim -142^{d}$	$\sim -99^{d}$

[a] Approximate stabilization energies relative to NH_2^+ calculated from eq 5, 6, or 7 as appropriate. [b] Singlet–triplet energy separation; negative value indicates a ground-state singlet. [c] Systematic error in the MNDO heat of formation of $CH_3NHCOCH_3$ of −10.0 kcal added to the value obtained from eq 6. [d] Systematic error in the MNDO heat of formation of $PhNHCOCH_3$ of 14.3 kcal mol^{-1} added to the value from eq 6.

Validity of the MNDO Technique. MNDO has been shown to give good estimates of energies and other properties of a variety of compounds containing the elements H, B, C, N, O, F, and Cl.[7,9,23] Nevertheless it was important at the outset to establish as completely as possible the limits of reliability of the method in the present context. The compounds studied here are derivatives of the aromatic hydrocarbons, benzene (**1**), naphthalene (**2**), fluorene (**3**), phenanthrene (**4**), and *trans*-stilbene (**5**). Planar alternant aromatic hydrocarbons generally pose least problems for quantitative theories of bonding, and, as expected, the MNDO calculated heats of formation are in good accord with experiment (obsd,[24] calcd: **1** 19.8, 21.2; **2** 36.0, 38.1; **3** 43.8,[25] 44.7; **4** 49.5, 55.4; **5** 56.1, 59.6), being in every case within the expected[7b] MNDO mean error for hydrocarbons of 6.3 kcal mol^{-1}. Carbon–carbon bond lengths are uniformly, but not seriously, overestimated (0.016 ± 0.013 Å) relative to the experimental values.[26] The nonplanar geometry of *trans*-stilbene (**5**) is reproduced by the MNDO calculation, although the calculated twist angle (54.6°) is larger than that (30 ± 5) estimated from an electron diffraction study.[27] This probably stems from the tendency of MNDO to slightly underestimate resonance interactions and overestimate nonbonded repulsions. Comparison of the mean absolute error in the heats of formation of the nitrogen compounds with the limited experimental data available for the arylamines (ΔH_f obsd,[24] calcd: aniline 20.8, 22.0; 1-naphthalenamine 37.8, 41.3; 2-naphthalenamine 34.2, 38.9) indicates that MNDO performs comparably in the present connection. Charge distri-

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butions are probably also well calculated by MNDO. Thus the dipole moment calculated for aniline (1.48 D) is reasonably close to the value 1.53 D deduced[28] from gas-phase dielectric measurements, while that calculated for 2-naphthalenamine (1.44 D) is close to the value 1.48 D measured[29] in cyclohexane solution. The calculated heats of formation of substituted acetamides seem to be systematically too positive. For acetamide itself this error is 9.8 kcal mol^{-1} (calcd -47.2, obsd[24] -57.0) and for acetanilide 14.3 kcal mol^{-1} (calcd -16.4, obsd[24] -30.7). The heat of formation of *N*-methylacetamide has not been determined but is estimated[30] to be about -57 kcal mol^{-1}, ~10 kcal mol^{-1} more negative than the MNDO value (-47.1 kcal mol^{-1}). Thus although the relative energies of the acetylated compounds are expected to be reliable, this systematic error must be remembered where comparisons are made with other classes of compounds.

The only nitrenium ion for which a reliable heat of formation has been measured is the parent, NH_2^+. This value[31] (304 kcal mol^{-1}) for the lowest singlet state can be compared with the calculated heat of formation of 313.4 kcal mol^{-1} (307 kcal mol^{-1} with the inclusion of configuration interaction with the first doubly excited state). The ability of MNDO to predict the energies of positive ions has been studied less thoroughly than for neutral molecules, although the limited comparisons (15 positive ions) made in ref 7b indicated that its performance was similar or only slightly worse.

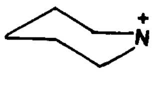
Results and Discussion

Ground Multiplicities of Nitrenium Ions. The calculated heats of formation of the parent nitrenium ion (**6**) and several aliphatic (**7**–**11**) and aromatic (**12**–**17**) derivatives are given in Table I. The geometries of **7**–**11** were completely optimized with respect to all geometrical variables for both singlet and triplet states. In similar complete optimizations we established that **12a** and the aromatic portion of **12b** were planar within the round-off limits of the DFP procedure. Since these slight deviations from planarity have a trivial effect on the energy but complicate the interpretation of the wave function, we constrained all the atoms of **12a**–**17a** to lie in the same plane. Similar constraints imposed on **12b**–**17b** were restricted to the atoms of the aromatic nucleus excluding the hydrogen atoms adjacent to the substituent.

H_2N^+ **6** $CH_3\overset{+}{N}H$ **7** $CH_3\overset{+}{N}CH_3$ **8**

CH_3NCOCH_3 **9**


10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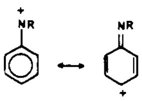
In the case of molecules (like those considered here) in which the ground and first doubly excited states are expected to be close in energy, an adequate description of either state may not be possible by using a single determinantal wave function.[32] We therefore recalculated the singlet states of **6**–**12** including configuration interaction (CI) with the lowest doubly excited configuration. The largest lowering in energy (relative to the single determinantal treatment) occured for **6** and here amounted to just 6 kcal mol^{-1} which is no more than that expected from the over compensation for correlation effects observed in "normal" molecules.[33] We therefore conclude that the inclusion of CI is not necessary in the present MNDO calculations, and all calculated heats of formation will refer to the single determinantal treatment. Thus according to the present calculations (Table I), the ground state of NH_2^+ (**6**) is a triplet, 21.2 kcal mol^{-1} more stable than the singlet state. No experimental determination of this energy separation has so far been reported, although there have been several theoretical studies[34-36] of this system. The most recent estimates (29.9[34] 29.1 kcal mol^{-1} [35]) from ab initio calculations using extremely large basis sets and extensive CI appear to be reliable. The larger values obtained earlier[36] were almost certainly due to the use of insufficiently flexible basis sets (cf. discussion of methylene in ref 37).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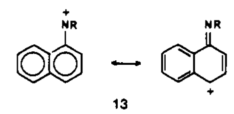
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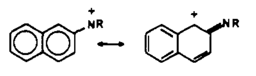
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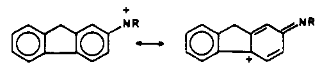
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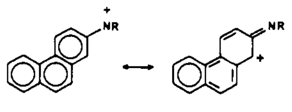
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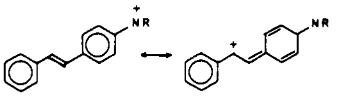
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a: R = H
b: R = Ac

The aliphatic nitrenium ions **7**–**9** are also predicted to be triplets, although with smaller S_0–T_1 separations, while the alicyclic **10**, **11** and aromatic **12**–**17** nitrenium ions are predicted to have singlet ground states.

However if the discrepancy (9 kcal mol^{-1}) between the MNDO and ab initio values for the singlet–triplet separation in **6** applies to the entire series and if the ab initio results are correct (which seems likely), then certainly **11** and probably **10** should be counted among the ground-state triplets.

Gassman and co-workers[38] have obtained evidence that aliphatic nitrenium ions (including **11**) generated by heterolysis of N-substituted amines exhibit accessible triplet states in solution. They found that these ions have a tendency to undergo hydrogen abstraction reactions which are enhanced in the presence of brominated solvents. This latter feature is especially convincing; if a triplet state were accessible, the presence of a compound containing a heavy atom such as bromine would be expected to promote the singlet–triplet conversion, whereas the alternative mechanism involving hydride transfer would presumably be unaffected.

In view of the larger differences involved, the MNDO prediction that arylnitrenium ions exist as ground-state singlets is probably correct.[39] Thus several experimental observations[41,42] which had

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[28] "Selected Values of Electric Dipole Moments for Molecules in the Gas Phase", Natl. Stand. Ref. Data Ser. (U.S., Natl. *Bur. Stand.*) **1967**, *NSRDS-NBS 10*.

[29] McClellan, A. L. "Tables of Experimental Dipole Moments"; W. H. Freeman: San Francisco, CA, 1963.

[30] Using a system of group additivities $\Delta H_f = -57.4$ kcal mol^{-1} is estimated: Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279. Alternatively, from the known[24] heats of formation of the *n*-butyl derivative, a value of -56.3 [= $\Delta H_f(n\text{-}C_4H_9NHCOCH_3) - \Delta H_f(n\text{-}C_4H_9NH_2) + \Delta H_f(CH_3NH_2)$] can be estimated.

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[33] Since MNDO was parameterized without the inclusion of CI, its inclusion leads to heats of formation for "normal" molecules, i.e., those without biradical character, which are too negative by ~5 kcal mol^{-1}. This is because the correction for electron correlation introduced by the CI procedure is also included in the parameters.

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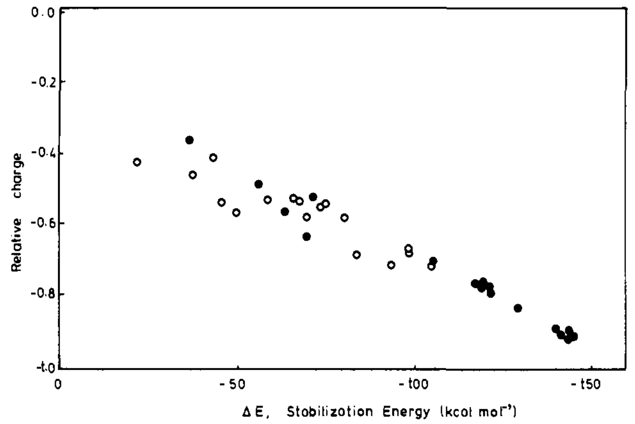

Figure 1. Stabilization of NR_2^+ by substituents R (relative to R = H) as a function of the electronic charge transferred to the nitrogen atom by the substituents (relative to R = H) for the singlet (●) and triplet (○) states.

earlier led to the suggestion[41,42] that the 2-(acetylamino)fluorenium ion **15b** existed in solution as a triplet may require reinterpretation. This is especially true in view of recent unpublished work in these laboratories by N. K. Scribner who found that the reduction of **15b** to the parent amide by aqueous ascorbic acid, originally interpreted as an H-atom transfer to triplet **15b**, was not catalyzed in the presence of a bromine-containing solute.

In order to understand the factors affecting the relative stabilities of the singlet and triplet nitrenium ions, it is convenient to express their energies on a common basis. This can be done by considering the formal heats of reaction of the appropriate "isodesmic reactions". Thus the enthalpy change associated with eq 3 can be associated with the stabilizing interaction between R and N^+H in excess of that between R and NH_2. Using the isodesmic reaction in this way allows us to neglect the energies of the remaining bonds which should approximately cancel. We can take this process a stage further by adding eq 4 to eq 3, changing the reference point from the interaction between R and NH_2 to that between $n\text{-}C_3H_7$ and NH_2 in $n\text{-}C_3H_7NH_2$ (a constant). Thus the significance of the enthalpy change in eq 5 can be described somewhat loosely as the *stabilization energy between R and N^+H in excess of that between C_3H_7 and NH_2*. The choice of $n\text{-}C_3H_7NH_2$ was largely arbitrary. Methylamine was avoided, methane being a somewhat atypical hydrocarbon. Since the MNDO heats of formation of $n\text{-}C_3H_7NH_2$ and C_3H_8 were both in excellent agreement with experiment, this was selected over other alternatives. Analogous expressions defining the stabilization energies of the disubstituted (eq 6) and alicyclic (eq 7) nitrenium ions may be obtained by obvious extensions of this procedure.

$$NH_2^+ + RNH_2 \rightarrow RNH^+ + NH_3 \qquad (3)$$

$$RH + n\text{-}C_3H_7NH_2 \rightarrow RNH_2 + C_3H_8 \qquad (4)$$

$$NH_2^+ + RH + n\text{-}C_3H_7NH_2 \rightarrow RN^+H + C_3H_8 + NH_3 \qquad (5)$$

$$NH_2^+ + RH + R'H + 2n\text{-}C_3H_7NH_2 \rightarrow RN^+R' + 2C_3H_8 + 2NH_3 \qquad (6)$$

$$NH_2 + HR\text{-}R'H + 2n\text{-}C_3H_7NH_2 \rightarrow R\text{-}N^+\text{-}R' + 2C_3H_8 + 2NH_3 \qquad (7)$$

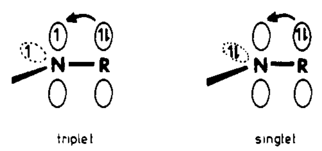

Figure 2. Mesomeric stabilization of singlet and triplet nitrenium ions.

Stabilization energies (ΔE) computed in this way are presented in Table I. A correction of -14.3 kcal mol^{-1} was applied to these energies for the acrylacetamide nitrenium ions calculated from eq 5 to compensate for the systematic error in MNDO (see previous section). A similar correction of -10.0 kcal mol^{-1} was applied to **9**. All heats of formation appearing in eq 2–6 were from published[7b] MNDO calculations or from those carried out here. As is clear from Table I, the stabilization of the triplet nitrenium ion by substituents is rather less than that of the corresponding singlets. Nevertheless in both cases the stabilization energies are quite large, being of the same order as those in substituted carbenium ions[43] and much larger than those in neutral carbenes.[37] Evidently, much of the calculated stabilization is due to the ability of the substituent to delocalized the positive charge. This effect is shown graphically in Figure 1 where the stabilization energy relative to NH_2^+ is plotted against the calculated electron densities transferred to the nitrogen atom by the substituent (relative to hydrogen) for both the singlet and triplet species. Both series are stabilized in an approximately parallel manner by electron donation from the substituent, although the absolute electron transfer in the triplets and thus the magnitude of the stabilizing effect is less. The differential stabilization of the singlet state by electron donors had been noticed before in carbenes by Baird and Taylor.[37] They pointed out that less electron transfer from the π (or pseudo π) orbitals of the substituent would be expected if the p orbital of the carbene was partly filled as it is in the triplet state (cf. Figure 2).

Geometries and Electronic Structures. The calculated ground-state (singlet) geometries of **12a–17a** are shown in Figure 3. Geometric distortions (relative to the parent hydrocarbons) indicate substantial contributions from the quinoid canonical structures shown in structures **12–17**. Thus the ring-nitrogen bonds at ~1.29 Å are considerably shorter than the corresponding bond in aniline,[44] being closer to that calculated for formimine (1.281 Å) indicating essentially a full double bond in this position. This is also in accord with the smaller than expected net charge calculated at the nitrogen atom (Table II). Among the bonds of the ring, those terminating at the substituted carbon atom show the greatest change. These are lengthened by approximately 0.08 Å relative to those in the corresponding hydrocarbon, while the adjacent bonds (e.g., 2–3 and 5–6 in **12**) are shortened by approximately 0.03 Å, again suggesting substantial contributions from the quinoid valence bond structures. The corresponding portions of the acetylated nitrenium ions **12b–17b** were very similar and are not therefore given here.[45] The stable conformations in this series were calculated to be those in which the acetyl group was rotated about the bond to the nitrogen, making an angle of approximately 70° with the plane containing the aromatic portion of the molecule. The preference for this conformation seems to have rather an interesting origin. In the amide grouping itself, mesomeric interaction between the nitrogen lone pair and the adjacent carbonyl group favors the planar conformation (Figure 4a). However, on conversion to the singlet acetylnitrenium ion, this pair of nonbonding electrons now occupies that lobe of the sp^2 hybrid orbital in the plane of the bonds to nitrogen, while the remaining p orbital perpendicular to these is formally vacant and mesomeric stabilization is lost (Figure 4b). Rotation about the

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(39) The open shell molecular orbitals of the triplet arylnitrenium ions are aromatic π and π^* types rather than the n and π^* types of the aliphatic ions. In this respect, the singlet–triplet transition of the arylnitrenium ions is akin to that of the parent hydrocarbons. In this case MNDO slightly overestimates the stability of the triplet state [obsd,[40] calcd (kcal mol^{-1}): **2**, 60.6, 56.8; **3** 67.4, 60.3; **4** 61.8, 59.9]. If applicable here, errors from this source therefore imply that the S_0–T_1 differences for the arylnitrenium ions should be more negative than those quoted in Table I.

(40) Evans, D. F. *J. Chem. Soc.* **1957**, 1351.

(41) Scribner, J. D.; Naimy, N. K. *Cancer Res.* **1973**, *33*, 1159.

(42) Scribner, J. D.; Naimy, N. K. *Experientia* **1975**, *31*, 470.

(43) For example, applying an equation similar to eq 5 and using known heats of formation for positive ions and neutral species involved, the stabilization of CH_3^+ by methyl substitution is estimated to be -35 kcal mol^{-1} and by C_6H_5 to be -76 kcal mol^{-1}.

(44) Calcd 1.423 Å, obsd 1.402 Å: Lister, D. G.; Tyler, J. K.; Hoeg, J. H.; Larsen, W. *J. Mol. Struct.* **1974**, *23*, 253.

(45) The calculated Cartesian coordinates of all species optimized in this work are provided as supplementary material.

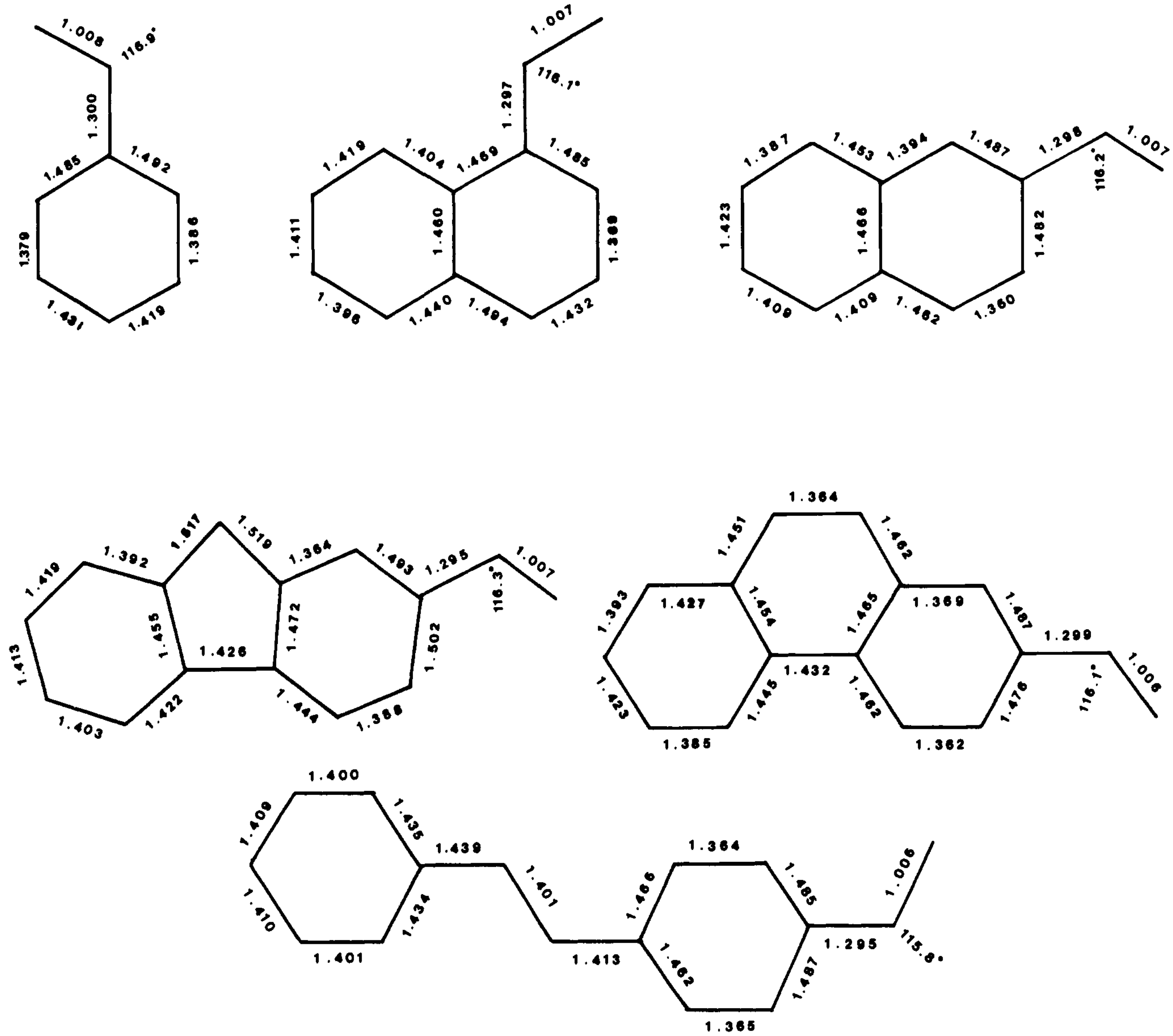

Figure 3. MNDO optimized structures of **12a**–**17a**.

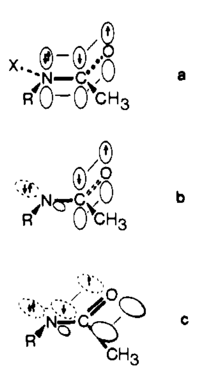

Figure 4. (a) Mesomeric stabilization in amides. (b) On conversion to the nitrenium ion (loss of X$^-$), the nitrogen lone pair is directed at 90° to the carbonyl π orbitals. (c) Rotation about the N–CO bond restores mesomeric stabilization.

N–C bond restores this mesomeric stabilization (Figure 4c).

The energy profiles for this rotation in **9** and **12b** are shown in Figure 5. In the case of the triplet nitrenium ions where the nonbonding orbitals are formally each singly occupied, the energy is far less sensitive to rotation. What variation remains presumably reflects the greater steric interference in the planar conformation.

The details of the calculated electron distributions for the arylnitrenium ions are given in Table II. Since the aryl ions **12b**–**17b** are nonplanar, no σ/π distinction is possible, and only the total charges are recorded for this series. These refer to the combined electronic charge associated with the carbon and (where applicable) the attached hydrogen atom. Expressing the data in this way reveals the close similarity between π and the total charges. Evidently, the latter are dominated by mesomeric distortion of the π system. Apparently, the *N*-acetyl group has a very slight effect on this charge distribution which is closely similar in both series.

In view of the continuing interest in frontier orbital coefficients,[46] i.e., the highest occupied molecular orbital (HOMO) of the nucleophile and the lowest unoccupied molecular orbital (LUMO) of the electrophile, as predictors of reactivity, we have included the LUMO coefficients for the ions **12a**–**17a** in Table II. In its simplest form[46] Kopman's[47] generalized perturbation equation predicts that a so-called hard nucleophile will add to an electrophilic at that position carrying the greatest positive charge, while a soft nucleophile will be directed to the position at which the LUMO coefficient has its greatest numerical value. Here (cf. Table II and Figure 6) these positions coincide[48] in each case,

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[46] See, for example: Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1976. See also ref 47a.

[47] (a) Klopman, G. In "Chemical Reactivity and Reaction Paths"; Wiley: New York, 1974; Chapter 4. (b) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223.

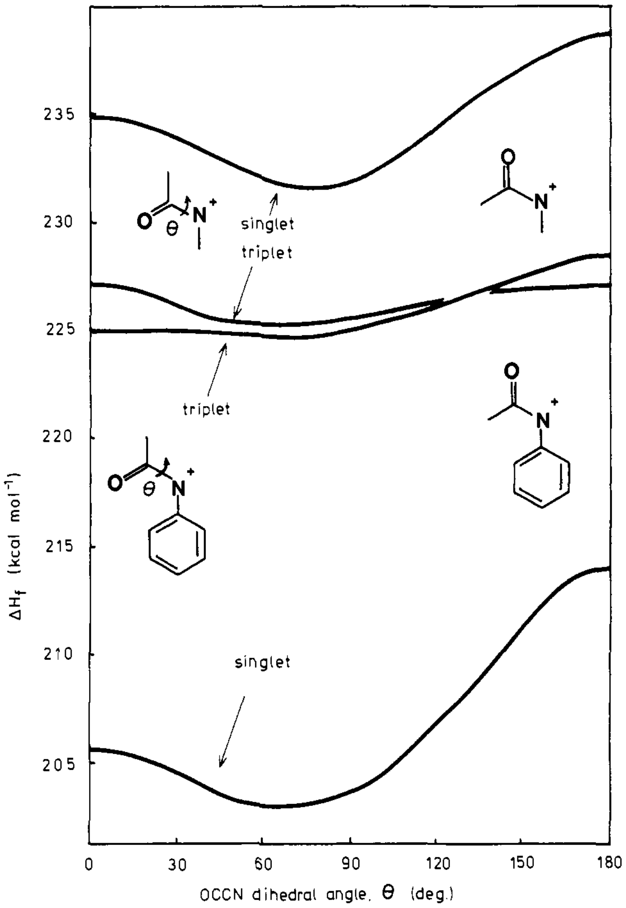
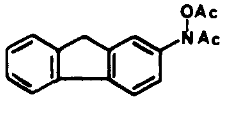


Figure 5. Energy profiles for rotation about the N–CO bonds in the singlet and triplet states of 9 and 12b.

except for the 2-phenanthrylnitrenium ion 16 where the LUMO coefficients at positions 1 and 4a are virtually identical. From what little is known of the reactivity of presumed arylnitrenium ion precursors, most of which refers to the acetyl series, the positions indicated in Figure 6 correspond approximately to the products obtained with simple nucleophiles [e.g., Cl^-, H_2O, ROH, $MeSCH_2CN(NH_2)CO_2H$]. This is true for 16b[41] and 17b[49] while the reactions of 15b usually take place at the 1 or 3 positions[50].



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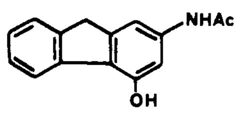

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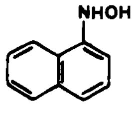

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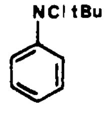

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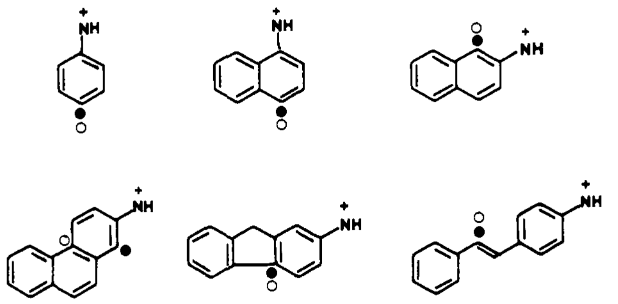

Figure 6. Positions at which the calculated charge (●) and LUMO coefficients (○) have their greatest values.

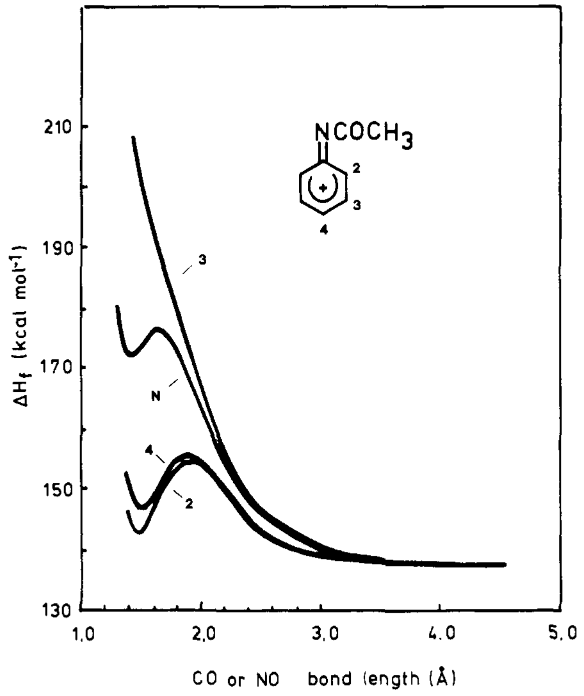

Figure 7. Minimum energy reaction paths for the addition of water to 12b.

In a rather unusual reaction the hydrolysis of 18, in 40% aqueous acetone, led to the 4-hydroxylated derivative 19. This was tentatively explained[50] via a mechanism involving addition of water to position 4a which was thought, on the basis of its LUMO coefficient, to be the most reactive position.[50] A completely analogous mechanism could have been written involving initial attack by water at the 3 position as is found for other nucleophiles[50] and predicted by the more detailed MNDO calculation presented in the next section. Solvolysis of 20 at various pH strengths gives[51] a mixture of the 2- and 4-hydroxynaphthylamines. Similarly the solvolysis of 21[52] gives mixtures of the 2- and 4-hydroxy-*N*-butylanilines. Thus the calculated charges (or LUMO coefficients apparently afford a rough guide to expected behavior of the nitrenium ions toward simple nucleophiles, although it is doubtful that they are significantly more useful in this connection than those for the corresponding arylmethylcarbenium ions which may be obtained (at least at the level of simple MO theory) by inspection.[53]

A major problem as far as the goals of this work are concerned is that, in contrast to the nucleophiles already mentioned which

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[48] This clearly follows from the analogy with the corresponding arylmethylcarbenium ion where at the Hückel level $q_i^{+} = a_{i0}^2$ where a_{i0} is the coefficient of the LUMO. See ref 53.

[49] Scribner, J. D. *J. Org. Chem.* **1976**, *41*, 3820.

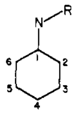
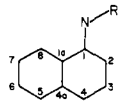
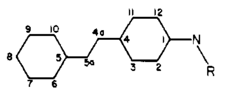
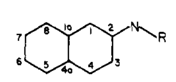
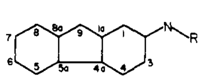
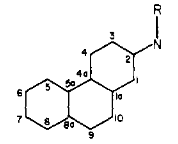
[50] Scribner, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 7383.

[51] Kadlubar, F. F.; Miller, J. A.; Miller, E. C. *Cancer Res.* **1978**, *38*, 3628.

[52] Gassman, P. G.; Campbell, G. A.; Frederick, R. C. *J. Am. Chem. Soc.* **1972**, *94*, 3884.

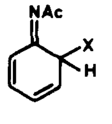
[53] Since the nitrenium and arylmethylcarbenium ions are isoconjugate, the LUMO of a given nitrenium ion differs from that of the carbon analogue only by the perturbing effect of the greater electronegativity of the nitrogen relative to the carbon atom. This has the effect of increasing the value of the charge (or LUMO coefficient) in the ring with a corresponding decrease on the nitrogen atom. Among those coefficients which are identical in the hydrocarbon, this effect seems to be a little greater for atoms more distant from the nitrogen. Since the carbenium ions are odd-alternant hydrocarbons, the coefficients of the LUMO can be found by inspection using the procedure of Coulson and Longuette-Higgins. See, for example: Dewar, M. J. S.; Dougherty, R. C. "The PMO Theory of Organic Chemistry"; Plenum, New York, 1975; Chapter 3.

Table II. Calculated Electronic Properties of Arylnitrenium Ions **12**–**17**

	R = H			R = $COCH_3$	R = H			R = $COCH_3$	R = H			R = $COCH_3$
	a_{LUMO}	q^{π}	q	q	a_{LUMO}	q^{π}	q	q	a_{LUMO}	q^{π}	q	q
	 **12**				 **13**				 **17**			
1	−0.087	−0.009	−0.065	0.009	−0.068	0.025	0.005	0.093	−0.063	0.026	−0.012	0.078
1a					−0.324	0.088	0.072					
2	−0.459	0.228	0.233	0.232	−0.434	0.218	0.209	0.213	−0.339	0.147	0.145	0.205
3	0.043	−0.029	−0.010	−0.011	0.046	−0.048	−0.027	−0.026	0.050	−0.054	−0.038	−0.042
4	0.580	0.401	0.382	0.383	0.589	0.388	0.377	0.380	0.542	0.304	0.237	0.235
4a					−0.046	−0.135	−0.190	−0.191	−0.071	−0.135	−0.114	−0.112
5	−0.004	−0.056	−0.041	−0.042	−0.337	0.178	0.198	0.201	0.065	−0.146	−0.185	−0.187
5a									−0.493	0.335	0.318	0.269
6	−0.496	0.323	0.346	0.333	−0.010	−0.002	0.015	0.015	0.210	0.115	0.127	0.132
					0.354	0.222	0.219	0.217	−0.015	−0.008	0.005	0.004
8					0.058	0.029	0.066	0.069	−0.209	0.158	0.160	0.161
9									−0.016	−0.009	0.003	0.005
10									0.210	0.117	0.131	0.131
11									0.012	−0.070	−0.046	−0.040
12									−0.340	0.191	0.221	0.149
N	0.444	0.141	0.001	−0.133	0.329	0.037	−0.083	−0.219	0.290	0.030	−0.081	−0.213
Σ^R			0.153	0.230			0.139	0.190			0.130	0.169
	 **14**				 **15**				 **16**			
1	−0.578	0.384	0.387	0.376	−0.374	0.219	0.268	0.252	−0.501	0.309	0.332	0.317
1a	0.047	−0.123	−0.187	−0.186	0.019	−0.095	−0.201	−0.198	0.037	−0.099	−0.159	−0.159
2	−0.074	0.014	−0.027	0.054	−0.075	0.018	−0.203	0.066	−0.082	0.016	−0.029	0.054
3	−0.251	0.066	0.091	0.096	−0.399	0.179	0.173	0.182	−0.316	0.107	0.124	0.132
4	0.039	0.009	0.050	0.049	0.057	−0.048	−0.007	−0.011	0.055	−0.018	0.007	0.004
4a	0.418	0.182	0.130	0.132	0.580	0.349	0.274	0.275	0.505	0.263	0.219	0.224
5	−0.049	−0.025	0.003	0.004	−0.285	0.152	0.184	0.185	−0.212	0.081	0.103	0.108
5a					−0.083	−0.135	−0.176	−0.175	−0.075	−0.096	−0.121	−0.123
6	−0.403	0.258	0.255	0.255	0.030	−0.009	0.008	0.008	0.020	0.016	0.029	0.029
7	0.008	−0.010	0.009	0.007	0.286	0.190	0.189	0.190	0.252	0.163	0.168	0.173
8	0.339	0.172	0.199	0.199	0.007	−0.006	0.033	0.033	0.020	−0.016	0.012	0.009
8a					−0.269	0.108	0.016	0.017	−0.304	0.134	0.087	0.091
9						0.029	0.193	0.191	0.008	0.014	0.047	0.044
10									0.202	0.060	0.102	0.103
N	0.372	0.073	−0.058	−0.190	0.329	0.049	−0.067	−0.201	0.367	0.066	−0.060	−0.195
Σ^R			0.148	0.204			0.137	0.188			0.141	0.191

tend to react at ring positions as expected from the consideration described above, the nucleic acid bases tend to react with nitrenium ions predominantly at the nitrogen.[54] Obviously the use of frontier orbital coefficients is inadequate here. In its complete form the Klopman perturbation equation[47] involves a consideration of all molecular orbitals and the introduction of a Hückel β integral between the reactants. When allowances for the angular dependence of β was made, this method, on the basis of a simple Hückel wave function, yielded indexes which correctly identified the products of the reactions of four arylnitrenium ions and the benzyl cation with guanosine.[55] While we are still pursuing this approach in our laboratory, we shall confine ourselves here to the quantitative treatment of chemical reactivity possible with the present methods.

Reactions with Simple Nucleophiles. As stated in the introduction, our ultimate goal is to develop a procedure capable of predicting the distribution of products expected in the reaction of a given carcinogen with various cellular nucleophiles, principally the nucleic acid bases. Here we outline a possible approach toward this goal by considering in detail simple prototypes of the reactions of arylnitrenium ions. Our first calculations referred to the reaction between water and the *N*-acetyl-*N*-phenylnitrenium ion **12b** to form the various σ complexes **22a**–**25a**. The minimum energy reaction paths for these reactions are shown in Figure 7.



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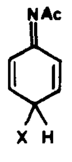

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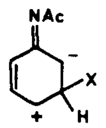

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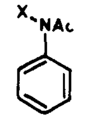

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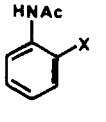

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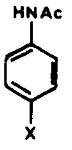

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a : X = $\overset{+}{O}H_2$

b : X = OH

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(54) Kriek, E.; Westra, J. G. "Chemical Carcinogens and DNA"; Grover, P. L., Ed.; Chemical Rubber Publishing Co.: Boca Raton, FL, 1979; Vol. 2, Chapter 1.

(55) Scribner, J. D.; Fisk, S. R. *Tetrahedron Lett.* **1978**, 4759.

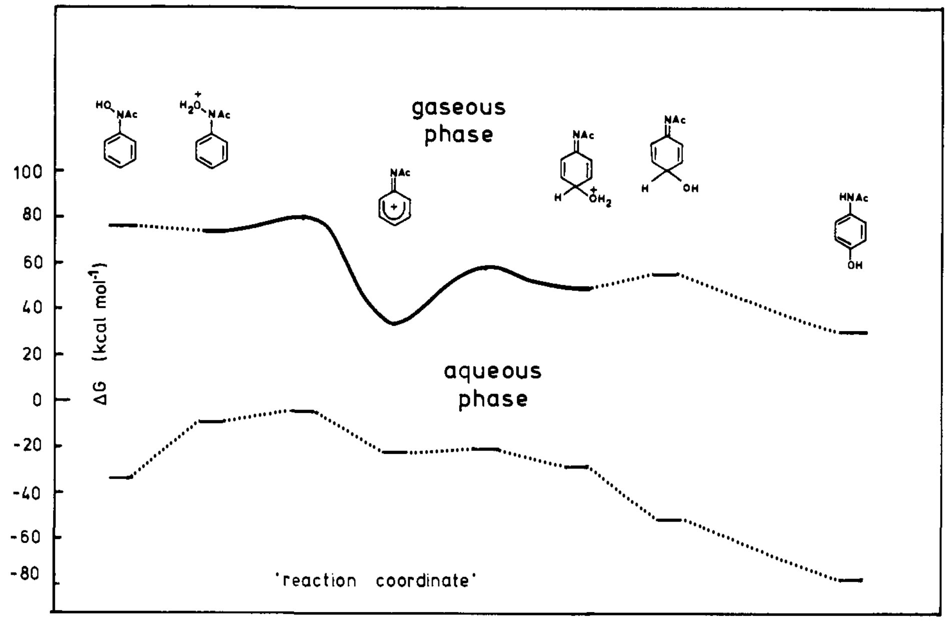

Figure 8. Calculated gas-phase and aqueous-phase profiles for addition of water to nitrogen (left) or para (right) positions of **12b**.

No stable adduct for the addition to the meta position (**24a**) apparently exists on the MNDO potential surface. In the case of N substitution, loss of a proton from **25a** leads directly to the neutral product **25b**. In the case of ring substitution, we assume that conjugate bases **22b** and **23b** also lie on the reaction paths, otherwise eventual conversion to the amides **26b** and **27b** would require doubly protonated intermediates. The MNDO heats of formation for each of these species are given in Table III together with additional data to be discussed below. In order to relate these results to the expected aqueous phase chemistry, we must estimate both the entropy contributions and the energies of hydration ($\Delta G^{g \rightarrow H_2O}$) if a realistic model is to result.

The absolute entropies of the various species calculated in the rigid rotor approximation ignoring vibrational contributions are given in Table III. Since we will eventually be concerned only with entropy *changes*, we expect contributions from the vibrational and internal rotational motion of the *N*-acetyl-*N*-phenyl skeleton to largely cancel. The rotational entropy contributed by the attached OH_2^+ and OH groups was included, by treating these groups as freely rotating tops. In this way, and including the appropriate counter molecules (H_3O^+ and H_2O) to conserve the atom balance, we constructed the gas-phase energy profile shown in the upper plot of Figure 8.

Table III. Calculated Heats of Formation and Absolute Entropies[a] and Estimated Free Energies of Hydration for Species Involved in the Hydrolysis of the *N*-Acetyl-*N*-phenylnitrenium Ion

compd	ΔH_f (MNDO), kcal mol^{-1}	$S°$, cal mol^{-1} K^{-1}	$\sim\Delta G^{g \rightarrow H_2O}$, kcal mol^{-1}
12b	203.0	70.2	-52^b
[22a]‡	154.5	77.1	-75^c
22a	143.4	76.9	-75^d
[23a]‡	155.5	77.2	-75^e
23a	147.1	77.0	-75^d
[25a]‡	176.6	76.8	-81^c
25a	170.7	76.8	$-81^{b,e}$
22b	−43.2	77.0	-12^d
23b	−41.2	77.1	-11^d
25b	−20.6	76.8	$-17^{b,e}$
26	−64.7	76.8	-15^g
27	−64.3	76.9	-15^g

[a] Excluding vibrational contribution and all internal degrees of rotational freedom except that of OH_2^+ or OH. [b] For benzyl ketone skeleton. [c] Assigned same value as corresponding adduct. [d] For the correspondœg methylene hexadiene skeleton. [e] Correcfed by −6.8 kcal mol^{-1}: $\Delta G^{g \rightarrow H_2O}(Me_2NCOCH_3)^f - \Delta G^{g \rightarrow H_2O}(Me_2CHCOMe)$. [f] Wolfenden, R. *Biochemistry* 1978, *17*, 201. [g] A group contribution for $NHCOCH_3$(C) of 8.00 deduced from $\Delta G^{g \rightarrow H_2O}[MeNHCOCH_3] = -5.8$ kcal mol^{-1} [f] was used.

The estimation of hydration energies is difficult. Recent careful studies at the ab initio STO 3G and 4-31G levels have successfully predicted small differences in solvation enthalpies arising from the effects of distant substituents on the hydrogen-bonding properties of pyridines[56] and aliphatic amines.[57] However, there is no currently available method for theoretically estimating *total* hydration energies of hydrogen-bonded species. We have therefore resorted to a thoroughly empirical approach. For the neutral species we used the groups additivity scheme devised by Hine and Mookerjee.[18] For the ions we used an extension of this method which we have described elsewhere.[20] This method seemed to work quite well for a collection of ammonium, oxonium, and pyridinium ions for which reliable energies of hydration had been tabulated by Taft[58] and Arnett et al.[59] An example of this method of estimating energies of hydration is given in the Appendix. The results are given in Table III and used to construct the lower curve of Figure 8. Comparing the upper and lower plots of this figure reveal that several unfamiliar aspects of the gas-phase profile have disappeared. In the upper plot the neutral species appear to be less stable than their conjugate acids. This is a result of the greater proton affinities of the alcohols relative to water in the gas phase. In the lower plot they revert to the expected order. The surprisingly deep well in which **12b** resides in the gas phase is almost entirely removed in the lower plot. Some 10 kcal mol^{-1} of this well in the gas phase is due to unfavorable loss of translational entropy on adduct formation. In the aqueous phase interaction with the solvent molecules reduces the translational freedom of all species (included in $\Delta G^{g \rightarrow H_2O}$), and the entropy contribution from this source is correspondingly less. The remaining reduction in the depth of this well is due to specific hydrogen bonding to the OH_2^+ group of the cationic adduct not present in **12b**. Provided that we can assume that whatever proton-transfer reactions connecting **22b** and **26b** or **23b** and **27b** occur rapidly in aqueous solution, then the stereochemical outcome of the hydrolysis reaction should be determined by the relative concentrations of the initially formed adducts. These in turn will be controlled by the magnitudes of the barriers separating them from the reactants. A complete description of these barriers must await a more so-

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(56) Arnett, E. M.; Chawla, B.; Bell, L.; Taagepera, M.; Hehre, W. J.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 5729.

(57) Taagepera, M.; DeFrees, D.; Hehre, W. J.; Taft, R. W. *J. Am. Chem. Soc.* **1980**, *102*, 424.

(58) Taft, R. W.; Wolf, J. F.; Beauchamp, J. L.; Scorrano, G.; Arnett, E. M. *J. Am. Chem. Soc.* **1978**, *100*, 1240.

(59) Arnett, E. M.; Chawla, B. *J. Am. Chem. Soc.* **1979**, *101*, 7141.

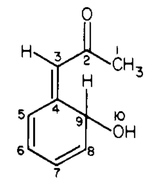
Table IV. Calculated (Observed) Heats of Formation, Absolute Entropies,[a] and Standard Free Energies of Hydration

molecule	ΔH_f,[b,c] kcal mol^{-1}	S_0,[c] cal mol^{-1} K^{-1}	$\Delta G^{g\rightarrow H_2O}$,[d] kcal mol^{-1}
H_3O^+	134.2 (139 ± 3)	45.9 (45.9)	−96.3[e]
H_2O	−60.9 (−57.8)	45.0 (45.1)	−4.4[f]
NH_3	−6.3 (−11.0)	45.9 (46.0)	−2.4[g]
Cl^-	−54.9[h] (−55.9)	36.6 (36.6)	−75.8[i]
HO^-	−5.8[j] (−34.4)	41.1 (41.2)	−90.6[i]

[a] Calculated for 298 K, neglecting the vibrational component. [b] Calculated values from ref 7b. [c] Observed values from ref 60. [d] Values refer to the transfer of 1 mol of the gaseous ion at 1 atm to a hypothetical aqueous solution of unit molality. [e] From the data in ref 58 using $\Delta G^{g\rightarrow H_2O}(NH_4^+) = -77.1$ kcal mol^{-1}. Arnett, E. M. In "Proton Transfer Reactions", Caldin, E., Gold, V., Eds.; Chapman and Hall; London, 1975; Chapter 3. [f] From ref 58 using $\Delta G^{g\rightarrow H_2O}(NH_3) = -2.4$ kcal mol^{-1}. [g] Jones, F. M., III; Arnett, E. M. *Prog. Phys. Org. Chem.* 1974, *11*, 263. [h] Reference 23b. [i] Friedman, H. L.; Krishnan, C. V. In "Water, A Comprehensive Treatise", Franks, F., Ed; Plenum: New York, 1973; Vol. 3, Chapter 1. [j] Reference 61. For a discussion of the discrepancy between the calculated and observed heats of formation, see text and ref 61. The observed value was used in the derivations of the data in Table V.

Chart I

(A)



I

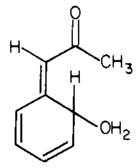
	group	contribution[18]
1	$CH_3(X)$	−0.62
2	$CO(C)_2$	4.03
3	CdH(CO)	0.28
4	Cd(C)(Cd)	0.86
5 = 6 = 7	CdH(Cd)	3 × 0.18
8	CdH(C)	0.22
9	$C(C)_2(O)$	0.12
10	OH(C)	4.45
	log γ	9.88

$\Delta G = -1.364 \log \gamma =$ −13.5

standard state correction = 1.9

$\Delta G^{g\rightarrow H_2O} =$ −11.6

(B)



II

group	group	contribution[18]
1-9		5.43
10	$O^+H_2(C)$	18.9[a]
	log γ	24.3

$\Delta G = -1.364 \log \gamma =$ −33.2

standard state correction = 1.9

Born charging component = −43.4

$\Delta G^{g\rightarrow H_2O} =$ −74.7

[a] Data from ref 20.

phisticated treatment of ion hydration energies. However, if an approximate rate–equilibrium relationship holds the free energy for the formation of the nitrenium ion/nucleophile complex should be an indicator of the relative reactivity of a given nucleophile for a particular site. We therefore obtained the MNDO heats of formation and estimated entropies and energies of hydration as described above for a further selection of adducts. Combining these with the data in Table IV gave the estimated free energies collected in Table V. For consistency we calculated the entropies of the nucleophiles ignoring the vibrational contributions; however, these agreed with the experimentally determined values[60] within 0.1 cal mol^{-1} K^{-1} in every case. Similarly we used the MNDO heats of formation in each case but that of HO^-. Here the MNDO value is far too positive. This failure is connected with the fact that the single ζ basis set does not allow for changes in the effective sizes of the orbitals. For normal molecules this is not usually serious but is apparently so for small highly localized anions both in MNDO and in other single ζ treatments.[61] In MeO^- [61] where the negative charge is somewhat delocalized or Cl^- [23b] where the orbital is more diffuse this ceases to be a problem in MNDO.

Turning to the results in Table V it can be seen that, at least to the approximation that we have been able to estimate them, the entropy contributions to the free energies of forming the complexes are essentially constant. No effect on the site of adduct formation is then expected from this source. For the reactions of the uncharged nucleophiles the hydration terms favor adduct formation. This arises in our treatment from the fact that the highly polar OH_2^+ and NH_3^+ groups are very much more strongly solvated than are the free nucleophiles. For the anionic nucleophiles the opposite is true. Notice in particular the enormously negative gas-phase energies of forming these adducts due to the annihilation of the charges associated with the fragments. Including the effects of solvation reduces the stability of the adduct to a level comparable to that of the neutral nucleophiles. From these energies the calculated nucleophilic strengths in aqueous solution increase in the order $H_2O < Cl^- < NH_3 < OH^-$ and approximately correlate with the Swain–Scott nucleophilic constants.[62] Since in the gas-phase reaction the anionic will always be stronger than the uncharged nucleophiles, the role of the solvent cannot be ignored. Treating the molecule as a uniformly charged sphere and assigning a constant hydrogen-bonding contribution to the attached nucleophile regardless of its environment is obviously a gross assumption. Nevertheless this procedure gives apparently reasonable results, although the more subtle effects from this source which may differentiate between different carbon atoms of the electrophile will clearly be obscured by this treatment.

Unimolecular Stability of Nitrenium Ions. Finally we ask how stable nitrenium ions are likely to be with respect to unimolecular decay. The azepenium ion **28** (ΔH_f = 225.9 kcal mol^{-1}) is calculated to be 16 kcal mol^{-1} more stable than **12a**. We have not studied the possible modes for this conversion. By analogy with MINDO/3 calculations[63] for the analogous conversion **29** → **30**, this would be expected to take place via the intermediates **31** (ΔH_f = 280.5 kcal mol^{-1}) and **32** (ΔH_f = 265.0 kcal mol^{-1}). The predicted activation energy is therefore at least 39 kcal mol^{-1}, seeming to rule out this mode of unimolecular decay at room temperature for **12a** and presumably related arylnitrenium ions. A greater variety of rearrangements suggest themselves for the acylnitrenium ions. The MNDO pathways for the conversion of **9** to dimethyloxaziranium cation **33** (ΔH_f = 237.8 kcal mol^{-1}) and the quaternary isocyanate **34** (ΔH_f = 166.9 kcal mol^{-1}) are shown in Figure 9. The transition state for **9** → **34** was located approximately from a two-dimensional grid search based on the Me–CO bond length and the C–CO–N bond angle. Since the stability of nonclassical species involving five-coordinate carbon

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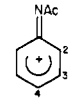
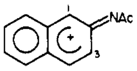
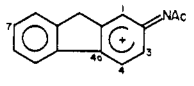
(60) Stull, D. R.; Prophet, H. "JANAF Thermochemical Tables", *Natl. Stand. Ref. Data Ser.* (U.S. Natl. Bur. Stand.) **1971**, *NSRDS-NBS37*.

(61) Dewar, M. J. S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 784.

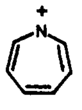
(62) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141. Pearson, R. G.; Sobel, H.; Songstad, J. *Ibid.* **1968**, *90*, 319.

(63) Cone, C.; Dewar, M. J. S.; Landman, D. *J. Am. Chem. Soc.* **1977**, *99*, 372.

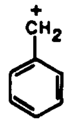
Table V. Calculated Free Energies for the Formation of *N*-Acetyl-*N*-arylnitrenium Ion/Nucleophile Adducts in the Gas Phase [ΔG(g)] and Corrected for the Estimated Effects of Hydration [$\Delta\Delta G^{g\rightarrow H_2O}$]

electrophile	adduct	ΔH(g), kcal mol^{-1}	$-T\Delta S$(g), cal mol^{-1} K^{-1}	ΔG(g), kcal mol^{-1}	$\sim\Delta\Delta G^{g\rightarrow H_2O}$, kcal mol^{-1}	ΔG(aq), kcal mol^{-1}
	*N*-H_2O	28.6	11.4	40.0	−25	15
	2-H_2O	1.3	11.4	12.7	−19	−6
	4-H_2O	5.0	11.4	16.4	−19	−3
	N-Cl	−141.5	10.4	−131.1	115	−16
	2-Cl	−155.3	10.3	−145.0	122	−23
	4-Cl	−156.2	10.3	−145.9	121	−25
	N-NH_3	−13.2	11.6	−1.6	−20	−22
	2-NH_3	−25.8	11.5	−14.3	−14	−28
	4-NH_3	−21.4	11.5	−9.9	−14	−24
	N-OH	−162.7	11.4	−151.3	126	−25
	2-OH	−185.3	11.4	−173.9	131	−43
	3-OH	−130.5	11.4	−119.1	132	13
	4-OH	−183.3	11.4	−171.9	132	−40
	*N*-H_2O	44.4	11.5	55.9	−27	29
	1-H_2O	3.7	11.5	15.2	−21	−6
	3-H_2O	20.5	11.5	32.0	−21	11
	1-Cl	−149.3	10.5	−138.8	114	−25
	3-Cl	−135.8	10.5	−125.3	114	−11
	*N*-H_2O	43.4	11.6	55.0	−27	28
	1-H_2O	16.2	11.6	27.8	−21	7
	3-H_2O	13.6	11.6	25.2	−21	4
	4a-H_2O	19.9	11.6	31.5	−21	11
	7-H_2O	26.0	11.5	37.5	−22	16
	1-Cl	−137.5	10.6	−126.9	114	−13
	3-Cl	−138.9	10.6	−128.3	114	−14
	4-Cl	−87.2	10.6	−76.6	113	36
	4a-Cl	−131.6	10.6	−121.0	114	−7
	7-Cl	−126.1	10.5	− 115.6	113	−3

are greatly underestimated by MNDO, we did not attempt to refine the transition-state geometry further.

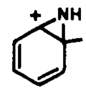


28

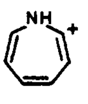


29

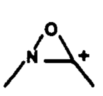
30



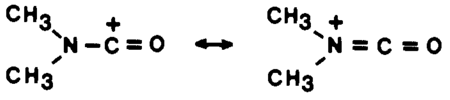
31



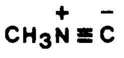
32



33



34

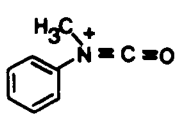


$CH_3\overset{+}{N}\equiv\overset{-}{C}$

35

$CH_3C\equiv N$

36



37

This failure, which does not apparently apply to the MNDO energies of cyclic oxonium or ammonium ions,[64] is common to ab initio calculations using small basis sets where it seems to be connected with the neglect of polarization functions. A good example is provided by the conversion of **35** to **36**. The calculated MNDO activation energy is ~65 kcal mol^{-1}[65], while a recent double ζ ab initio calculation gave a value of 60.4 kcal mol^{-1}.[66] Including d functions on the carbon and nitrogen atoms reduced this barrier to 45.5 kcal mol^{-1},[67] 4.6 kcal mol^{-1} of the remaining discrepancy between this and the experimental value (38.4 kcal mol^{-1}[68]) being ascribed[67] to zero-point and correlation energy terms. Here therefore we suspect that the barrier separating **9**

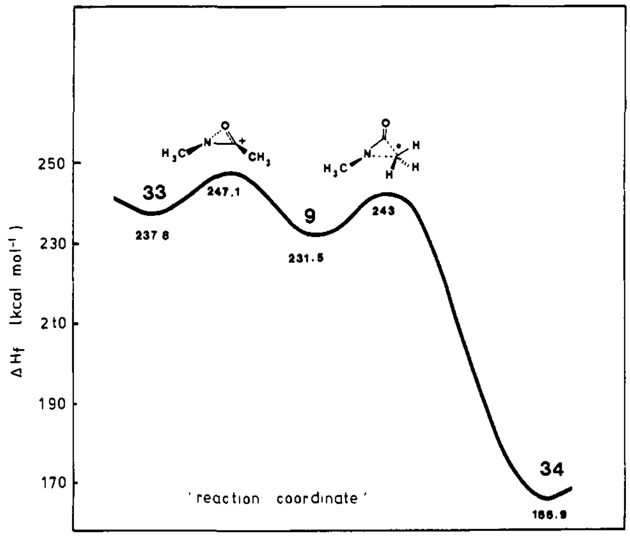


Figure 9. Calculated energy profile for conversion of **9** to **33** and **34**.

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[64] Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1979**, *101*, 783.

[65] Rzepa, H. S., private communication.

[66] Liskow, D. H.; Bender, C. F.; Schaeffer, H. F., III *J. Am. Chem. Soc.* **1972**, *94*, 5178. *J. Chem. Phys.* **1972**, *57*, 4509.

[67] Saxe, P.; Yamaguchi, Y.; Pulay, P.; Schaeffer, H. F., III *J. Am. Chem. Soc.* **1980**, *102*, 3718.

[68] Schneider, F. W.; Rabinovitch, B. S. *J. Am. Chem. Soc.* **1962**, *84*, 4215. Rabinovitch, B. S.; Gilderson, P. W.; Schneider, F. W. *Ibid.* **1965**, *87*, 158.

and **34** is considerably less than that predicted by the MNDO calculations and may not exist at all. In either case the *N*-methyl-*N*-acetylnitrenium ion **9** is expected to be unstable with respect to conversion to **34**. In the aromatic series the situation is slightly different, the conversion of **12b** to **37** (ΔH_f = 193.1 kcal mol^{-1}) being much less exothermic. The reaction is therefore expected to be much less facile. However, as discussed above, our procedure does not allow a theoretical estimate of the activation barrier in this particular case. We also examined the conversion of **12b** to a species analogous to **33**, finding that such a structure did not represent a statble point on the MNDO potential surface.

Conclusion

The parent nitrenium ion **6** is a ground-state triplet. Substitution of the hydrogen atoms leads to considerable electron transfer to the nitrogen atom, especially in the aromatic series where the NH or $NCOCH_3$ group carries only ~20% of the positive charge. Electron transfer stabilizes both states approximately equally although the actual transfer of charge in the singlet is greater, the net result being a differential stabilization of the singlet which in the aromatic series falls below the triplet state.

The coefficients of the nonbonding orbital of the isoconjugate arylmethyl cations give a rough guide to the most reactive positions of the arylnitrenium ions toward simple nucleophiles. Detailed MNDO calculations give an apparently consistent picture of the same type of reactivity. Entropy effects appear to be unimportant in determining regioselectivity. Hydration energies must be taken into account if the order of reactivity of nucleophiles toward the nitrenium ions is to be predicted correctly. It is suggested that the calculated free energy for the formation of the nucleophile/nitrenium ion adduct be used as an indicator of relative reactivity.

Aryl nitrenium ions are not expected to undergo unimolecular decay at a significant rate. There is a high (>39 kcal mol^{-1}) barrier to rearrangement of the *N*-phenylnitrenium ion **12a** to the azepenium ion **28**. A quanternary isocyanate **37** is more stable than **12a**, but the limitations of the theoretical procedure prevent the estimation of the activation energy for this process.

Acknowledgment. We thank the National Institutes of Health for financial support for this research through Contract CP 85628 and Grant No. CA 23712.

Appendix

Estimation of Hydration Energies (See Chart I). In the absence of parameters for *N*-acetylimines we replace the nitrogen atom by CH. Hydration energies calculated in this way will be too positive by an amount corresponding approximately to the hydrogen-bonding interaction between the imine-like nitrogen and the solvent. This error should, however, be considerably smaller than the difference between the hydration energies of benzene and pyridine (3.4 kcal mol^{-1}).

In the Hine and Mookerjee scheme, log γ is evaluated in terms of group contributions where γ is the activity coefficient in the ideal gas phase relative to infinitely dilute aqueous solution. The hydration energy of, for example, **22b** is calculated as follows. The individual contributions corresponding to the numbering scheme in I total 9.88. This is then converted to free energy and changed from the concentration-based standard used by Hine to that used here (cf. footnote *d* of Table IV). The determination for the oxonium ion **22a** proceeds similarly, using the log γ contribution for $OH_2{}^+(C)$ deduced before. In this case, since it is an ion, we add the contribution due to charging the cavity in which the molecule resides. This is calculated from eq 2 as described under Procedure.

Supplementary Material Available: Optimized Cartesian coordinates for all species studied in this report (35 pages). Ordering information is given on any current masthead page.

Charge-Transfer Band of 7-Norbornenone. Circular Dichroism of (1*R*)-2-Deuteriobicyclo[2.2.1]hept-2-en-7-one and (1*R*)-2-Methylbicyclo[2.2.1]hept-2-en-7-one

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Received December 26, 1980

Abstract: (1*R*)-[2-^{2}H]Bicyclo[2.2.1]hept-2-en-7-one (**1**), bicyclo[2.2.1]hept-2-en-7-one (7-norbornenone) (**2**), and (1*R*)-2-methylbicyclo[2.2.1]hept-2-en-7-one (**3**) were prepared from (1*R*)-7,7-dimethoxybicyclo[2.2.1]heptan-2-one *p*-toluenesulfonylhydrazone of known absolute configuration and optical purity. Circular dichroism spectra of deuterio ketone **1** ($\Delta\epsilon_{273}{}^{\max}$ −0.033, $\Delta\epsilon_{224}{}^{\max}$ −0.028, and $\Delta\epsilon_{213}{}^{\max}$ +0.029) and methyl ketone **3** ($\Delta\epsilon_{275}{}^{\max}$ −0.62, $\Delta\epsilon_{226}{}^{\max}$ +2.10, and $\Delta\epsilon_{208}{}^{\max}$ −3.0) confirm the existence of a new low-lying electronic transition near 225 nm whose existence and origin have been questioned during the past 20 years. The partial charge-transfer nature of this band is supported by preliminary calculations in the localized orbital random phase approximation.

7-Norbornenone (**2**) and its derivatives have been of interest to chemists for more than 20 years, with respect to both the phenomenon of neighboring group participation (or interaction)[2] and the existence and nature of a "mystery band" reportedly[3] occurring near 233 nm (ϵ 1290) in the ultraviolet (UV) absorption spectrum of **2**. This band was attributed to "a very unique transannular interaction between the non-conjugated double bond and the carbonyl group".[3] The 233-nm absorption band was shortly thereafter cited as evidence for an intermolecular charge-transfer $\pi \rightarrow \pi^*$ transition.[4-6] 7-Norbornenone also

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[1] (a) University of Nevada. (b) On leave from Adam Mickiewicz University, Poznan, Poland. (c) H. C. Ørsted Institute. (d) Southern Illinois University, Edwardsville.

[2] (a) Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183–4184. (b) For a recent summary, see: Tanida, H. *Acc. Chem. Res.* **1968**, *1*, 239–245.

[3] Norton, C. J. Ph.D. Dissertation, Harvard University, 1955; pp 103, 122 ff.

[4] Wilcox, C. F.; Winstein, S.; McMillan, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5450–5454.

0002-7863/81/1503-4291$01.25/0