than that of C_2H_4 by at least 13 kcal/mol.

The application of such acid–base models to hydrocarbon reactivity is by no means restricted to Ag(110). For example, Kokes[35] previously noted that propylene and toluene could be dissociatively adsorbed on zinc oxide whereas ethylene could not. This behavior was explained in terms of a cutoff in the activity for dissociative adsorption between $pK_a = 35$ and 36 based on aqueous dissociation constants. This behavior is also consistent with the gas-phase acidities of these species; indeed, the acidity difference between C_3H_6 and C_2H_4 is much greater in the gas phase than in aqueous solution. These correlations point out the importance of acid–base properties in catalytic processes such as oxidative dehydrogenation which may involve proton-transfer reactions.

Conclusions

1. Propylene reacts facilely with O(a) on Ag(110) at 140 K to yield OH(a) and C(a). 2. The reaction probability for this reaction is higher than that of ethylene with O(a). A propylene precursor state appears involved. 3. Propylene is less reactive than C_2H_2 which can react to form and displace H_2O from the surface at this temperature. 4. Thermal desorption experiments following the reaction of C_3H_6 with O(a) produce H_2O, CO_2, and C(a). There is no evidence for partially hydrogenated carbon species on the surface at any temperature, although there is evidence for association of C and O in the mixed adlayer leading to CO_2 formation.

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Registry No. Propylene, 115-07-1; silver, 7440-22-4; oxygen, 17778-80-2.

Theoretical Study of Gas-Phase Methylation and Ethylation by Diazonium Ions and Rationalization of Some Aspects of DNA Reactivity[1]

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Abstract: MNDO semiempirical molecular orbital calculations were carried out for the bimolecular reactions of the methyl- and ethyldiazonium ions with formamide, imidazole, pyrimidine, methylamine, and water with complete geometry optimization of all stable species and transition states. The activation barriers for methylation were larger, spanned a wider range, and indicated a greater preference for N- rather than O-alkylation than did those for ethylation. These results were rationalized on the basis of structural and electronic features of the transition states and in turn provided a simple explanation for the parallel behavior observed experimentally when DNA is exposed to diazonium ion precursors and which has been widely discussed in terms of the carcinogenic potency of the latter.

Introduction

Many carcinogenic alkylating agents are believed to owe their activity to conversion to highly reactive diazonium ions (**1**). Among these are the *N*-alkyl-*N*-nitrosoureas,[2a] *N*-alkyl-*N'*-nitro-*N*-nitrosoguanidines,[2b] 1,3,3-trialkyltriazenes,[2c] *N*,*N*-dialkylnitrosamines,[2d] 1-aryl-3,3-dialkyltriazenes,[2e] and probably the dialkylhydrazines.[2f] In vivo and in vitro DNA binding studies, in which sufficiently complete product analyses have been carried out, reveal that a great many of the nucleophilic sites are simultaneously alkylated by these agents.[3] However, a clear distinction exists between the methylating and ethylating agents of this type in that the latter react more extensively with the oxygen, relative to the nitrogen centers, than do the former.[4] This observation is of special significance in the search for meaningful relationships between chemical structure and biological activity since O^6-alkylation of guanine and possibly O^4-alkylation of thymine are believed to be critical mutagenic events, whereas 7-alkylation of guanine (the principal site of methylation) may be innocuous.[5] Thus several workers have sought an explanation for the different reactivities of ethylating and methylating agents of this kind toward the oxygen atoms of nucleic acids and their constituents. Swain–Scott constants,[9] hard–soft acid–base in-

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(1) Presented in part at the Sanibel Symposium on Quantum Biology and Quantum Pharmacology, Palm Coast, Fla., March 5–7, 1981.

(2) (a) Snyder, J. K.; Stock, L. M. *J. Org. Chem.* **1980**, *45*, 1990–1999. (b) Lawley, P. D.; Thatcher, C. J. *Biochem. J.* **1970**, *116*, 693–707. (c) Sieh, D. H.; Michejda, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 442–445. (d) Lai, D. L.; Arcos, J. C. *Life Sci.* **1980**, *27*, 2149–2165. (e) Preussman, R.; von Hodenberg, A.; Hengy, H. *Biochem. Pharmacol.* **1969**, *18*, 1–13. (f) Preussman, R.; Druckrey, H.; Ivankovic, S.; von Hodenberg, A. *Ann. N. Y. Acad. Sci.* **1969**, *163*, 697–716.

(3) See, for example: (a) Beranek, D. T.; Weiss, C. C.; Swenson, D. H. *Carcinogenesis* **1980**, *1*, 595–606. (b) Margison, G. P.; O'Connor, P. J. In "Chemical Carcinogens and DNA"; Grover, P. L., Ed.; CRC Press: Boca Raton, Fla., 1979; Vol. 1, pp 111–159. (c) Singer, B. *Prog. Nucleic Acid Res.* **1975**, *15*, 219–284.

(4) Singer, B. *Nature (London)* **1976**, *264*, 333–339. Singer, B. *J. Natl. Cancer Inst.* **1979**, *62*, 1329–1339.

(5) For example, the carcinogenic potency of alkylating agents has been shown to correlate with the extent to which they lead to O^6- but not 7-alkylation of DNA guanine residues[6] while the production of tissue-specific tumors correlates with the persistence of O^6-alkylguanine in the susceptible tissues.[7] It has also been shown that templates containing O^6-alkylguanine give rise to transcriptional errors in both DNA and RNA in vitro syntheses, whereas those containing 7-alkylguanine resides do not.[8]

(6) Lawley, P. D. *Brit. Med. Bull.* **1980**, *36*, 19–24. Newbold, R. F.; Warren, W.; Medcalf, A. S. C.; Amos, J. *Nature (London)* **1980**, *283*, 596–599. Loveless, A. *Ibid.* **1969**, *223*, 206–207.

(7) Kleihues, P.; Doerjer, G.; Keefer, L. K.; Rice, J. M.; Roller, P. P., Hodgson, R. M. *Cancer Res.* **1979**, *39*, 5136–5140. Frei, J. V.; Swenson, D. H.; Warren, W.; Lawley, P. D. *Biochem. J.* **1978**, *174*, 1031–1044. Goth, R.; Rajewsky, M. F. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 639–643.

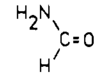
(8) O'Connor, P. J.; Saffhill, R.; Margison, G. P. In "Environmental Carcinogenesis. Occurrence, Risk Evaluation and Mechanisms"; Emmelot, P., Kriek, E., Eds.; Elsevier/North Holland: Amsterdam, 1979; p 73–96. Singer, B. *Prog. Nucl. Acid Res.* **1979**, *23*, 151–194.

0002-7863/83/1505-0349$01.50/0

teractions,[9] and calculated alkyl group affinities[10] have been variously invoked. However, while some of these studies successfully correlate the observations, none satisfactorily explain the underlying physical interactions responsible. We have, therefore, undertaken a theoretical study of the gas-phase reactions of **1a** and **1b** with a group of simple oxygen and nitrogen nucleophiles with functional groups characteristic of those in the nucleic acid bases. In this way we hoped to uncover fundamental electronic properties of the species involved which may be of value in the interpretation of the solution-phase reactions of related species, particularly the nucleic acid bases themselves.

$R\overset{+}{N}\equiv N$

1



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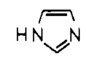
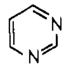


3



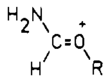
4

CH_3NH_2

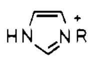
5

H_2O

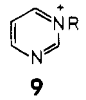
6



7



8



9

$CH_3\overset{+}{N}H_2R$

10

$H_2\overset{+}{O}R$

11

a $R=CH_3$ b $R=C_2H_5$

Procedure

All calculations were carried out by using the MNDO semiempirical molecular orbital procedure described by Dewar and Thiel.[11] For open-shell systems the "half-electron" approximation[12] was used. Where CI was introduced this was based on the eigenvectors of the first excited singlet as described by Dewar and Doubleday.[13] With a few exceptions noted in the text, the geometries of all species were completely optimized with no geometrical constraints. Transition-state geometries were first located approximately from contour maps of the type discussed later. The latter were generated by fixing the forming and breaking bonds at the appropriate lengths (varied in steps of 0.2 Å) and minimizing the energy of the system with respect to the remaining variables within the constraints of C_s symmetry. Smoothed plots were obtained by quadratic interpolation. Approximate transition-state geometries deduced in this way were refined in a procedure involving the minimization of the scalar gradient of the energy as suggested by McIver and Komornicki.[14] Where calculation and diagonalization of the force constant matrix revealed the presence of more than one negative eigenvalue (and the structure therefore not a genuine transition state[14]), a "down-hill" displacement based on the eigenvectors for each process not connected with the reaction was made and the structure rerefined until the single negative eigenvalue criterion[14] was satisfied.

Results and Discussion

Methyl and Ethyl Diazonium Ions. The calculated structures and charge distributions of **1a** and **1b** are shown in Figure 1. The MNDO geometry of **1a** is very similar to that predicted by ab initio calculations at the 4-31G[15a] and double-ζ[15b] levels. In particular, the present calculations reproduce the interestingly short N–N distance commented upon by Vincent and Radom.[15a] The calculated charge distribution is also similar to that predicted by the ab initio calculations[15] although MNDO underestimates the polarity of the CH groups. The MNDO heat of formation of **1a** (223.5 kcal mol^{-1}) is close to an earlier[16] ion cyclotron resonance spectroscopic determination (223 kcal mol^{-1}) but higher than a subsequent[17] photoionization value (209.4 kcal mol^{-1}). From the latter, and a recent determination of 261.3 kcal mol^{-1} for the heat of formation of CH_3^+, the experimental heat of reaction for eq 1 is 51.9 kcal mol^{-1}, which is almost identical with the ab initio STO-3G result[15a] (51.6 kcal mol^{-1}). Paradoxically, calculations employing superior basis sets lead to markedly lower values. Thus Vincent and Radom[15a] obtained ΔH = 28.5 kcal mol^{-1} at the 4-31G level, while Simonetta and co-workers, using a slightly more flexible basis set designated (9/5), obtained a value of 25.5 kcal mol^{-1} which fell to 18.4 kcal mol^{-1} when polarization functions were added.[15b]

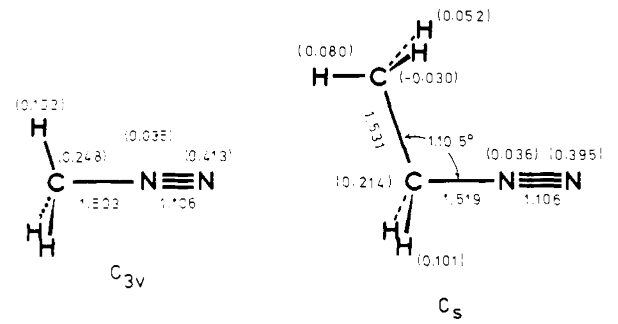


Figure 1. Calculated geometries and (charge distributions) in **1a** and **1b**.

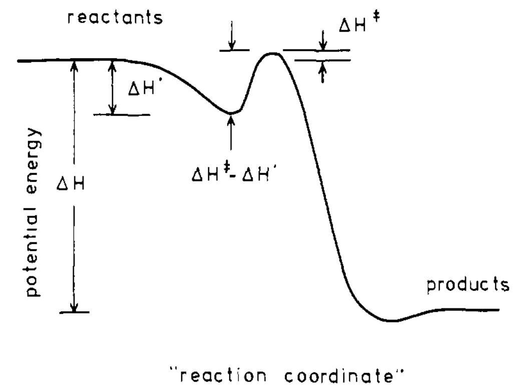


Figure 2. Calculated reaction profile (schematic) corresponding to eq 3 and 4.

$$CH_3N_2^+ \rightarrow CH_3^+ + N_2 \quad (1)$$

$$C_2H_5N_2^+ \rightarrow C_2H_5^+ + N_2 \quad (2)$$

The corresponding MNDO value is 28.4 kcal mol^{-1}. This unfortunately includes a fairly large, nonsystematic, error in the calculated heat of formation of CH_3^+ which is underestimated by 17.4 kcal mol^{-1}. Using the experimental heat of formation for CH_3^+ leads to a semiempirical prediction of ΔH = 45.8 kcal mol^{-1} for eq 1. From the calculated heats of formation of $C_2H_5^+$ (219.7 kcal mol^{-1}, obsd, 216.0 kcal mol^{-1} [18]) and of **1b** (213.8 kcal mol^{-1}),

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[9] Lawley, P. D. In "Chemical Carcinogens"; Searle, C. E., Ed.; ACS Monograph, No. 173, American Chemical Society: Washington D.C., 1976, pp 83–244. Lawley, P. D. In ref 3b, pp 1–36.

[10] Pullman, A.; Armbruster, A. M. *Theor. Chim. Acta* **1977**, *45*, 249–256.

[11] Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907, 4907–4917. *Theor. Chim. Acta* **1977**, *46*, 89–104.

[12] Dewar, M. J. S.; Hashmall, J. A.; Vernier, C. G. *J. Am. Chem. Soc.* **1968**, *90*, 1953–1957. Longuet-Higgins, H. C.; Pople, J. A. *Proc. Phys. Soc., London*, **1955**, *68A*, 591–600.

[13] Dewar, M. J. S.; Doubleday, C. *J. Am. Chem. Soc.* **1978**, *100*, 4935–4941.

[14] McIver, J. W., Jr.; Komornicki, A. *Chem. Phys. Lett.*, **1971**, *10*, 303–306. Flanigan, M. C.; Komornicki, A.; McIver, J. W., Jr. In "Modern Theoretical Chemistry"; Segal, G. A., Ed.; Plenum Press: New York, 1977; Vol. 9.

[15] (a) Vincent, M. A.; Radom, L. *J. Am. Chem. Soc.* **1978**, *100*, 3306–3312. (b) Demontis, P.; Ercoli, R.; Gamba, A.; Suffritti, G. B.; Simonetta, M. *J. Chem. Soc., Perkin Trans. 2* **1981** 488–493.

[16] Foster, M. S.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1972**, *94*, 2425–2431.

[17] Foster, M. S.; Williamson, A. D.; Beauchamp, J. L. *Int. J. Mass Spectrom. Ion Phys.* **1974**, *15*, 429–436.

[18] Traeger, J. C.; McLoughlin, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 3647–3652.

Table I. Calculated Energetics[a] of the Gas-Phase Bimolecular Alkylation of **2**–**6** by $CH_3N_2^+$ (1a) and $C_2H_5N_2^+$ (1b)

	ΔH_f[b]	methylation				ethylation			
		$\Delta H'$[c]	$\Delta H^{\ddagger}$[d]	$\Delta H^{\ddagger} - \Delta H'$	ΔH[e]	$\Delta H'$[c]	$\Delta H^{\ddagger}$[d]	$\Delta H^{\ddagger} - \Delta H'$	ΔH[e]
formamide	−39.5	−9.8	7.6	17.4	−47.6	−9.2	1.8	11.0	−44.8
imidazole	33.2	−10.2	−0.4	9.8	−64.9	−9.7	1.3	11.0	−60.2
pyrimidine	34.9	−3.9	10.2	14.1	−48.3	−4.8	7.7	12.5	−43.6
methylamine	−7.5	−5.4	8.9	14.3	−45.7	−3.2	7.5	10.7	−41.7
water	−60.9	−5.7	15.2	20.9	−19.7	−5.3	7.4	12.7	−16.5

[a] All energies in kcal mol^{-1}. [b] Calculated heat of formation of nucleophile. Other values: $\Delta H_f(\mathbf{1a}) = 223.5$; $\Delta H_f(\mathbf{1b}) = 213.8$; $\Delta H_f(N_2) = 8.0$. [c] Stabilization energy of ion–dipole complex. $\Delta H' = \Delta H_f(\text{complex}) - \Sigma \Delta H_f(\text{reactants})$. [d] Activation barrier relative to reactants. $\Delta H^{\ddagger} = \Delta H_f(\text{transition state}) - \Sigma \Delta H_f(\text{reactants})$. [e] Heat of reaction.

$\Delta H = 13.9$ kcal mol^{-1} is predicted for eq 2. Thus this process is predicted to be ~32 kcal mol^{-1} less endothermic than that of eq 1. The corresponding experimental data are not available. However, some confidence in the MNDO result can be derived from the satisfactory prediction of the analogous quantity for the isoelectronic species CH_3CO^+ and $C_2H_5CO^+$(calcd,[19] 33.8; obsd,[20] 38.0 kcal mol^{-1}).

Even taking into account the likely effects of solvation,[21] the large endothermicity of eq 1 essentially excludes this mode of decomposition of **1a** in aqueous solution at ordinary temperatures while the MNDO results suggest that this cannot be ruled out for **1b** on similar grounds. However, from a comprehensive survey of the available literature, Friedman[22] has concluded that there is no experimental basis for invoking free carbenium ions in the reactions of primary alkyldiazonium ions. More recent experimental studies of the alkylation of nucleic acids and their constituents by precursors of $n\text{-}PrN_2^+$ also argue strongly against the significant involvement of the corresponding carbenium ions.[23]

Gas-Phase S_N2 Reactions. Next we studied the bimolecular alkylation of the nucleophiles **2**–**6** (Table I) leading to **7**–**11** according to eq 3 and 4. The general shapes of the calculated

$$Nu + CH_3N_2^+ \rightarrow NuCH_3^+ + N_2 \qquad (3)$$

$$Nu + C_2H_5N_2^+ \rightarrow NuC_2H_5^+ + N_2 \qquad (4)$$

reaction profiles (Figure 2) for the processes described by eq 3 and 4 were similar to those currently accepted for gas-phase ion–molecule reactions.[24] In particular, the transition states were preceded by shallow minima corresponding to loose ion–dipole complexes. In each case the nucleophile and the diazonium ion were separated by 3.0–3.4 Å with the former oriented such that its permanent dipole moment was approximately directed toward the centroid of charge of the latter. The binding in these species was judged to be entirely electrostatic on several criteria: (a) the calculated geometries of the nucleophile and diazonium ion moieties were essentially those of the isolated species (distortions present amounted to <1 kcal mol^{-1}); (b) the electron transfer between the two components was calculated to be $<10^{-3}$ e; and (c) a fair correlation ($r = 0.93$) existed between $\Delta H'$ and the permanent dipole moments of the nucleophiles. The relevant energy quantities, which refer to completely optimized geometries of all energy minima and transition states, are summarized in Table I. The overall activation barriers, $\Delta H^{\ddagger}$, for methylation are calculated to increase in the order **3** < **2** < **5** < **4** < **6**, while those for ethylation vary considerably less and lead to a different order in which those for *O*- are reduced relative to those for N-alkylation: **3** ≲ **2** < **6** ≲ **5** ≲ **4**. These trends exactly parallel the observed behavior of nucleic acids with precursors of **1a** and **1b** in aqueous solution discussed in the Introduction. Obviously the extrapolation of the present results calculated for the isolated reactants in the gas phase to aqueous solution entails several uncertainties. Nevertheless, a detailed understanding of the fundamental determinants of the gas-phase behavior, especially the heights of the activation barriers, should provide a valuable framework within which to discuss the solution-phase results. The relative $\Delta H^{\ddagger}$ values recorded in Table I can be rationalized in terms of a superposition of electrostatic and orbital mixing or, in Klopman's terminology, covalent interactions.[25] The form of the potential energy profile itself (Figure 2) affords a convenient *qualitative* separation of this kind. Thus the depths of the wells in which the ion–dipole complexes reside should provide an approximate indication of the magnitudes of the *electrostatic* stabilization of the transition states. The operation of stabilizing *covalent* interactions should then be reflected in the heights of the central barriers above the corresponding complexes. These trends can indeed be seen among the reactions of **1a**. Thus the lower values of the barriers $\Delta H^{\ddagger} - \Delta H'$ (Table I) are associated with lower ionization potentials of the corresponding nucleophiles (Table II) and more negative heats of reaction (ΔH in Table I), factors related to the availability of the nucleophile electrons to participate in bond formation and the strengths of the bonds formed by them. In contrast, the calculated barriers to decomposition of the complexes with **1b** are approximately constant (11.7 ± 1.0 kcal mol^{-1}), indicating a far smaller dependence on these factors. This appears to be the key to the different behavior of **1a** and **1b** toward **2**–**6**. For ethylation the order of increasing activation barriers is determined largely by electrostatic interactions while for methylation this order is modified by the superposition of covalent interactions which are greater for those nucleophiles in which the electrons are least tightly bound. The picture which emerges is therefore similar to that discussed by Klopman[25] in his analysis of Pearson's empirical hard–soft acid–base theory. In the language used by Klopman, **1b** is a "harder" electrophile than **1a** while, for example, **3** is a "softer" nucleophile than **2**.

Table II. Calculated (Observed) Adiabatic Ionization Potentials and Dipole Moments of **2**–**6**

molecule	IP (eV)	dipole moment (D)
formamide	10.2 (10.3[a])	3.09 (3.37[b])
imidazole	8.6 (8.8[c])	3.48 (3.8[d])
pyrimidine	9.9 (9.3[e])	2.00 (2.33[f])
methylamine	9.5 (9.0[a])	1.48 (1.31[b])
water	11.8 (12.6[a])	1.78 (1.85[b])

[a] Reference 21. [b] Nelson, R. D., Jr.; Lide, D. R.; Maryott, A. A. *Natl. Stand. Ref. Data Ser., Natl. Bur. Stand.* **1967**, *10*, 1. [c] Vertical IP: Cradock, S.; Findlay, R. H.; Palmer, M. H. *Tetrahedron* 1973, *29*, 2173–2181. [d] Griffiths, J. H.; Wardley, A.; Williams, V. E.; Owen, N. L.; Sheridan, J. *Nature (London)* 1967, *216*, 1301. [e] Asbrink, L.; Fridh, C.; Jonsson, B. Ö.; Lindholm, E. *Int. J. Mass. Spectrom. Ion Phys.* **1972**, *8*, 215–227. [f] Blackman, G. L.; Brown, R. D.; Burden, F. R. *J. Mol. Spectrosc.* **1970**, *35*, 444–454.

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(19) Using the experimental[18] value for $\Delta H_f(CH_3^+)$.

(20) Data from *J. Phys. Chem. Ref. Data* **1977**, *6*, Suppl. 1.

(21) McGarrity, J. F.; Smyth, T. *J. Am. Chem. Soc.* **1980**, *102*, 7303–7308.

(22) Friedman, L. In "Carbonium Ions"; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1970; Vol. 2, pp 655–713.

(23) Park, K. K.; Archer, M. C.; Wishnok, J. S. *Chem.-Biol. Interact.* **1980**, *29*, 139–144. Scribner, J. D.; Ford, G. P. *Cancer Lett.* **1982**, *16*, 51–56.

(24) Brauman, J. I.; Pellerite, M. J. *J. Am. Chem. Soc.*, **1980** *102*, 5993–5999. Wolfe, S.; Mitchell, D. J.; Schlegel, H. B. *Ibid.* **1981**, *103*, 7692–7694, 7694–7696. Sen Sharma, D. K.; Kebarle, P. *Ibid.* **1982**, *104*, 19–24.

(25) Klopman, G. In "Chemical Reactivity and Reaction Paths"; Klopman, G., Ed.; Wiley-Interscience: New York, 1974; pp 55–165.

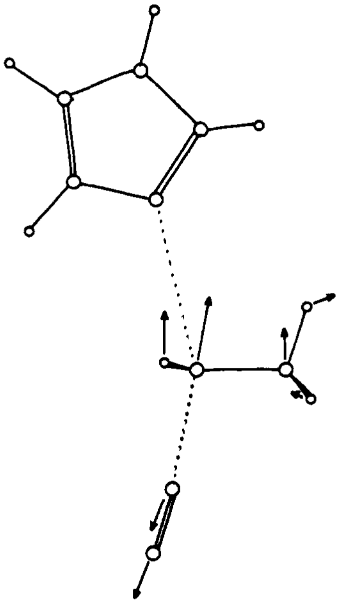

Figure 3. Calculated transition state structure for **1b** + **3**. The arrows indicate the form of the imaginary vibrational mode interconverting reactants and products.

The qualitative distinction between the transition states for methylation and ethylation is reflected in the calculated charge transfer between the nucleophile and the diazonium ion, this being much larger in the former series. The calculated transition-state geometries themselves correspond to the established representation of the S_N2 transition state in which the entering group, leaving group, and inverting carbon atom are approximately colinear. One example (**1b** + **3**) is shown in Figure 3, and key features of each are collected in Table III. The calculated bond lengths and the frequencies of the imaginary vibrations (calculated from the appropriate eigenvector of the force constant matrix[14]), interconverting reactants, and products show the transition states for ethylation to be "looser" than those for methylation. This result is conveniently discussed in terms of an approach elaborated by Jencks[26] and More O'Ferrall[27] and is especially interesting from the point of view of the present calculations. These provide a quantitative test of the relationships between the shapes of the potential energy surfaces of related species which must be assumed in the Jencks–More O'Ferrall approach.[28]

Contour diagrams of the MNDO potential energy surfaces corresponding to eq 3 and 4 for Nu = **3** are shown in Figures 4a and 4b, respectively. The pseudominimum energy pathways[29] connecting the reactant (upper right) and product (lower left) channels trace paths across the surfaces perpendicular to the isoenergy contours. Such diagrams are somewhat arbitrary in that they are not independent of the coordinate system.[30] However, this is of no consequence for the simple argument which follows. Taking the reaction of **3** + **1a** as a reference point, a perturbation which stabilizes the isolated carbenium ion, i.e., produces a lowering of the energy in the lower right region of the diagram, is expected to result in a displacement of the path containing the transition state in this direction. Comparing Figures 4a and 4b, it can be seen that this expectation is qualitatively confirmed, as it was in the cases (cf. Table III) of each of the other nucleophiles. This is of course just a two-dimensional application of the Hammond postulate[31] or Bell-Evans-Polanyi principle.[32]

The different behavior of **1a** and **1b** toward nucleophiles is directly related to their transition-state geometries which are themselves determined by the thermodynamics of a different reaction: the unimolecular dissociation of the corresponding diazonium ions. Since the covalent interactions diminish far more rapidly with distance than do the electrostatic,[33] their relative magnitudes in the transition states for methylation and ethylation emerge naturally in this picture.

By relating the transition-state structure to the thermodynamics of the S_N1 reaction, the Jencks–More O'Ferrall approach attaches a more precise meaning to the concept of "S_N1 character" in formally bimolecular reactions. Most previous discussions[9,34] of the tendencies of "S_N1-like reagents" to produce higher proportions of O-alkylated nucleic acids have taken place within the context of the Swain–Scott equation.[35] However, this implies that the observed behavior is due simply to the lower selectivity of ethylating agents, whereas it is evident from the careful in vitro studies of Beranek et al.[3a] that O-alkylation by ethylnitrosourea is significantly larger than would be expected on this basis.[36] The present calculations suggest a plausible rationalization of this behavior in terms of a different blend of electrostatic (long) and covalent (short) range interactions in the transition states in the two series. It is important to note that this difference is not reflected in the overall thermodynamics of the bimolecular reaction. Thus an almost perfect correlation ($r = 0.999$) exists between the calculated heats of reaction in the two series. Moreover, a similar correlation can be demonstrated between experimentally determined methyl and ethyl cation affinities of neutral bases and reveals no special affinity of $C_2H_5^+$ for oxygen.[37]

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(26) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705–718.

(27) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274–277.

(28) Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry" Harper & Row: New York, 1976; pp 246–250. Harris, J. M.; Shafer, S. G.; Moffatt, J. R.; Becker, A. R. *J. Am. Chem. Soc.*, **1979**, *101*, 3295–3300.

(29) Fukui, K. *J. Phys. Chem.*, **1970**, *74*, 4161–4163.

(30) Maggiora, G. M.; Christoffersen, R. E. In "Transition States of Biochemical Processes"; Gandour, R. D.; Schowen, R. L., Eds.; Plenum Press: New York, 1978; pp 119–163.

(31) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.

(32) Bell, R. P. *Proc. R. Soc. London, Ser. A* **1936**, *154*, 414–429. Evans, M. G.; Polanyi, M. *Trans. Faraday Soc.* **1935**, *31*, 875–894; **1936**, *32*, 1333–1360; **1938**, *34*, 11–29.

(33) The electrostatic interaction is expected to vary with the inverse first or second power of distance, tending to the latter at greater distances. In contrast, the covalent interactions should be roughly proportional to the squares of the relevant overlap integrals,[25] which themselves decay with the inverse third to seventh power of distance in the range 2.0–3.0 Å. Cf. Mulliken, R. S.; Rieke, C. A.; Orloff, D.; Orloff, H. *J. Chem. Phys.* **1949**, *17*, 1248–1267.

(34) Hathway, D. E.; Kolar, G. F. *Chem. Soc. Rev.* **1980**, *9*, 241–264. Lawley, P. D.; Orr, D. J.; Jarman, M. *Biochem. J.* **1975**, *145*, 73–84.

(35) Swain, C. J.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141–147.

(36) According to Swain and Scott,[35] the ratio of the second-order rate constants for the reactions of nucleophiles characterized by n_i and n_j, with an electrophile characterized by s, is given by eq i from which eq ii follows, the primed quantities referring to the reaction with a second electrophile.

$$\log (k_i/k_j) = (n_i - n_j)s \qquad \text{(i)}$$

$$\log (k_i/k_j) = \log (k_i'/k_j')(s/s') \qquad \text{(ii)}$$

Thus, allowing for the composition of the particular DNA type involved, the yields of alkylated bases relative to 7-alkylguanine produced by exposure to methyl and ethylnitrosoureas (MNU and ENU) should be linearly correlated with zero intercept and a slope of s(MNU)/s(ENU). Plotted in this way the data of Beranek et al.[3a] revealed an approximate correlation of this kind at the *nitrogen* positions, while the data for O^6-alkylation of guanine and O^4- (but curiously not O^2-) alkylation of thymine fell significantly off the trend line, indicating rates of ethylation ~5 and ~140 times those expected on the basis of the correlation for the remaining data.

(37) Experimental methyl and ethyl cation affinities of the neutral bases BH (MA[BH] and EA[BH]) were deduced from published data[38,39] via the equations:

$$\mathrm{MA[BH]} = \Delta H_f[\mathrm{BH}] - \Delta H_f[\mathrm{BMe}] - \Delta H_g{}^\circ[\mathrm{BMe}] + \Delta H_f[\mathrm{Me}^+] - \Delta H_f[\mathrm{NH_4}^+] + \Delta H_f[\mathrm{NH_3}]$$

$$\mathrm{EA[BH]} = \Delta H_f[\mathrm{BH}] - \Delta H_f[\mathrm{BEt}] - \Delta H_g{}^\circ[\mathrm{BEt}] + \Delta H_f[\mathrm{Et}^+] - \Delta H_f[\mathrm{NH_4}^+] + \Delta H_f[\mathrm{NH_3}^+]$$

where $\Delta H_g{}^\circ$[BR] refers to the enthalpy of the gas-phase proton-transfer equilibrium[38]

$$\mathrm{NH_4}^+ + \mathrm{BR} \rightleftarrows \mathrm{BRH}^+ + \mathrm{NH_3}$$

Linear regression gave MA = 1.070EA + 26.03, with a correlation coefficient of 0.999 and a standard deviation of 0.5 kcal mol^{-1} for seven oxygen and eight nitrogen bases.

(38) Taft, R. W.; Wolf, J. F.; Beauchamp, J. L.; Scorrano, G.; Arnett, E. M. *J. Am. Chem. Soc.* **1978**, *100*, 1240–1249, and sources cited there.

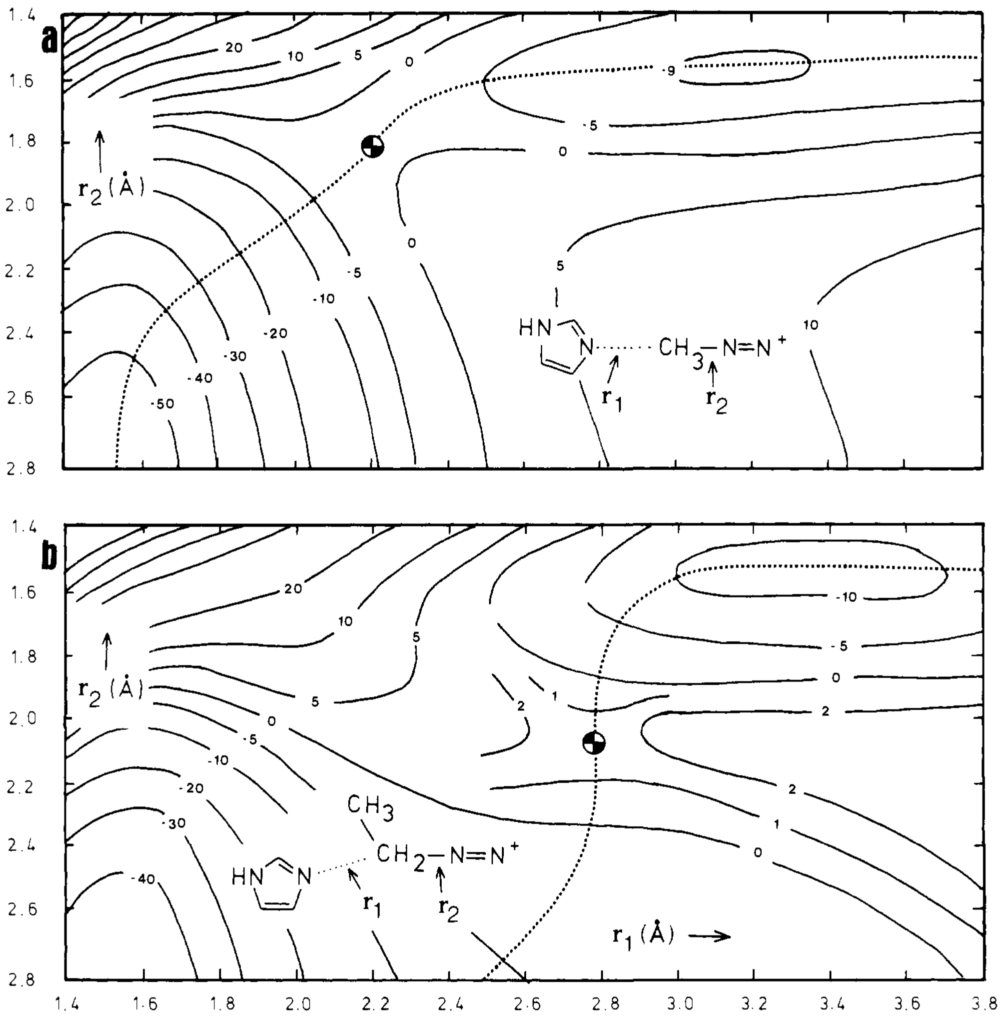

Figure 4. MNDO potential energy surfaces for the reactions of (a) **1a** + **3** and (b) **1b** + **3**. Energies in kcal mol^{-1} relative to isolated reactants. Pseudominimum energy pathweays, (----); transition states, ⊕.

Figure 5 shows the relationships between the calculated activation energies and heats of reaction in the two series derived from the data in Table I with additional data calculated for the degenerate reactions with N_2 as the nucleophile. The approximate linear relationship between these quantities for the reactions of **1a** is very much less precise for those of **1b**. As discussed above, covalent interactions between the alkyl group and the nucleophile, which are at a maximum in the product and paralleled in the transition states of **1a**, are largely absent in those involving **1b**. The partial correlation which does remain reflects the parallel between the electrostatic components alone.

Surface Crossing and the Inclusion of CI. In a context similar to the present one, Kaufman has cautioned that the potential energy surfaces for certain cation-molecule reactions are complicated by the presence of biradical states lying below those for the ion-molecule pairs at the reaction asymptotes.[40] This occurs in those reactions in which the electron affinity of the cationic reactant exceeds the ionization potential of its neutral partner. This is not the case for the processes described by eq 3 and 4. Thus, while the electron affinities of **1a** and **1b** have not been accurately determined, a value of 6.9 eV[41] can be estimated for that of **1a** and is significantly smaller than the adiabatic ionization potentials of **2**–**6**. The corresponding value for **1b** should, of course, be similar to, or somewhat less than, that for **1a**. On the other hand, the electron affinity of CH_3^+ (9.8 eV[18]) but not of $C_2H_5^+$ (8.3 eV[18,20]) exceeds the ionization potentials of **3**–**5**. Thus a surface crossing involving a state corresponding to the methyl radical and the radical cation of the nucleophile is expected when both the forming and breaking bonds are large. To probe this further we recalculated the energy surface for **1a** + **3** (Figure 4a) at the previously optimized geometries using a CI treatment[13] involving 24 configurations generated from single and double excitations among the four highest occupied and three lowest unoccupied orbitals of the "ground-state" configuration. The latter was found to dominate the CI wave function over the entire surface spanned by Figure 4a for which we were able to achieve SCF convergence in the S_1 state. This was unfortunately not possible on a small section of the upper right region. The calculated *difference* in energy between the ground and S_1 state for the remainder of the surface is shown in Figure 6. As expected the biradical state discussed above (labeled 1a″ in Figure 6) corresponds to the first excited singlet over much of the lower right portion of the surface. In further calculations in which the partial bonds to the CH_3 moiety were extended equally, the surface crossing occurred at 3.9 Å. This procedure is somewhat uncertain because of the use of geometries optimized with the single determinantal wave function and to the theoretical inconsistency inherent in the use of CI with the MNDO procedure.[42] Nev-

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(39) Pedley, J. B.; Rylance, J. "Sussex-N.P.L. Computer Analysed Thermochemical Data: Organic and Organometallic Compounds"; Sussex University: Brighton, England, 1977.

(40) Kaufman, J. J. *Int. J. Quantum Chem.: Quantum Biol. Symp. 6* **1979**, 503–510.

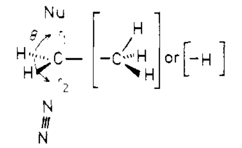
(41) This value follows from $\Delta H_f(CH_3N_2^+) = 209.4$ kcal mol^{-1} [17] and an estimate $\Delta H_f(CH_3N_2\cdot) \sim 50.1$ kcal mol^{-1}: Engel, P. S.; Wood, J. L.; Sweet, J. A.; Margrave, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 2381–2387.

(42) This arises because correlation effects are incorporated in the MNDO parametrization,[11] which is carried out without the inclusion of CI. Later inclusion of CI therefore results in a spurious energy lowering which typically amounts to ~5 kcal mol^{-1} for normal moelcules. For further discussion and parametrization of a correlated version of MNDO, see: Thiel, W. *J. Am. Chem. Soc.* **1981**, *103*, 1413–1420, 1420–1425, 1425–1431.

Table III. Calculated Properties of Transition States for Alkylation by Diazonium Ions

nucleophile	symmetry	$r_1{}^a$ (Å)	$r_2{}^a$ (Å)	θ^a	Σq^b	$i\nu$ (cm^{-1})^c
			$CH_3N_2^+$ (1a)			
formamide	$C_1{}^d$	2.41	2.22	180	0.924	294
imidazole	C_s	2.21	1.80	179	0.718	560
		(2.28^e)	(1.93^e)	(179^e)	(0.801^e)	
pyrimidine	C_s	2.16	1.85	179	0.718	563
methylamine	$C_1{}^f$	2.22	1.83	180	0.706	588
water	$C_s{}^g$	2.82	2.42	179	0.966	153
			$C_2H_5N_2^+$ (1b)			
formamide	$C_1{}^h$	2.97	2.19	155	0.921	272
imidazole	C_s	2.89	2.06	153	0.922	312
pyrimidine	C_s	3.26	2.15	150	0.923	267
methylamine	$C_1{}^i$	3.17	2.14	152	0.924	267
water	C_s	3.17	2.17	154	0.929	248

[a] Definition of r_1, r_2, and θ:



All transition-state geometries were calculated to have approximately the symmetry indicated above with deviations from formal symmetry due to rotations of the nucleophile out of the plane of the remainder of the skeleton as indicated. [b] Charge associated with the CH_3 or C_2H_5 group. [c] Frequency of the imaginary vibration corresponding to passage through the transition state. [d] NH_2 nonplanar. [e] 7 × 7 half-electron CI calculation. [f] Dihedral angle CNCH = 67°. [g] Dihedral angle HOCC = 0°. [h] Dihedral angle COCC = 211°. [i] Dihedral angle CNCC = 64°. [j] Dihedral angle HOCC = 90°.

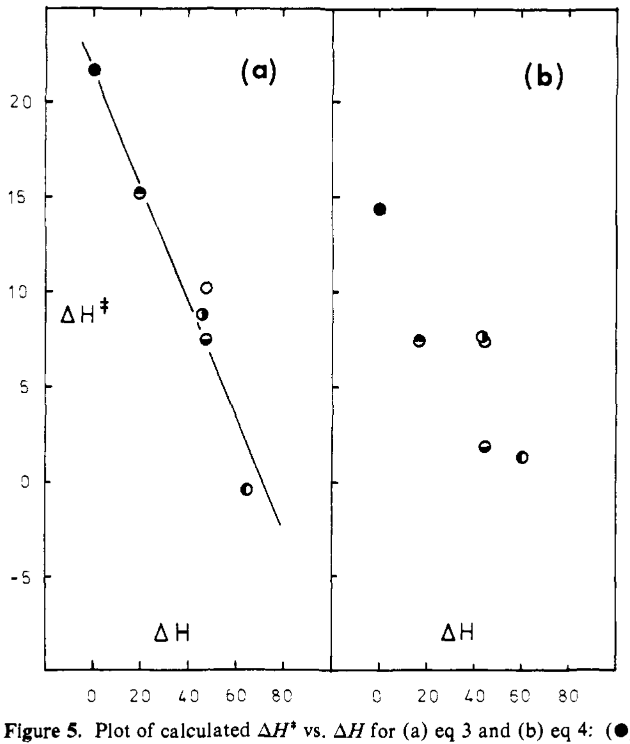


Figure 5. Plot of calculated $\Delta H^\ddagger$ vs. ΔH for (a) eq 3 and (b) eq 4: (●) N_2, (◒) formamide (2), (◐) imidazole (3), (○) pyrimidine (4), (◑) methylamine (5), (◓) water (6).

ertheless, the qualitative conclusion that the *bimolecular* reaction involving **1a** and **3** takes place entirely on the closed-shell energy surface that we were able to study should be reliable. This is also expected to hold for the remaining nucleophiles since these have

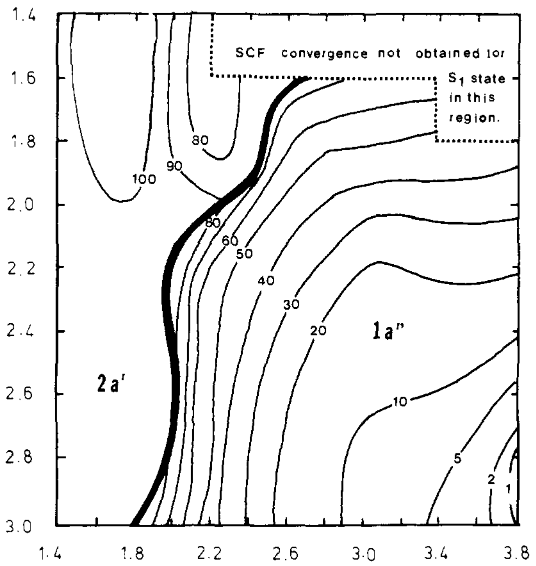


Figure 6. S_1–S_0 separation (kcal mol^{-1}) for the reaction of **1a** + **3**. Axes correspond to those of Figure 4. Heavy line indicates the crossing of the 1a″ and 2a′ states.

ionization potentials greater than that for **3**. Moreover, relocating the transition-state geometry for **1a** + **3** in a CI calculation (based on the seven largest contributing configurations) led to a geometry very similar to that obtained with the single determinantal wave function (cf. Table III).

Conclusions

The gas-phase S_N1 dissociation of the ethylidazonium ion (**1b**) is calculated to be ~32 kcal mol^{-1} less endothermic than that for the methyl analogue (**1a**).

The calculated gas-phase reaction profiles for the S_N2 alkylation of six nucleophiles studied revealed the presence of energy minima corresponding to ion–dipole complexes separating the reactants and transition state in each case. The overall activation energies for methylation were roughly correlated with the corresponding heats of reaction, indicating some parallel between the energy-lowering interactions operating in the transition states and products. For ethylation the transition states were much "looser" and the covalent interactions (short-range forces) largely absent. The parallel between ΔH and $\Delta H^\ddagger$ was therefore far less precise, the activation energies being now determined principally by electrostatic interactions. A direct consequence of this phenomenon is that while the activation energy for O-methylation of formamide (**2**) is calculated to be 8.0 kcal mol^{-1} higher than that for N-methylation of the more nucleophilic imidazole (**3**), this difference was reduced to 0.5 kcal mol^{-1} for ethylation. It is suggested that an effect of this kind is the principal determinant of the far higher proportions of O-alkylated products obtained when nucleic acids and their constituents are exposed to precursors of ethyldiazonium, relative to the methyldiazonium ions. Biradical states are believed not to be involved in the S_N2 reactions discussed here.

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Registry No. **1a**, 20404-06-2; **1b**, 84027-64-5; **2**, 75-12-7; **3**, 288-32-4; **4**, 289-95-2; **5**, 74-89-5; **6**, 7732-18-5.

Supplementary Material Available: Calculated Cartesian coordinates for all species optimized in this report (13 pages). Ordering information is given on any current masthead page.