

the incoming electrophile. The importance of this coordination effect by the heteroatom is related to the nature and the probability of the attractive interaction with the ionic electrophile, whether electrostatic involving its protons or covalent involving its carbocationic center.

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Gas-Phase Heteroaromatic Substitution. 13.¹ A Quantitative Application of the Curve-Crossing Reactivity Model to Heteroaromatic Substitution

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Abstract: Gas-phase kinetic data concerning the electrophilic attack of free, unsolvated cations, such as CH₃⁺, C₂H₅⁺, *i*-C₃H₇⁺, *t*-C₄H₉⁺, C₆H₅⁺, CF₃⁺, (CH₃)₂F⁺, (CH₃)₃Si⁺, CH₃CO⁺, and C₆H₅CO⁺, toward simple five-membered heteroarenes have been embodied into Klopman's charge and frontier orbital control reactivity model. The origin of the deviations from a linear correlation between the positional selectivity of some of the above electrophiles and their SCF STO-3G calculated LUMO energy has been investigated. The influence of the computational level used for estimating the LUMO eigenvalues of the ionic reactants has been assessed by increasing the basis set dimensions from the STO-3G to the 6-31G*. Similar positional selectivity vs LUMO energy correlations have been obtained at both computational levels, revealing no significant difference at the two levels of theory employed. Direct evaluation of the activation parameters governing the gas-phase electrophilic attack on pyrrole by some representative ionic reactants, such as *i*-C₃H₇⁺, *t*-C₄H₉⁺, CF₃⁺, and (CH₃)₂F⁺, has been derived from their Arrhenius plots, measured within the temperature interval 30–140 °C. The curve-crossing reactivity model has been quantitatively applied to interpret the experimental kinetic results. A satisfying linear relationship between the intramolecular selectivity of the electrophiles considered and their *G* values has been obtained, the *G* parameter being a function of the vertical ionization potential IP_v of the heteroarene and of the vertical electron affinity EA_v of the electrophile. The influence of the *G* parameter in determining the nature of the transition states and the relative height of the activation barriers involved in the attack of the ionic electrophile on the α and β carbons of pyrroles has been discussed and compared with the effects of Klopman's HOMO (donor)–LUMO (acceptor) energy gap on the corresponding positional selectivity. A close relationship between the *G* parameter and the HOMO–LUMO gap, both reflecting the properties of the unperturbed donor–acceptor pair, has been verified.

Introduction

In earlier Parts of this series, specifically designed radiolytic and nuclear-decay kinetic procedures have been extensively applied to the study of the reactivity and selectivity properties of free, unsolvated ionic electrophiles toward five-membered heteroarenes in the dilute gaseous state, where complications due to interaction with the solvent and the counterion are eliminated.^{1,2} The emerging picture characterizes gas-phase heteroaromatic substitution as generally proceeding via the classical S_E2 mechanism, unless a quasisonant single-electron transfer (SET) from the heteroarene to the electrophile is allowed. Almost exclusive α substitution is observed for those electrophiles undergoing the SET event, e.g. the acylium ions, while the site selectivity of those following the donor–acceptor S_E2 mechanism qualitatively conforms to that expected on the grounds of Klopman's charge and frontier orbital control concept.³ Accordingly, the selectivity properties of a number of ionic electrophiles toward simple five-membered heteroarenes, such as pyrrole, appear primarily determined by the energy gap between the HOMO of the heteroaromatic donor and the LUMO of the cationic acceptor, as indicated in Figure 1 by the approximately linear correlation between the β vs α substitution ratio (log (β/α)) in pyrrole and

the SCF STO-3G calculated LUMO energy of the electrophile. A similar correlation is found for *N*-methylpyrrole. Although these trends are acceptable, the linear correlation of Figure 1 is rather unsatisfying from the quantitative point of view. In fact, appreciable deviations from the linearity are actually observed for several ionic electrophiles, reflecting a measured positional selectivity toward pyrrole somewhat different from that expected on the grounds of their SCF STO-3G calculated LUMO energy.

The aim of the present investigation is to ascertain whether the origin of such deviations from Klopman's predictions is due to

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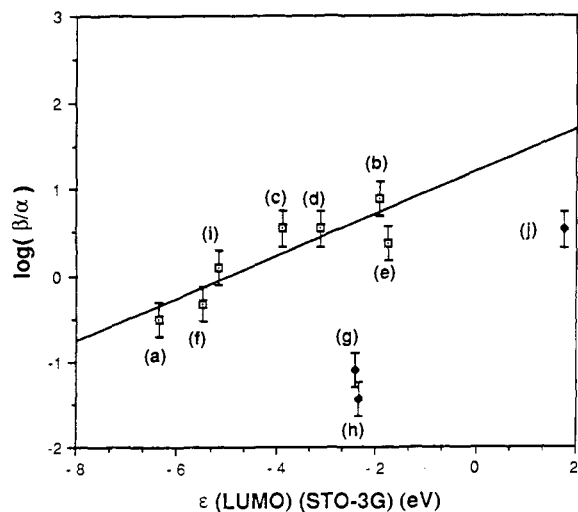


Figure 1. Plot of site selectivity, measured at 298 K, of ionic electrophiles toward the β and α carbons of pyrrole, expressed as the $\log(\beta/\alpha)$, as a function of SCF STO-3G calculated LUMO eigenvalues of the ionic electrophiles: (a) CH_3^+ ; (b) proton-bridged C_2H_5^+ ; (c) $i\text{-C}_3\text{H}_7^+$; (d) $t\text{-C}_4\text{H}_9^+$; (e) $(\text{CH}_3)_2\text{Si}^+$; (f) C_6H_5^+ ; (g) CH_3CO^+ ; (h) $\text{C}_6\text{H}_5\text{CO}^+$; (i) CF_3^+ ; (j) $(\text{CH}_3)_2\text{F}^+$. The interpolating line refers to the open square points only.

the level of calculations adopted to evaluate the LUMO energy of the ionic electrophiles or, rather, to factors reflecting the intimate nature of the potential energy profile governing the substitution process in the gas phase. To this purpose, computation of the SCF eigenvalues of the LUMO's of all the ionic electrophiles investigated is upgraded in the present study to the 6-31G* level of theory.⁴ Besides, a direct insight into the potential energy hypersurface determining the reactivity and selectivity properties of several representative ionic reactants, such as $i\text{-C}_3\text{H}_7^+$, $t\text{-C}_4\text{H}_9^+$, CF_3^+ , and $(\text{CH}_3)_2\text{F}^+$, toward pyrrole is provided by the relevant Arrhenius plots, measured in the gas phase under conditions ensuring thermal equilibration of all the species involved. The entire body of experimental evidence concerning the gas-phase reactivity of five-membered heteroarenes toward ionic electrophiles is finally discussed in the framework of the configuration mixing model for organic reactivity.⁵ It is thereby hoped to provide a unique experimental yardstick against which the potential validity of the configuration mixing concept, as a unifying reactivity model for electrophilic heteroaromatic substitution, can adequately be assessed.

Experimental Section

Materials. Methyl fluoride, carbon tetrafluoride, methane, ethylene, propane, neopentane, oxygen, ammonia, and trimethylamine were research grade gases from Matheson Co., with a minimum purity of 99.5 mol %. Pyrrole was a research grade chemical from Fluka AG, its purity being checked with the same techniques used in the gas chromatographic (GC) analysis of the radiolytic products. Alkylated derivatives of pyrrole were obtained from commercial sources, or prepared according to unexceptional procedures,^{1,2} their identity being checked by conventional IR, NMR, and GC-mass spectrometry (GC-MS).

Procedure. The experimental procedures adopted for the preparation of the gaseous samples and their γ -irradiation in a variable-temperature 220 Gammacell (Atomic Energy Canada Ltd.) have repeatedly been described.^{1,2} Typical experimental conditions were the following: parent gas of the electrophile, 760 Torr; pyrrole, 1.0 Torr; O_2 , 4 Torr; NMe_3 , 2 Torr; temperature, 30–140 °C, with an accuracy of ca. ± 3 °C. The total dose received by the samples was 3.2×10^4 Gy at a rate of ca. 4×10^3 Gy h^{-1} , as measured with a Fricke dosimeter. The irradiated samples were analyzed by GC and GC-MS with respectively a Perkin-Elmer 8320 and Sigma 3 gas chromatographs, equipped with FID units,

and a Hewlett-Packard 5970B mass selective detector on the following columns: (i) a 50-m long, 0.32 mm i.d., fused-silica column, coated with CP-Wax 52 CB, Chrompack, Italy, operated at temperatures ranging from 55 to 150 °C; (ii) a 5-m long, 3.2 mm i.d., stainless-steel column, packed with 25% Silicone Oil E 301 on 60–80 mesh Chromosorb W, operated at 90 °C; (iii) a 3-m long, 3.2 mm i.d., stainless-steel column, packed with 10% Carbowax 20M, 1% KOH on Chromosorb W 60–80 mesh, operated at temperatures ranging from 85 to 110 °C.

The identity of the products was established by comparison of their retention volumes with those of authentic samples, as well as from their mass spectra in the GC-MS separations. The amounts of the products formed were determined from the areas of the corresponding elution peaks using the internal calibration method. Blank runs, carried out at the highest reaction temperature employed in the irradiation experiments, excluded that alkylated derivatives of pyrrole arise by the thermolysis of the gaseous mixtures.

Computational Details. Standard quantum-mechanical calculations, with the Gaussian 80⁶ set of programs, were performed in order to evaluate the SCF 6-31G*⁷ eigenvalues of the LUMO's of CH_3^+ , C_2H_5^+ , $i\text{-C}_3\text{H}_7^+$, $t\text{-C}_4\text{H}_9^+$, CF_3^+ , C_6H_5^+ , CH_3CO^+ , $\text{C}_6\text{H}_5\text{CO}^+$, and SiMe_3^+ and of the HOMO of pyrrole. Geometry optimizations were performed in order to obtain the SCF 6-31G* optimized wave functions and orbital eigenvalues. D_{3h} symmetry was assumed for CH_3^+ and CF_3^+ , C_{3v} for $i\text{-C}_3\text{H}_7^+$, C_2H_5^+ , and SiMe_3^+ , and C_{2v} for $t\text{-C}_4\text{H}_9^+$, C_6H_5^+ , $\text{C}_6\text{H}_5\text{CO}^+$, and pyrrole. The computed LUMO eigenvalues (eV) are as follows: CH_3^+ (−7.63, ground state; −8.63, vibrationally excited), C_2H_5^+ (−3.79, nonclassical; −6.19, classical), $i\text{-C}_3\text{H}_7^+$ (−5.10), $t\text{-C}_4\text{H}_9^+$ (−4.42), CF_3^+ (−7.24), C_6H_5^+ (−4.96, ground state; −6.46, vibrationally excited state), CH_3CO^+ (−3.46), $\text{C}_6\text{H}_5\text{CO}^+$ (−3.51). The calculated HOMO eigenvalue for pyrrole is −7.96 eV.

Results and Discussion

Theoretical Calculations. Figure 1 indicates that an approximately linear relationship is established between the observed intramolecular selectivity within the pyrrole ring ($\log(\beta/\alpha)$) by a variety of ionic electrophiles and their SCF STO-3G calculated LUMO eigenvalues. A similar correlation does exist for *N*-methylpyrrole. Although the trends are acceptable, these linear correlations appear unsatisfying from the quantitative standpoint, being characterized by a correlation coefficient of 0.752 for pyrrole and of 0.718 for *N*-methylpyrrole. This would suggest either that Klopman's model can hardly provide a quantitative description of the reactivity of pyrroles toward free ionic electrophiles or that the level of theory used for estimating the LUMO eigenvalues of the ionic reactants is inadequate. To critically evaluate this latter hypothesis, we decided first to check the performance of the theoretical model employed.

It is generally recognized⁸ that, at least for small carbocations, the level of agreement between calculated SCF STO-3G and the measured bond lengths and angles is reasonable, an overestimate of ca. 0.04 Å of the bond distances to the formal carbocationic center being often observed. A more satisfactory agreement is found at the SCF double- ζ (3-21G) level of theory, and the inclusion of polarization functions leads to equilibrium structures for these ions which are in much better accord with the experimental data. As far as the accuracy of the computed LUMO eigenvalues is concerned, a general evaluation is prevented by the paucity of the reported data. However, it has been observed^{4,8} that if we assume the negatives of the LUMO energies of a molecule as a measure of its electron affinity, the absolute values calculated in this way are strongly dependent on the nature of the basis set. With these considerations in mind, we thought it was useful to investigate the basis set influence on the $\log(\beta/\alpha)$ vs LUMO energies previously obtained on the grounds of STO-3G calculations. Thus, the SCF 6-31G* eigenvalues of the corresponding optimized molecular orbitals were computed for all the selected electrophiles.

As a general observation, the use of the larger 6-31G* basis set leads to values that are more negative than the STO-3G ones.

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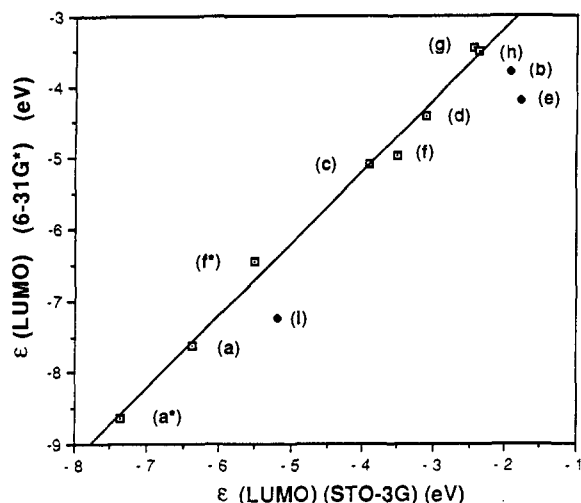


Figure 2. Plot of SCF 6-31G* vs SCF STO-3G calculated LUMO eigenvalues of the ionic electrophiles (*, vibrationally excited): (a) CH_3^+ ; (b) proton-bridged C_2H_5^+ ; (c) $i\text{-C}_3\text{H}_7^+$; (d) $t\text{-C}_4\text{H}_9^+$; (e) $(\text{CH}_3)_3\text{Si}^+$; (f) C_6H_5^+ ; (g) CH_3CO^+ ; (h) $\text{C}_6\text{H}_5\text{CO}^+$; (i) CF_3^+ . The interpolating line refers to the open square points only.

Consistently, a 1.32-eV decrease from -6.64 to -7.96 eV for the HOMO energy of pyrrole is observed in passing from the STO-3G to the 6-31G* computational level. It should be noted that the latter value closely approaches the experimental value of the first ionization potential of pyrrole, -8.20 eV,⁹ which, according to Koopmans' theorem,¹⁰ can represent its HOMO energy limit.

Restricting the analysis to the computed LUMO eigenvalues for CH_3^+ , $i\text{-C}_3\text{H}_7^+$, $t\text{-C}_4\text{H}_9^+$, C_6H_5^+ , and acylium ions, whose structural features are expected to be adequately described by using both small and large basis sets, the following interpolating linear equation (corr coeff = 0.993) is obtained:

$$\epsilon(\text{LUMO})(6\text{-}31\text{G}^*) \text{ (eV)} = 1.007\epsilon(\text{LUMO})(\text{STO-}3\text{G}) - 1.17 \text{ (eV)} \quad (1)$$

which supports the view of a mere 1.17 eV energy gap separating the 6-31G* set of data from the STO-3G one. This conclusion extends to pyrrole itself, whose 6-31G* calculated HOMO eigenvalue is 1.32 eV lower than that calculated at the STO-3G level.

For CF_3^+ , $(\text{CH}_3)_3\text{Si}^+$, and bridged C_2H_5^+ ions, whose calculated LUMO eigenvalues do not fit into eq 1, the inclusion of polarization functions in the basis set leads to a better description of their structures. It follows that, for these ions, the computed differences between STO-3G and 6-31G* LUMO eigenvalues do not depend only upon the basis set expansion, as for classical alkyl carbocations, but also from a more adequate structural description. In the $(\text{CH}_3)_3\text{Si}^+$ ion, in fact, the inclusion of polarization functions accounts for the tendency of silicon atom to expand its valence shell to the unoccupied, but easily accessible, 3d orbitals.¹¹ A better description of the LUMO of this ion is therefore obtained by allowing some d-type function participation. Similarly, the nature and the energy of the LUMO of CF_3^+ may depend as well on the inclusion of polarization functions. In fact, at the 6-31G* level of theory, a better description of the mixing of the lone pairs of fluorine atoms with the empty p-orbital of the carbon center is expected. Finally, the inclusion of polarization functions proved of crucial importance even for small carbocations, such as the ethyl cation C_2H_5^+ . Indeed, at the 6-31G* level of theory, the non-classical, bridged form was found to be more stable than the classical, open structure by 7 kcal mol⁻¹.⁸ Although the stability

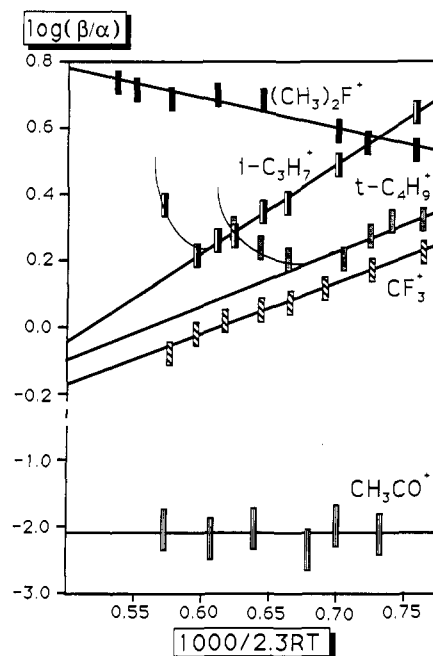


Figure 3. Arrhenius plots for the competitive attack of ionic electrophiles toward the β and α carbons of pyrrole at 760 Torr and in the presence of 2 Torr of NMe_3 . In the runs with CF_3^+ , 7 Torr of ethylene added as well. The vertical bars refer to the reproducibility of data from different irradiations carried out under identical conditions.

gap may change, the order is found to never reverse even at the highest levels of calculation.⁸

From the above considerations, we are inclined to conclude that the observed deviations of CF_3^+ , $(\text{CH}_3)_3\text{Si}^+$, and bridged C_2H_5^+ from eq 1 are essentially due to a SCF STO-3G overestimate of orbital-mixing effects.

The unity slope of the interpolating curve of Figure 2 indicates that the $\log(\beta/\alpha)$ vs $\epsilon(\text{LUMO})$ correlation of Figure 1 does not substantially improve by upgrading the level of the computation of the frontier orbitals of the reacting species from STO-3G to 6-31G*. A simple ca. 1.3-eV shift of the curve of Figure 1 on the left is obtained by replacing the STO-3G LUMO eigenvalues with the 6-31G* ones. This is also true for the CH_3CO^+ ion, whose exceedingly large deviation from the correlation of Figure 1 ($\log(\beta/\alpha) < -1.1$; $\epsilon(\text{LUMO}) = -2.4$ eV (STO-3G); -3.5 eV (6-31G*)) does not originate from the specific LUMO calculation level, but essentially from its peculiar two-step substitution mechanism, as demonstrated in a previous investigation.²¹

Arrhenius Plots. In view of the above conclusions, a temperature-dependence study of the site selectivity of several representative ionic electrophiles, i.e. $t\text{-C}_4\text{H}_9^+$, $i\text{-C}_3\text{H}_7^+$, CF_3^+ , and $(\text{CH}_3)_2\text{F}^+$, toward gaseous pyrrole has been undertaken with the aim of estimating the activation parameters governing the relevant substitution reactions as well as of ascertaining the origin of any conceivable discrepancy between the measured selectivity properties of the ionic reactant and those predicted by Klopman's model (Figure 1). In compliance with previous related indications,¹² the experiments have been carried out under conditions, i.e. at atmospheric pressure and in the presence of sufficient concentrations of a powerful base (NMe_3 , 2 Torr), ensuring complete thermal equilibrium of the reaction intermediates as well as their deprotonation prior to undesired isomerization events. In this way, the isomeric distribution of the alkylated derivatives of pyrrole closely reproduces the relative population of their parent primary heteroarenium intermediates, whose dependence from the reaction temperature provides meaningful activation parameters of their formation process by standard kinetic treatments. The results are visualized in Figure 3, together with those concerning CH_3CO^+ , taken from a previous study for comparison purposes.²¹

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The Arrhenius plots relative to CF_3^+ and $(\text{CH}_3)_2\text{F}^+$ are linear over the entire temperature interval (30–140 °C) covered, while those relative to $i\text{-C}_3\text{H}_7^+$ and $t\text{-C}_4\text{H}_9^+$ are characterized by a marked inflection occurring at temperatures over 110 and 60 °C, respectively, which denotes a relative increase of β -substitution on the pyrrole molecule. Besides, while Arrhenius curves for alkyl cations display a distinct negative temperature dependence, that concerning the halonium ion $(\text{CH}_3)_2\text{F}^+$ is characterized by the reverse trend.

Before proceeding to discuss the results of Figure 3, the preliminary problem arises of establishing whether the observed trend reflects indeed the temperature dependence of the electrophilic attack of the ionic reagents on pyrrole, rather than of other steps of the reaction sequence which eventually yields the neutral alkylated pyrroles. In fact, temperature changes could conceivably affect the processes responsible for the formation of the ionic reactant, its electrostatic trapping by the substrate, as well as the isomerization and the deprotonation of the ensuing heteroarenium intermediates. In view of the fact that the measured Arrhenius plots refer to intramolecular competition of the ring carbons of the pyrrole molecule for the ionic electrophile, the first possibility is quite irrelevant even if the formation sequences of the selected electrophiles, besides proved rather temperature insensitive,¹³ were highly temperature dependent. In fact, in this latter hypothesis, temperature would affect the stationary concentrations of the electrophilic reagent and, therefore, only the absolute yield of the substituted products, leaving unaffected their isomeric distribution. The absolute lack of intermolecular discrimination in the gas-phase electrophilic substitutions on heteroarenes, observed in related investigations,² indicates that formation of the electrostatic encounter pair between pyrrole and an ionic electrophile is irreversible. This rules out the second possibility, i.e. that the temperature dependence can be ascribed to its differential effect on competing back-dissociation of the primary electrostatic encounter pairs vs their conversion into the corresponding σ -bonded intermediates. The last possibility, i.e. that the observed temperature effects can be traced to isomerization within the isomeric heteroarenium intermediates or to their deprotonation, has been ruled out by carrying out the alkylations at two widely different temperatures (e.g. 30 and 100 °C) in the presence of two different concentrations of base NMe_3 (2–5 Torr). No significant changes of the selectivity ratios ($\log(\beta/\alpha)$) could be detected, showing that deprotonation of heteroarenium intermediates as well as temperature dependence is not kinetically relevant.

Another preliminary problem concerns the inflection of the Arrhenius plots occurring only for $i\text{-C}_3\text{H}_7^+$ and $t\text{-C}_4\text{H}_9^+$ above 100 and 60 °C, respectively. As mentioned before, the presence of the powerful base NMe_3 in the reaction mixtures excludes that such an effect be due to alkyl-group shifts within the primary heteroarenium intermediates, whose initial population in this case would not any longer reflect the orientation of the electrophile by the substrate. A reasonable explanation of the inflections of Figure 3 can be based on the fact, independently supported by mass spectrometric evidence,¹⁴ that $i\text{-C}_3\text{H}_7^+$ and $t\text{-C}_4\text{H}_9^+$ may act as Brønsted acids toward pyrrole especially under conditions preventing collisional stabilization of the alkylated adducts, e.g. low pressures and high temperatures, wherein entropy-favored proton-transfer processes may predominate over the competing

substitution reactions. Further support to this rationale is provided by the lack of similar inflections by CF_3^+ and $(\text{CH}_3)_2\text{F}^+$ ions, which, differently from alkyl carbocations, may act exclusively as Lewis-type acids toward pyrrole, even at low pressures and high temperatures.¹⁴

Having addressed the preliminary problems of identifying the processes responsible for the observed temperature effects and of accounting for the curvature of the Arrhenius plots relative to $i\text{-C}_3\text{H}_7^+$ and $t\text{-C}_4\text{H}_9^+$ above 100 and 60 °C, respectively, we can turn to the primary object of this study. Regression analysis of the data in the linear portions of the Arrhenius plots leads to the following equations

$$\log(\beta/\alpha) = \log(A_\beta/A_\alpha) + 1000\Delta E^*/2.303RT;$$

$$\Delta E^* = E_\alpha^* - E_\beta^* \text{ (kcal mol}^{-1}\text{)} \quad (2)$$

$$\log(A_\beta/A_\alpha) = -1.1 (t\text{-C}_4\text{H}_9^+); -1.5 (i\text{-C}_3\text{H}_7^+); -1.1 (\text{CF}_3^+);$$

$$+1.3 ((\text{CH}_3)_2\text{F}^+)$$

and

$$\Delta E^* \text{ (kcal/mol)} = +2.1 (t\text{-C}_4\text{H}_9^+); +2.9 (i\text{-C}_3\text{H}_7^+);$$

$$+1.8 (\text{CF}_3^+); -1.0 ((\text{CH}_3)_2\text{F}^+)$$

From the analysis of eq 2, a positive difference $\Delta E^* = E_\alpha^* - E_\beta^*$ of several kilocalories per mol between the empirical activation energy for the attack at the α and β positions of pyrrole emerges for alkylating carbocations. The opposite situation is found instead in the attack on pyrrole by the $(\text{CH}_3)_2\text{F}^+$ halonium ion. At any rate, the pronounced temperature dependence measured for the selected gaseous electrophiles clearly contrasts with the lack of temperature effects on the site selectivity pyrrole by CH_3CO^+ ions, due to their SET mode of attack on the substrate. Such a completely different behavior between $t\text{-C}_4\text{H}_9^+$, $i\text{-C}_3\text{H}_7^+$, CF_3^+ , and $(\text{CH}_3)_2\text{F}^+$, on the one hand, and CH_3CO^+ , on the other, further supports the conclusion of the preceding paper¹ that the attack of gaseous ionic electrophiles on pyrrole proceeds via the classical donor-acceptor $\text{S}_{\text{E}}2$ mechanism, except when an entropy-favored quasisonant SET event is allowed, as for CH_3CO^+ .²¹

It is of interest to compare the results of Figure 3 both with the available experimental evidence and with the theoretical predictions. To our knowledge, the present study represents the first attempt at a quantitative evaluation of the activation parameters of classical heteroaromatic substitution by gaseous ionic electrophiles over an extended temperature range (110 °C) which has hardly been approached in related studies in solution. Concerning similar estimates for aromatic substitutions in the gas phase, the activation barrier difference $\Delta E^* = E_\alpha^* - E_\beta^* = 2.1$ kcal mol⁻¹, measured for the attack of $t\text{-C}_4\text{H}_9^+$ on the α and β carbons of pyrrole, compares well with the $E_{\text{m}}^* - E_{\text{p}}^* = \text{ca. } 3$ kcal mol⁻¹ activation energy difference for the attack of the same gaseous ion on the meta and para positions of toluene.¹⁵

The nature of the electrophiles employed, i.e. free, unsolvated carbenium and halonium ions, as well as the gaseous reaction environment, which excludes interference from solvation and ion-pairing phenomena, confers to the present experimental results an unusual degree of generality and of relevance for comparison with current reactivity theories, such as Klopman's model. Klopman's concept of charge vs orbital control in donor-acceptor reactions, as determined by the energy level, the shape, and the charge distribution of the *unperturbed* HOMO of the donor and of the LUMO of the acceptor, is recognized, on the basis of the correlation of Figure 1, as a qualitative model for electrophilic heteroaromatic reactivity in the gas phase. Nevertheless, it appears inherently inadequate for a quantitative description of the heteroaromatic reactivity in the gas phase, which is based upon a kinetic evaluation of the relevant potential energy hypersurfaces, determined by the *mutual perturbation* of the orbitals of the donor and of the acceptor along the reaction coordinate. An enlightening example is provided by the reversal of the positional selectivity of gaseous CF_3^+ toward pyrrole as a function of temperature

(13) The selected ionic reactants are formed from the γ -radiolysis of their parent gases either by direct, temperature-independent primary ionization (e.g. CF_3^+ from CF_4) or via a very fast reaction sequence initiated by attack of a fragment ion on its parent molecule (e.g. C_2H_5^+ on C_3H_8). Most of such reaction sequences show negligible, if any, temperature dependence within the temperature interval considered in the present study (cf. Bowers, M. T., Ed. *Gas-Phase Ion Chemistry*; Academic Press: New York, 1979). It follows that, in view of the large excess of the bath gases over the pyrrolic substrate in the radiolytic samples (over 700:1), even a large variation in the reaction temperature is by far insufficient to cause any detectable change in the stationary concentration of the ionic electrophile.

(14) Independent FT-ICR experiments revealed that protonation of pyrrole by $i\text{-C}_3\text{H}_7^+$ and $t\text{-C}_4\text{H}_9^+$ represents a major process at total pressures of the order of 5×10^{-7} Torr, whose rates approach the collision limit. The same process has been observed, although to a very minor extent, under radiolytic conditions (Laguzzi, G., private communication).

(15) Cacace, F.; Ciranni, G. *J. Am. Chem. Soc.* **1986**, *108*, 887.

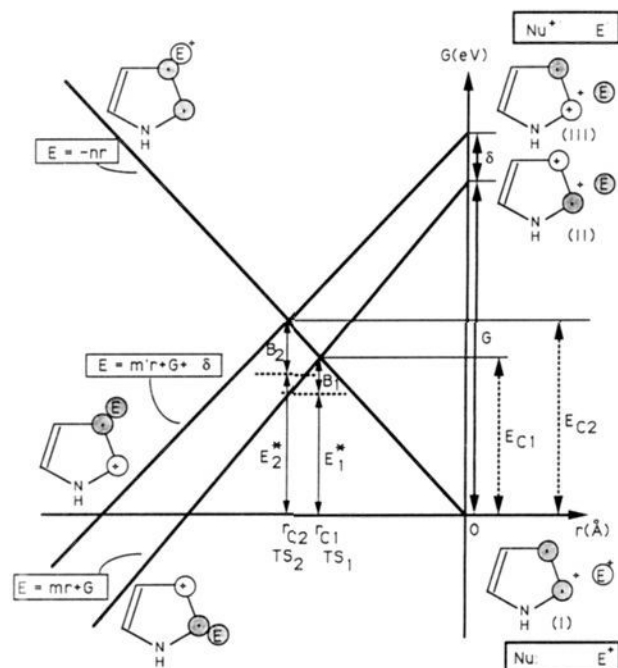


Figure 4. State correlation diagram for a Nu⁺/E⁺ donor-acceptor reaction representing a typical gas-phase heteroaromatic substitution by an ionic electrophile. The reaction coordinate r refers to the distance between the formally charged center of the electrophile and the specific ring carbon of the substrate, taking as a zero for the r scale the real value of 4.1 Å (see text).

(Figure 3), which cannot find any rationalization on the exclusive grounds of Klopman's concept, but calls for a quantitative application of more refined models, such as the curve-crossing model by Shaik and Pross,⁵ which anchors the theoretical treatment of the experimental kinetic data to factors determining the activation barriers in a typical donor-acceptor reaction.

The Quantitative Curve-Crossing Model for Heteroaromatic Reactivity in the Gas Phase. The essence of the curve-crossing model is to use electronic configurations of the reactants and of the products as building blocks from which the entire energy profile along a reaction coordinate may be generated. For donor-acceptor reactions, such as those considered in the present study involving a neutral pyrrole nucleophile (Nu:) and a cationic electrophile (E⁺), the reactant configuration is depicted by the Nu:/E⁺ pair, while the configuration that describes the substituted heteroaromatic product is depicted by Nu⁺/E⁺. It can be seen that all that is required to convert the reactant pair into the heteroaromatic product is a *formal* single electron transfer from Nu: to E⁺, described by the Nu:/E⁺-Nu⁺/E⁺ configuration mixing along the reaction coordinate. In the framework of the valence-bond configuration mixing (VBCM) model,^{5b} the electrophilic attack of a cation E⁺ on pyrrole Nu: can be conceived as involving essentially the lowest energy empty orbital of E⁺ and the formally localized substituted C=C π bond of pyrrole Nu:. This latter is obtained by deconvoluting the delocalized molecular π orbitals of pyrrole into the localized ones. In this way, a pyrrole molecule can be treated as an enamine molecule, whose π orbital is the one obtained by the pyrrole molecular π-orbitals localization procedure.

In this view, the active configurations I-III (Figure 4) must be employed to build up the adiabatic potential energy profile for the electrophilic addition of E⁺ on pyrrole. In Figure 4, the origin of the vertical axis, reporting the energy of the reactant and the product configurations in eV, is taken as the absolute energy of the Nu:/E⁺ configuration I. The horizontal axis refers to the distance r (in Å) between the positively charged center of E⁺ and the C atoms of Nu:. This parameter is assumed as the reaction coordinate, and its zero value is taken at a real distance between E⁺ and Nu: of 4.1 Å, which is the minimum distance where to C-C orbital overlap is still negligible (see Figure 5). As can be observed from Figure 4, two different product configurations of Nu⁺/E⁺,

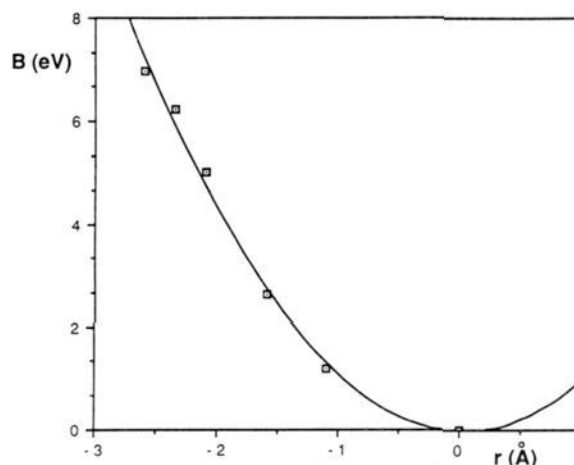


Figure 5. Best-fit parabolic equation representing the dependence upon the reaction coordinate r of the resonance integral B between 2p orbitals of interacting carbon atoms ($B = 1.054r^2$; B in eV and r in Å). The variable r refers to the distance between the 2p orbitals, taking as a zero for the r scale the real value of 4.1 Å (see text).

i.e. II and III, must be considered, the first with an electron vacancy at the β carbon of pyrrole, collapsing eventually to the α-substituted heteroaromatic product, and the other with an electron vacancy at the α carbon of the nucleophile, leading to the β-substituted heteroaromatic isomer. As a first approximation, only one reactant configuration, i.e. I, involving the localized π orbital of pyrrole can be assumed. Besides, in order to make quantitatively tractable the kinetic data of Figure 1 in the framework of the curve-crossing model, a linear dependence of the energy of each configuration, at least for a limited range of the reaction coordinate, is assumed. For the donor-acceptor reaction described in Figure 4, the initial energy gap G between configurations I and II will be given by the difference between the vertical ionization potential of Nu: ($IP_v(\text{Nu:})$) and the vertical electron affinity of E⁺ ($EA_v(E^+)$), which represents approximately the energy necessary to transfer vertically an electron from the β carbon of the donor Nu: to the acceptor E⁺. If, instead, the transition involves configuration III, with the electron vacancy at the α carbon of the donor, the configuration energy gap is represented by the $G + \delta$ term, where δ is the energy gap between II and III. In view of the predominant spin-density localization at the α carbons of pyrrole radical cation,¹⁶ a positive value for the energy parameter δ is expected.

The equation $E(I) = -nr$, with $n > 0$, describes the dependence of the energy of the reactant configuration upon the reaction coordinate r . The curves reporting the energy of the product configurations II and III as a function of r obey the following equations: $E(II) = mr + G$ and $E(III) = m'r + G + \delta$, respectively. In order to build up the entire potential energy profile, the interaction of the involved configurations at any point of the reaction coordinate must be allowed. From the perturbation theory,¹⁷ this interaction involves a stabilization energy SE relative to the energy of the most stable of the interacting configurations, which is expressed by $SE = B^2/\Delta E$, where ΔE represents the energy interval between the two interacting configurations along the reaction coordinate and B is an energy parameter. At the curve-crossing point, where the interacting configurations become degenerate at an energy value of E_C , the stabilization energy is simply equal to B . Here, the reaction coordinate r_C is that of the transition state, whose energy E^* therefore can be estimated from the $E_C - B$ difference. Since it is referred to the energy of the unperturbed reactant configuration, taken equal to zero, $E^* = E_C - B$ represents the activation energy of the process. For the

(16) Shiotani, M.; Nagata, Y.; Tasaki, M.; Sohma, J.; Shida, T. *J. Phys. Chem.* **1983**, *87*, 1170.

(17) Libit, L.; Hoffmann, R. *J. Am. Chem. Soc.* **1974**, *96*, 1370 and references therein.

interaction of two configurations, such as for instance I and II, which are related by a *formal* single electron transfer, the magnitude of B is essentially proportional to the overlap between the two atomic orbitals which differ in one-electron occupancy.¹⁸ Since, in our case, most of the atomic orbitals involved in the *formal* electron transfer are 2p's of carbon, the resonance integral B can be described satisfactorily by the equation $B = \kappa r^2$, with $\kappa = 1.054 \text{ eV } \text{Å}^{-2}$, which is found to be the best interpolating parabolic function (Figure 5; correlation coefficient = 0.994), expressing the dependence of the CNDO/2 calculated B resonance integral value for σ overlap between the 2p orbitals of two C atoms with their distance r .¹⁹ The $B = \kappa r^2$ equation implies that a different B value is associated to any given value of the reaction coordinate r_C corresponding to the transition state relative to the attack of E^+ on each position of pyrrole. For the attack on its α carbons, the reaction coordinate corresponding to the relevant transition state is given by r_{C1} and the relative stabilization energy is expressed by $B_1 = \kappa r_{C1}^2$. For attack on its β centers, the reaction coordinate of the corresponding transition state is taken as r_{C2} and the relative stabilization energy is expressed by $B_2 = \kappa r_{C2}^2$.

It follows that the activation barriers for the attack of E^+ on the α and β carbons of pyrrole can be expressed respectively by

$$E_1^* = E_{C1} - B_1 \quad (3a)$$

$$E_2^* = E_{C2} - B_2 \quad (3b)$$

where $E_{C1} = nG/(m+n)$, $E_{C2} = n(G+\delta)/(m'+n)$ and $B_1 = \kappa G^2/(m+n)^2$, $B_2 = \kappa(G+\delta)^2/(m'+n)^2$.

Therefore, the difference between the activation barriers for the two competing paths is expressed by

$$E_2^* - E_1^* = \kappa G^2/(m+n)^2 - \kappa G^2/(m'+n)^2 + nG/(m'+n) - nG/(m+n) - 2\kappa G\delta/(m'+n)^2 + n\delta/(m'+n) - \kappa\delta^2/(m'+n)^2 \quad (4)$$

This is a parabolic equation, which can be reduced to the following linear one under the reasonable assumption that $m = m'$.

$$E_2^* - E_1^* = -2\kappa G\delta/(m+n)^2 + n\delta/(m+n) - \kappa\delta^2/(m+n)^2 \quad (5)$$

Support to this assumption can be found in the observation that configurations II and III as well as their corresponding α and β heteroarenum intermediates are characterized by the same stability order.²⁰

Since

$$\log(k_2/k_1) = \log(A_2/A_1) - (E_2^* - E_1^*)/2.303RT \quad (6)$$

it follows

$$\log(k_2/k_1) = \log(A_2/A_1) + 35.71\delta G/(m+n)^2 + 17.85\delta^2/(m+n)^2 - 16.94n\delta/(m+n) \quad (7)$$

if $T = 298 \text{ K}$ and the energy parameters are expressed in eV.

For competing electrophilic attack of E^+ on the unencumbered α and β centers of pyrrole, we may assume in the first approximation that $A_2 = A_1$, so that

$$\log(k_2/k_1) = 35.71\delta G/(m+n)^2 + 17.85\delta^2/(m+n)^2 - 16.94n\delta/(m+n) \quad (8)$$

As indicated before, the G term can be estimated from the $IP_v(\text{Nu}) - EA_v(E^+)$ difference, where $IP_v(\text{Nu})$ refers to the vertical ionization potential of the formally localized $\pi C_\alpha=C_\beta$ bond of the pyrrole molecule, whereas $EA_v(E^+)$, whose values are not available from the literature, can be roughly estimated as equal

(18) (a) Salem, L.; Leforestier, C.; Segal, G.; Wetmore, R. *J. Am. Chem. Soc.* **1975**, *97*, 479. (b) Epiotis, N. D. *Theory of Organic Reactions*; Springer-Verlag: Heidelberg, 1978.

(19) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.

(20) It is generally recognized that the Wheland intermediates from alkyl-cation attack on the α carbons of pyrrole are more stable than those from attack on the β positions of the same molecule by several kilocalories per mol. Independent SCF STO-3G calculations indicate that the energy gap ranges from ca. 10 (alkyl group: CH_3) to ca. 4 kcal/mol (alkyl group: CF_3).

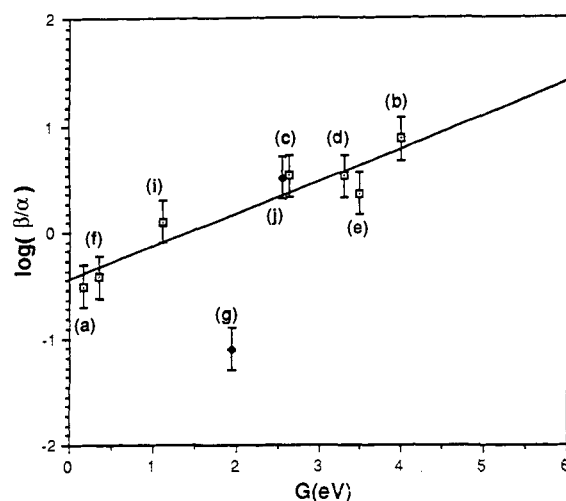


Figure 6. Plot of site selectivity, measured at 298 K, of ionic electrophiles toward the β and α carbons of pyrrole, expressed as the $\log(\beta/\alpha)$, as a function of calculated G values: (a) CH_3^+ ; (b) proton-bridged C_2H_5^+ ; (c) $i\text{-C}_3\text{H}_7^+$; (d) $t\text{-C}_4\text{H}_9^+$; (e) $(\text{CH}_3)_3\text{Si}^+$; (f) C_6H_5^+ ; (g) CH_3CO^+ ; (i) CF_3^+ ; (j) $(\text{CH}_3)_2\text{F}^+$. The interpolating line refers to the open square points only.

to $IP_a(E^+)$. A linear combination of bonding orbitals (LCBO) analysis of the UV photoelectron spectrum of pyrrole allows the assignment of a value of ca. 10 eV for the vertical ionization potential of its localized $\pi C_\alpha=C_\beta$ bonds. By combining this value with the available $IP_a(E^+)$ data, the G energy gap for each of the selected ionic electrophiles can be derived. Figure 6 reports a correlation between the estimated G values for any given electrophile and its positional selectivity ($\log(k_2/k_1) = \log(\beta/\alpha)$) toward pyrrole, as measured at 298 K.²¹ A similar correlation is found for *N*-methylpyrrole. According to the approximate eq 8, a linear dependence of $\log(\beta/\alpha)$ on the G values is found, obeying the following equations

$$\log(\beta/\alpha) = 0.311G - 0.454 \quad (\text{corr coeff} = 0.894) \quad \text{for pyrrole} \quad (9)$$

$$\log(\beta/\alpha) = 0.204G - 0.324 \quad (\text{corr coeff} = 0.732) \quad \text{for } N\text{-methylpyrrole} \quad (10)$$

For each pyrrolic substrate, comparison between the best-fit linear correlation (eqs 9 and 10) and the theoretical expression 8 allows an estimate of the δ and n parameters, once a reasonable value is attributed to the m term. This can be obtained by assuming the same $\sigma \text{C}(\text{ring})\text{-C}(\text{alkyl})$ bond energy (ca. 87 kcal mol⁻¹) and equilibrium length (ca. 1.55 Å) for either α - and β -substituted heteroarenum intermediates. This leads to a value for m of 1.48 eV Å⁻¹, from which $\delta = 1.42 \text{ kcal mol}^{-1}$ and $n = 1.18 \text{ eV } \text{Å}^{-1}$ for pyrrole and $\delta = 1.08 \text{ kcal mol}^{-1}$ and $n = 1.38 \text{ eV } \text{Å}^{-1}$ for *N*-methylpyrrole can be derived. It is interesting to point out that similar n values for both pyrroles are obtained which approach closely the estimated m parameter. Besides, the order of magnitude of the positive δ energy gap values compares well with the relative stability of α - and β -substituted heteroarenum intermediates.

The Performance of the Curve-Crossing Model. It is worthwhile to discuss from a general point of view the performance of the curve-crossing model in predicting some outstanding features of pyrrole reactivity in the gas phase. A first important aspect arising from inspection of Figure 1 is the reversal of site selectivity in passing from ionic electrophiles with low-lying LUMO's, e.g. the CH_3^+ ion, to ionic reactants with high-lying LUMO's e.g. the bridged C_2H_5^+ cation, through rather unselective cations with

(21) As pointed out by one of the Referees, a temperature dependence of the $\log(\beta/\alpha)$ vs G curves is expected. As a matter of fact, according to eqs 6–8, a family of linear correlations should be observed, whose slopes and intercepts would decrease by increasing the temperature. However, any of these linear curves, including the one obtained at 298 K, can be used to estimate the δ and n parameters, which are largely independent of T .

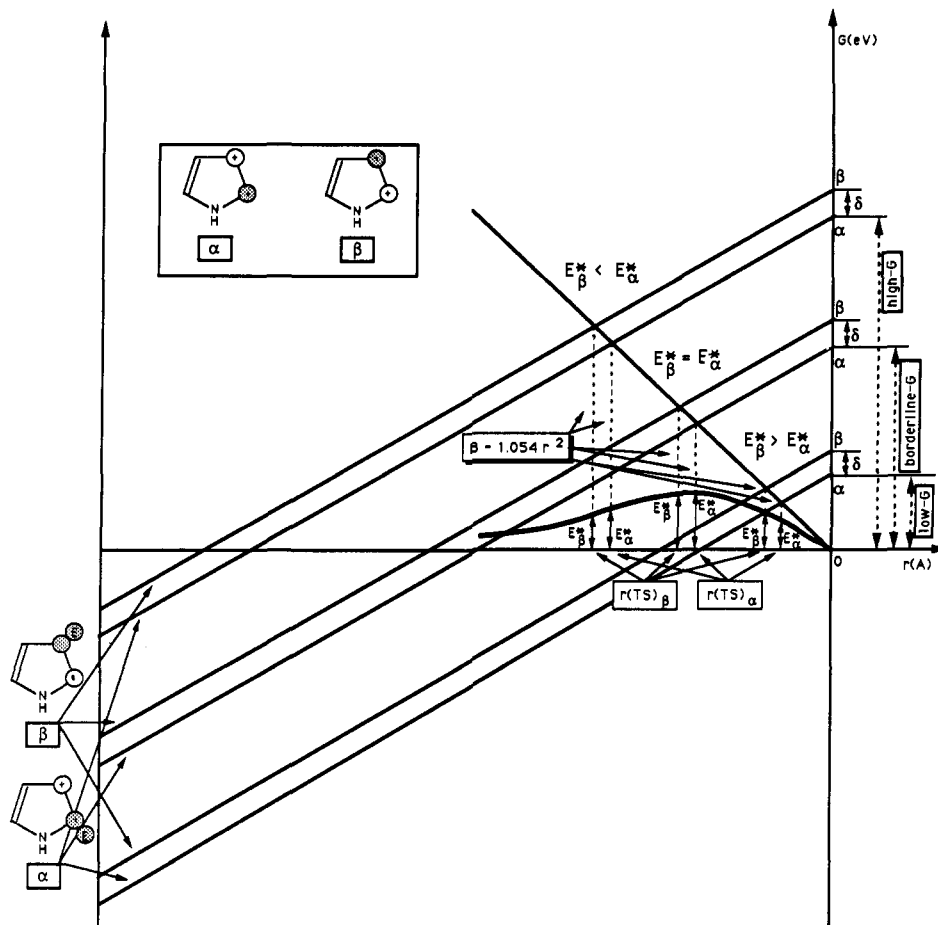


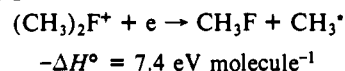
Figure 7. State correlation diagram for a Nu:/E⁺ donor-acceptor reaction representing a typical gas-phase heteroaromatic substitution by an ionic electrophile. Effect of the *G* value on the nature of the transition states and the relative height of the activation barriers involved in the attack of the electrophile on the α and β positions of pyrrole.

borderline LUMO's, such as CF₃⁺. In the framework of the curve-crossing model, such a selectivity reversal appears as an immediate consequence of the substantially different *G* values estimated for the corresponding electrophiles. Figure 7 visualizes the effect of *G* in determining the relative magnitude of E_{α}^* vs E_{β}^* , as well as the relative position of the corresponding transition states along the reaction coordinate *r*. Accordingly, low-*G* electrophiles, e.g. CH₃⁺, are characterized by $E_{\alpha}^* < E_{\beta}^*$ and by early transition states, whereas high-*G* reactants, e.g. bridged C₂H₅⁺, exhibit late transition states with $E_{\alpha}^* > E_{\beta}^*$. For borderline-*G* species, such as CF₃⁺, $E_{\alpha}^* \approx E_{\beta}^*$ as a consequence of the intermediate position of the relevant transition states along the reaction coordinate *r*.

Furthermore, for each given electrophile, the transition state for β substitution on pyrroles is invariably predicted to be late relative to that governing α substitution. This may involve a less favorable activation entropy factor for β attack, which is somewhat reflected in the experimental $A_{\alpha} > A_{\beta}$ values obtained from the Arrhenius plots of Figure 3. In this connection, the CH₃CO⁺ ion, whose *G* value can be estimated as ca. 1.95 eV, is expected to show a site selectivity toward pyrroles ranging around $\log(\beta/\alpha) =$ ca. 0.15. As a matter of fact, the experimental $\log(\beta/\alpha)$ is invariably below -1.1 for pyrroles,²¹ which implies a large deviation from the corresponding linear $\log(\beta/\alpha)$ vs *G* correlations (see Figure 6). As previously pointed out,²¹ similar deviations from the $\log(\beta/\alpha)$ vs $\epsilon(\text{LUMO})$ relationships were observed for acylium ions (Figure 1). No reasonable explanation of such deviations could be provided by Klopman's charge and frontier orbital control model, which conceives the description of reactivity in terms of the properties of the unperturbed donor-acceptor pair. On the other hand, in view of the aptitude of the more refined curve-crossing model to describe reactivity in terms of configuration mixing along the entire reaction coordinate, it was hoped that this

model could comprehend the reactivity properties of CH₃CO⁺ toward pyrrole. However, such an expectation seems frustrated by the results of the present study, which confirm previous indications of a mechanistic changeover of CH₃CO⁺ toward pyrroles from the classical donor-acceptor S_E2 mechanism, followed by all the other electrophiles studied, to a two-step mechanistic sequence involving a first single electron transfer (SET) step followed by recombination of the ensuing radicals. A plausible rationale for such a peculiar mechanistic changeover for CH₃CO⁺ toward pyrroles just resides in its particular *G* = ca. 1.95 eV value, reflecting a IP_v(pyrrole) - EA_v(CH₃CO⁺) difference approaching zero. It follows that, along the reaction coordinate, energy degeneracy between pyrrole and CH₃CO⁺ is readily reached at even limited mutual perturbation of the reactants so that a rapid SET event may occur from the donor to the acceptor well before their interacting configurations become degenerate, as required by the classical donor-acceptor S_E2 process. This conclusion can be taken as a general warning, when applying curve-crossing model to predict the reactivity of a donor-acceptor pair for which a SET event is made highly likely relative to the competing two-electron substitution mechanism by the specific electronic features of the reactants.

The treatment of the positional selectivity data of (CH₃)₂F⁺ toward pyrroles within the framework of Klopman's model (Figure 1) appears to be rather inadequate. However, an attempt to insert these data into the $\log(\beta/\alpha)$ vs *G* correlations obtained by quantitative application of the curve-crossing approach appeared at first glance rather promising. In fact, a rough estimate of ca. 2.6 eV for the *G* value of (CH₃)₂F⁺ can be obtained, by taking for EA_v((CH₃)₂F⁺) the - ΔH° of the following reaction



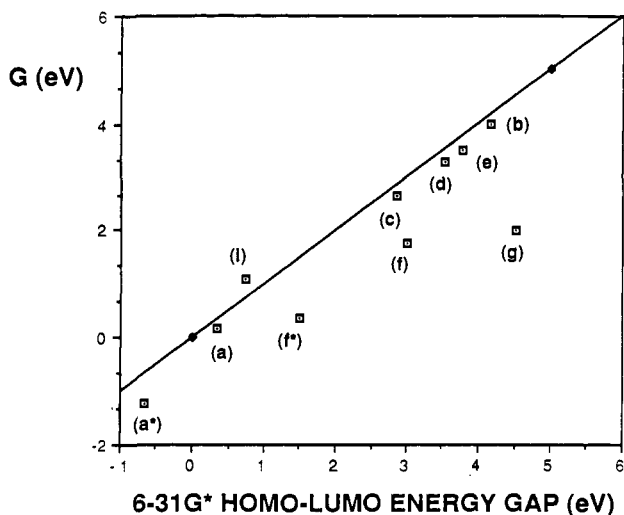


Figure 8. Plot of the G values vs the SCF 6-31G* calculated HOMO-LUMO energy gap for the attack of ionic electrophiles on pyrrole (*, vibrationally excited): (a) CH_3^+ ; (b) proton-bridged C_2H_5^+ ; (c) $i\text{-C}_3\text{H}_7^+$; (d) $t\text{-C}_4\text{H}_9^+$; (e) $(\text{CH}_3)_3\text{Si}^+$; (f) C_6H_5^+ ; (g) CH_3CO^+ ; (i) CF_3^+ . The solid line represents the coincidence between the G values and the SCF 6-31G* calculated HOMO-LUMO energy gaps.

Even by using such an approximate G value, a good fitting of the $(\text{CH}_3)_2\text{F}^+$ positional selectivity toward pyrroles as a function of the G parameter emerges (Figure 6). However, this coincidence is fortuitous, as suggested by the peculiar Arrhenius plot of $(\text{CH}_3)_2\text{F}^+$ ions toward pyrrole (Figure 3). In fact, the kinetic parameters order controlling the gas-phase attack of $(\text{CH}_3)_2\text{F}^+$ ions toward pyrrole, i.e. $E_\alpha^* < E_\beta^*$ and $A_\alpha < A_\beta$, is opposite that characterizing all other electrophiles employed. This evidence can be taken as a major indication against indiscriminate extension of the assumptions adopted in the previous section for quantitative curve-crossing treatment of heteroaromatic reactivity. In fact, within these assumptions, $E_\alpha^* > E_\beta^*$ and $A_\alpha > A_\beta$ trends would be expected for $(\text{CH}_3)_2\text{F}^+$ ($G = \text{ca. } 2.6 \text{ eV}$), as actually obtained for $i\text{-C}_3\text{H}_7^+$ ($G = 2.64 \text{ eV}$). However, the mode of attack of onium ions, such as $(\text{CH}_3)_2\text{F}^+$, toward pyrrole cannot be regarded as a simple addition process, such as for free carbenium ions, but rather as a nucleophilic displacement process. As a consequence, quantitative treatment of data concerning $(\text{CH}_3)_2\text{F}^+$ -ion attack on pyrrole must take into account that the relevant activation

barrier can arise not only by bond formation between pyrrole and the C center of the electrophile but also by bond breaking between the outgoing methyl group and the CH_3F moiety of the electrophile.

Conclusions

A comparison between the performance of Klopman's charge and frontier orbital control concept and the curve-crossing model, quantitatively applied, for the kinetic analysis of the gas-phase attack of a number of cations on pyrroles has been presented in this study. In the framework of the first model, the experimental intramolecular selectivity is rationalized in terms of the HOMO-LUMO gap between the *unperturbed* molecules of the pyrrole donor and of the ionic acceptor. On the other hand, a better description of the experimental kinetic data is provided by the more refined curve-crossing model, which builds the entire potential energy profile by allowing mixing of the appropriate electronic configurations, along the reaction coordinate. Accordingly, for a typical donor-acceptor reaction, such as those reported in the present investigation, the activation barriers originate by the combination of two factors: (i) the initial energy separation, G , between the *unperturbed* reactant and product configurations, which determines the transition-state position along the reaction coordinate, and (ii) the extent of configuration mixing at the transition state, which is in turn determined by the same G value. It is interesting to point out that an approximate linear correlation does exist between the G energy gap and the $\epsilon(\text{LUMO})(\text{E}^+) - \epsilon(\text{HOMO})(\text{pyrrole})$ difference for each given electrophile, which is shown in Figure 8. On the grounds of this observation, we are inclined to conclude that Klopman's approach to the description of the gas-phase reactivity of pyrrole toward electrophiles can be thought of as included in the more general curve-crossing model. In this view, the initial HOMO(donor)-LUMO(acceptor) energy gap introduced in the former model can be interpreted, through G , as a function of physically more meaningful quantities, such as the vertical ionization potential of the donor and the vertical electron affinity of the acceptor.

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