Gas-phase Heteroaromatic Substitution. Part 6.[1] Alkylation of Pyrrole, *N*-Methylpyrrole, Furan, and Thiophene by Isopropyl Cation

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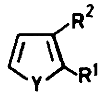
Isopropyl cation, obtained in the dilute gas state from the γ-radiolysis of propane, has been allowed to react with pyrrole (**1**), *N*-methylpyrrole (**2**), furan (**3**), and thiophene (**4**), both neat and in competition with benzene, in the pressure range 50—760 Torr, and in the presence of variable concentrations of a gaseous base (NMe_3). Both the reactivity of the selected heteroaromatic compounds and the isomeric distribution of their isopropylated derivatives depend upon the total pressure of the system and the concentration of NMe_3. The apparent heteroaromatic substrate (S) *vs.* benzene (B) selectivity k_S/k_B ratios decrease slightly with increasing pressure. At atmospheric pressure, the k_S/k_B ratios for pyrroles are found to increase with NMe_3 concentrations reaching a value of 0.7 (**1**) and 0.8 (**2**) at the highest base concentration [$P(NMe_3)$ 10 Torr]. The k_S/k_B values concerning furan and thiophene are found to decrease slightly with the NMe_3 concentration, levelling off to 0.3 (**3**) and 0.8 (**4**) at $P(NMe_3)$ 10 Torr. Under the same conditions, predominant β substitution takes place in pyrroles [β:α:N 70:20:10 for (**1**) and β:α 61:39 for (**2**)], whereas α-attack is favoured in the case of furan (β:α 29:71). Thiophene (**4**) displays no significant positional discrimination (β:α 49:51). The mechanism of substitution, and the subsequent isomerization and dealkylation processes, are discussed, and the substrate and positional selectivity of $i\text{-}C_3H_7^+$ compared with that of related gaseous alkylating reactants. The hypothesis of gas-phase electrophilic alkylation reactions of simple five-membered heteroaromatic compounds regulated essentially by electrostatic interations within the encounter pair is confirmed in the present study.

In earlier Parts the application of specifically designed radiolytic and nuclear decay techniques to the study of heteroaromatic substitution by positive ions in the dilute gas state has been reported.[1] In particular, the intrinsic orientation and reactivity features of simple five-membered heteroaromatic rings toward free, unsolvated alkyl cations have been evaluated by their reactions with $t\text{-}C_4H_9^+$ ions.[1e]

We now report the extension of the study to the gas-phase alkylation of the same substrates (**1**)—(**4**), both neat and in competition with benzene, by $i\text{-}C_3H_7^+$ ions from the radiolysis of propane.[2] The investigation has been primarily undertaken to bring to a sharper focus the correlation between reactivity and selectivity of gaseous cations by comparing the known behaviour of $t\text{-}C_4H_9^+$ with that of a considerably stronger, yet closely related, reagent, such as $i\text{-}C_3H_7^+$, toward the same heteroaromatic substrates. Furthermore, the mechanistic features of the gas-phase heteroaromatic isopropylation can be directly evaluated and compared with those of related alkylation processes that occur both in the gas phase and in solution.



(**1**) Y = NH, R^1 = R^2 = H
(**2**) Y = NMe, R^1 = R^2 = H
(**3**) Y = O, R^1 = R^2 = H
(**4**) Y = S, R^1 = R^2 = H
(**5**) Y = NPr^i, R^1 = R^2 = H
(**6**) Y = NH, R^1 = Pr^i, R^2 = H
(**7**) Y = NH, R^1 = H, R^2 = Pr^i
(**8**) Y = NMe, R^1 = Pr^i, R^2 = H
(**9**) Y = NMe, R^1 = H, R^2 = Pr^i
(**10**) Y = O, R^1 = Pr^i, R^2 = H
(**11**) Y = O, R^1 = H, R^2 = Pr^i
(**12**) Y = S, R^1 = Pr^i, R^2 = H
(**13**) Y = S, R^1 = H, R^2 = Pr^i

Experimental

Materials.—Propane, oxygen, and trimethylamine were research grade gases from Matheson Co., with a stated purity of 99.99 mol%, and were used without further purification. Benzene, pyrrole, *N*-methylpyrrole, furan, and thiophene were research grade chemicals from Fluka AG. These compounds were analysed by g.l.c. to check for the absence of alkylated impurities. Isomeric isopropylpyrroles, isopropyl-*N*-methylpyrroles, isopropylfurans, and isopropylthiophenes, used as gas chromatographic standards together with isopropylbenzene (Fluka AG), were prepared according to established procedures[3] and purified by preparative g.l.c. Their purity was checked by g.l.c. analysis on a Perkin-Elmer Sigma 1 gas chromatograph, equipped with a flame ionization detection (f.i.d.) unit, on the same columns employed for the analysis of the irradiation mixtures, and their identity verified by conventional ^1H n.m.r. spectroscopy.

Procedure.—The experimental procedure used for the preparation of the gaseous mixtures and their irradiation have been described in detail elsewhere.[4] Typical experimental conditions were: propane, 50—760 Torr; heteroaromatic substrate, 0.5—2.0 Torr; O_2, 4 Torr; NMe_3, 0—10 Torr. The radiation dose, as measured with a neopentane dosimeter,[5] was 3×10^4 Gy, delivered at the rate of 1×10^4 Gy h^{-1}, for all samples at 37.5 °C

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in a ^{60}Co γ-cell (Atomic Energy Canada Ltd.). A few runs, carried out at a dose of 1×10^5 Gy, revealed no significant differences in the relative rates of formation of neutral isopropylated products and their isomeric composition.

Product Analysis.—The analysis of the products was carried out by injecting measured portions of the irradiated reaction mixture into a Perkin-Elmer Sigma 1 gas chromatograph equipped with an f.i.d. unit. In order to avoid selective losses of the products by adsorption on the glass walls of the vessel and, therefore, to obtain reproducible and meaningful yields, the analysis was repeated after washing the bulb walls with freshly purified ethyl acetate. Satisfactory agreement was observed in all runs between analytical results arising from gaseous mixtures and those involving the corresponding ethyl acetate extracts. The irradiation products were identified by comparison of their retention volumes with those of authentic standards. Their yields was determined from the area of the corresponding elution peaks, using appropriate calibration curves for the detector reponse.

Results

Gas-phase attack of isopropyl ion, generated by γ-radiolysis of propane in the presence of a thermal radical scavenger, such as O_2, on the selected heteroaromatic substrates (**1**)—(**4**) yields the corresponding isopropylated derivatives, namely (**5**)—(**7**) from (**1**); (**8**) and (**9**) from (**2**); (**10**) and (**11**) from (**3**); (**12**) and (**13**) from (**4**). Their absolute yields, expressed as the number of molecules M produced per 100 eV of energy absorbed by the gaseous mixtures ($G_{(M)}$ values), have been measured under various experimental conditions, at a constant temperature of 37.5 °C and for a total dose of 3×10^4 Gy (dose rate 1×10^4 Gy h^{-1}). A monotonic decrease of the relevant $G_{(M)}$ values is observed by increasing the total pressure of the system (Figure 1) and the concentration of an efficient ion trap, such as NMe_3 (Figure 2). The latter effect demonstrates the ionic nature of the isopropylated products. In addition, comparison of the overall absolute yield of isopropylated products recovered at 200 Torr with the known $G_{(\mathrm{Pr}^{i+})}$ values, which approach 3.0 at the same pressure,[2,6] demonstrates that addition of the isopropyl cation to the heteroaromatic substrate is a highly efficient process, amounting to 30% for (**1**), 38% for (**2**), 82% for (**3**), and 77% for (**4**).

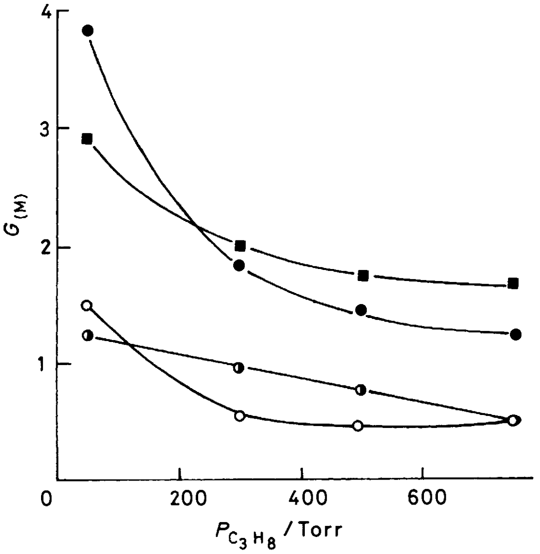


Figure 1. Dependence of the overall absolute yields of isopropyl derivatives of simple heteroaromatics upon the total pressure of the irradiated system [$P(C_3H_8)$]: ○, isopropylpyrroles (**5**)—(**7**); ◑, isopropyl-*N*-methylpyrroles (**8**), (**9**); ●, isopropylfurans (**10**), (**11**); ■, isopropylthiophenes (**12**), (**13**)

Figures 3 and 4 show the results of competition experiments, with benzene as the reference substrate, carried out at pressures ranging from 50 to 760 Torr and in the presence of variable amounts of NMe_3. In general, a regular decrease of the apparent heteroaromatic substrate (S) *vs.* benzene (B) selectivity ratio k_S/k_B is observed as the total pressure of the sample is increased

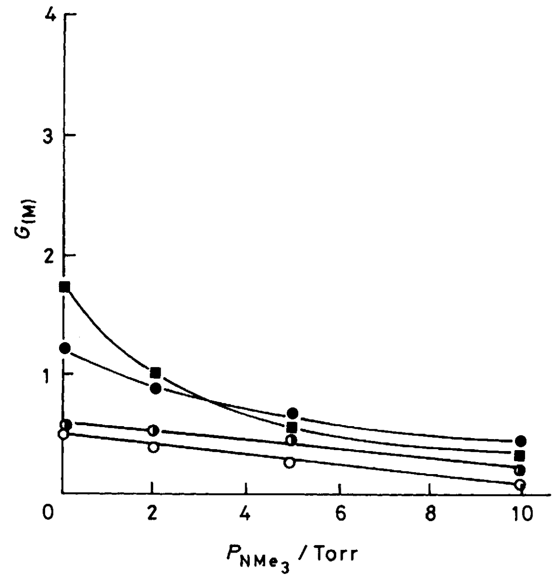


Figure 2. Dependence of the $G_{(M)}$ values on the partial pressure of NMe_3 [$P(NMe_3)$]: ○, isopropylpyrroles (**5**)—(**7**); ◑, isopropyl-*N*-methylpyrroles (**8**), (**9**); ●, isopropylfurans (**10**), (**11**); ■, isopropylthiophenes (**12**), (**13**). Total pressure of the systems: $P(C_3H_8)$ 760 Torr

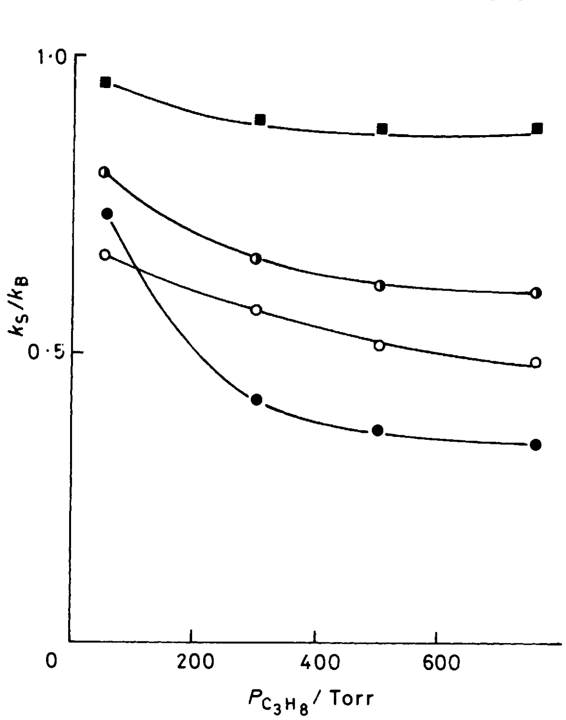


Figure 3. Dependence of the apparent k_S/k_B ratios on the total pressure [$P(C_3H_8)$] of the competition systems: ○, pyrrole (**1**)–benzene; ◑, *N*-methylpyrrole (**2**)–benzene; ●, furan (**3**)–benzene; ■, thiophene (**4**)–benzene

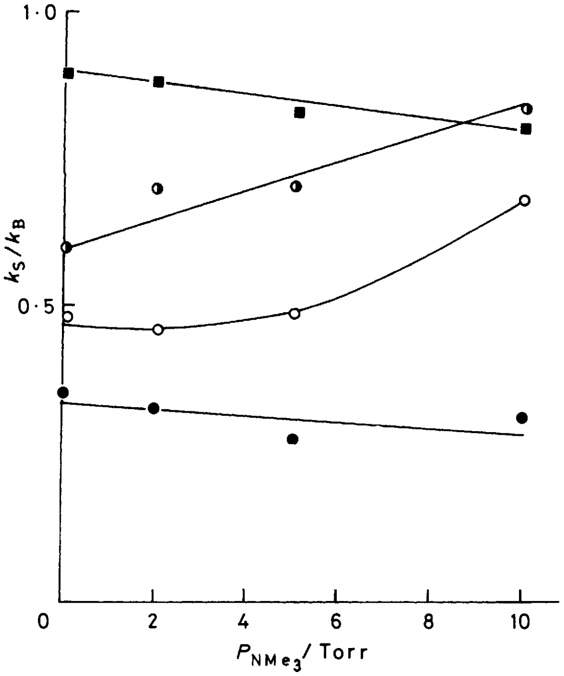


Figure 4. Dependence of the apparent k_S/k_B ratios on the partial pressure of NMe$_3$ [P(NMe$_3$)] at a total pressure of 760 Torr: ○, pyrrole (**1**)-benzene; ◑, *N*-methylpyrrole (**2**)-benzene; ●, furan (**3**)-benzene; ■, thiophene (**4**)-benzene

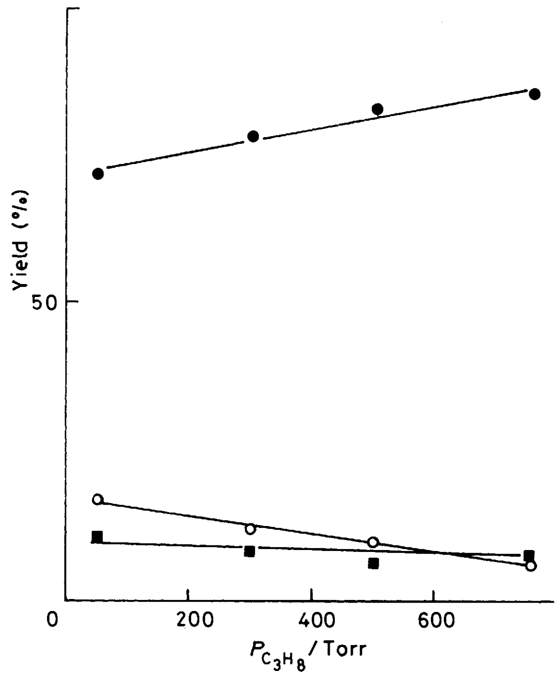


Figure 5. Relative yields of isomeric isopropylpyrroles (**5**)—(**7**) from i-$C_3H_7^+$ ion attack on pyrrole (**1**) as a function of the total pressure [$P(C_3H_8)$] of the system, in the absence of NMe$_3$: ■, *N*-isopropylpyrrole (**5**); ○, 2-isopropylpyrrole (**6**); ●, 3-isopropylpyrrole (**7**)

(Figure 3). While the k_S/k_B ratios relative to furan and thiophene are rather insensitive to the presence of NMe$_3$, those of pyrroles were found to increase with the NMe$_3$ concentrations (Figure 4). An appreciable dependence of the k_S/k_B ratios is also found as a function of the heteroaromatic *versus* benzene concentration ratio ([S]:[B]) at atmospheric pressure.

The isomeric composition of the products from isopropylation of the selected heteroaromatics (**1**)—(**4**), either neat or in competition with benzene, has been measured under largely different experimental conditions and is reported in Figures 5—12. Inspection of Figures 5—8 reveals that β isopropylation of pyrroles (**1**) and (**2**) predominates under all conditions, reaching the maximum relative extent (85%) at atmospheric pressure and in the absence of NMe$_3$. A slight decrease of the β:α ratios with the sample pressure is observed (Figures 5 and 7), which becomes more significant at increasing concentrations of NMe$_3$ (Figures 6 and 8). At atmospheric pressure and at the highest concentrations of NMe$_3$, the relative distribution of isopropylated pyrroles levels off at values of β:α:N 70:20:10 for pyrrole (**1**) and of β:α 61:39 for *N*-methylpyrroles (**2**).

The α-substituted derivatives of furan (**3**) and thiophene (**4**) are instead formed predominantly under all conditions, their relative yields tending to increase appreciably at atmospheric pressure and in the presence of NMe$_3$ (Figure 9—12). In particular, a significant increase of the β:α ratio is observed at low pressures in the furan samples (Figure 9), whereas the same ratio from thiophene appears to be rather independent of the system pressure (Figure 11). In the presence of NMe$_3$, the relevant β:α ratios are appreciably lower, albeit tending to increase slightly with the NMe$_3$ concentration (Figures 10 and 12) to reach the values of β:α 39:71 for (**3**) and 49:51 for (**4**). In the competition experiments, the presence and concentration of the benzene competitor do not significantly modify the isomeric distribution of the isopropylated heteroaromatic, especially at high pressures and NMe$_3$ concentrations. At the lowest pressures, a certain increase of the relative yields of the β isopropylated derivatives of pyrroles (**1**) and (**2**), and of thiophene (**4**), is observed.

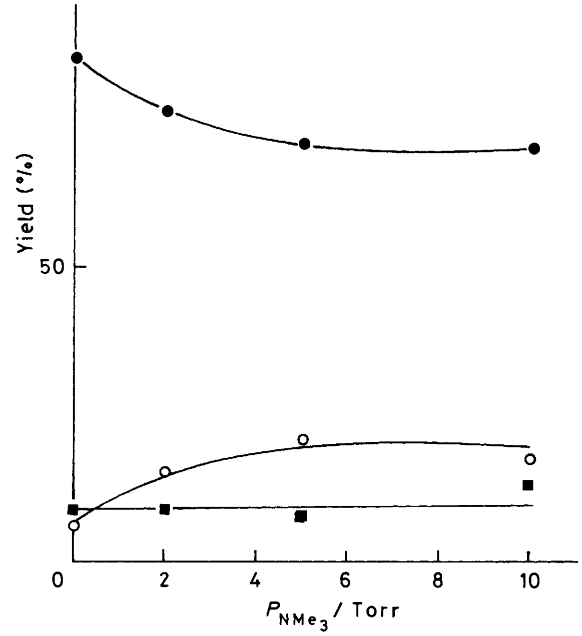


Figure 6. Relative yields of isomeric isopropylpyrroles (**5**)—(**7**) from i-$C_3H_7^+$ ion attack on pyrrole (**1**), at 760 Torr, as a function of the partial pressure of NMe$_3$ [P(NMe$_3$)]: ■, *N*-isopropylpyrrole (**5**); ○, 2-isopropylpyrrole (**6**); ●, 3-isopropylpyrrole (**7**)

In conclusion, the major features of gas-phase isopropylation of the selected substrates can be summarized as follows. (i) Pyrroles (**1**) and (**2**), furan (**3**), and thiophene (**4**), as well as benzene, are efficiently alkylated by the isopropyl cation in the

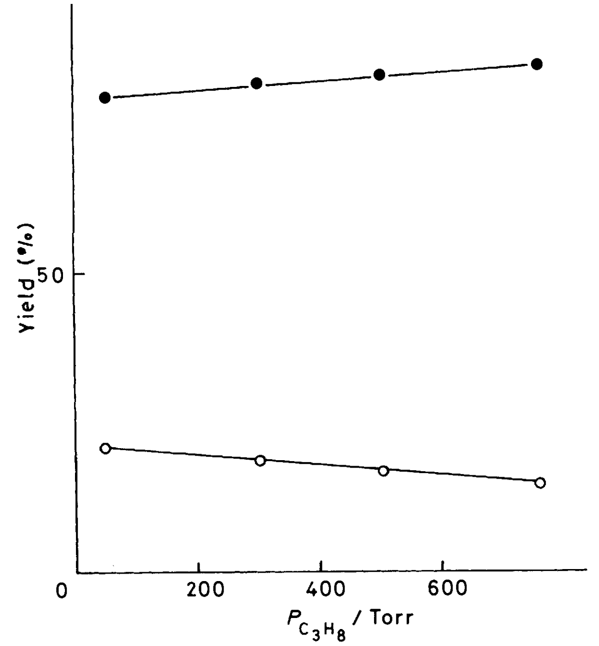


Figure 7. Relative yields of isomeric isopropyl-*N*-methylpyrroles (8) and (9) from i-$C_3H_7^+$ ion attack on *N*-methylpyrrole (2) as a function of the total pressure [$P(C_3H_8)$] of the system, in the absence of NMe_3: ○ 2-isopropyl-*N*-methylpyrrole (8); ●, 3-isopropyl-*N*-methylpyrrole (9)

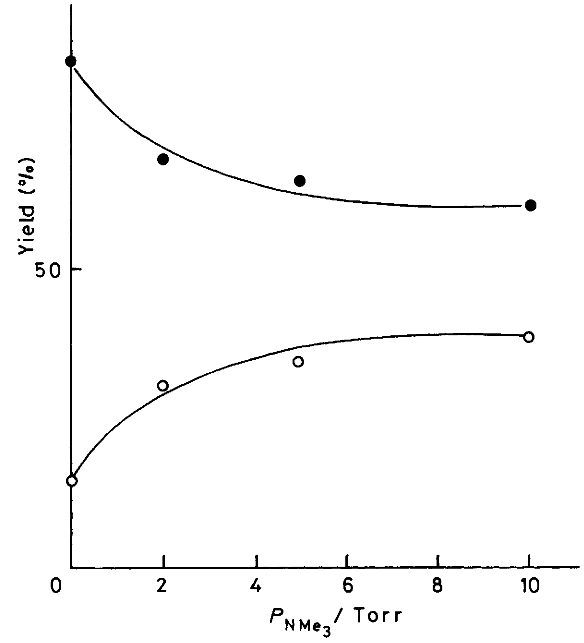


Figure 8. Relative yields of isomeric isopropyl-*N*-methylpyrroles (8) and (9) from i-$C_3H_7^+$ ion attack on *N*-methylpyrrole (2), at 760 Torr, as a function of the partial pressure of NMe_3 [$P(NMe_3)$]: ○, 2-isopropyl-*N*-methylpyrrole (8); ●, 3-isopropyl-*N*-methylpyrrole (9)

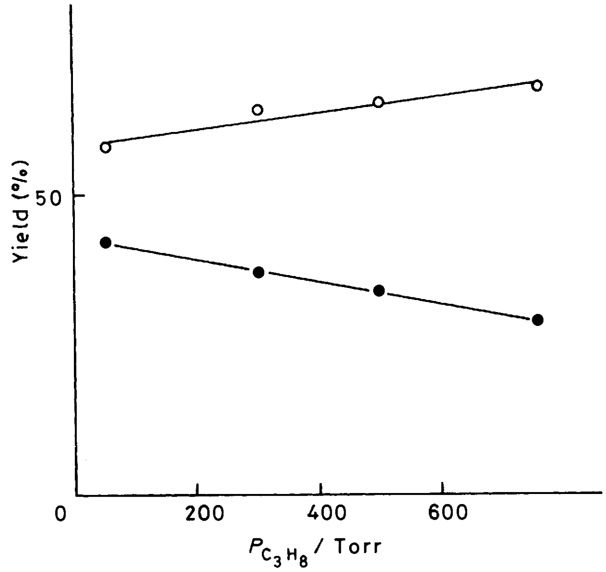


Figure 9. Relative yields of isomeric isopropylfurans (10) and (11) from i-$C_3H_7^+$ ion attack on furan (3) as a function of the total pressure [$P(C_3H_8)$] of the system, in the absence of NMe_3: ○, 2-isopropylfuran (10); ●, 3-isopropylfuran (11)

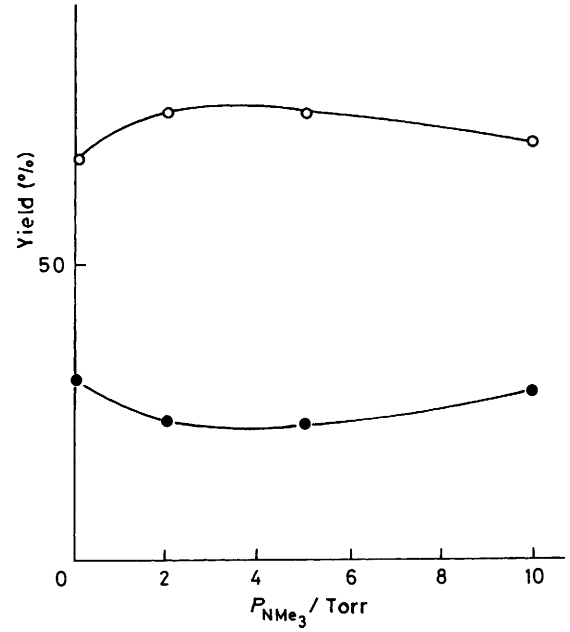


Figure 10. Relative yields of isomeric isopropylfurans (10) and (11) from i-$C_3H_7^+$ ion attack on furan (3), at 760 Torr, as a function of the partial pressure of NMe_3 [$P(NMe_3)$]: ○, 2-isopropylfuran (10); ●, 3-isopropylfuran (11)

gas phase. (ii) Apparent k_S:k_B ratios below unity have been measured for all systems under all conditions. The rate constant ratios from furan (3) and thiophene (4) systems appear to be rather independent of the NMe_3 concentration, whereas those from pyrroles (1) and (2) increase with NMe_3. (iii) Gas-phase attack of i-$C_3H_7^+$ on pyrroles (1) and (2) leads to predominant β substitution under all experimental conditions. Appreciable substitution at the N atom of (1) is also observed (*ca.* 10%). No evidence for i-$C_3H_7^+$ attack at the N atom of (2) is obtained. (iv) The relative distribution of the isopropylated derivatives of (1) and (2) is much affected by NMe_3. (v) Predominant α-substitution is found for furan (3) and thiophene (4), reaching maximum levels at high pressures and in the presence of 2—5 Torr NMe_3. (vi) In competition experiments, no significant effect due to the presence of benzene is observed. Slightly enhanced relative yields of the β-substituted derivatives are observed at low pressures and in the absence of added NMe_3.

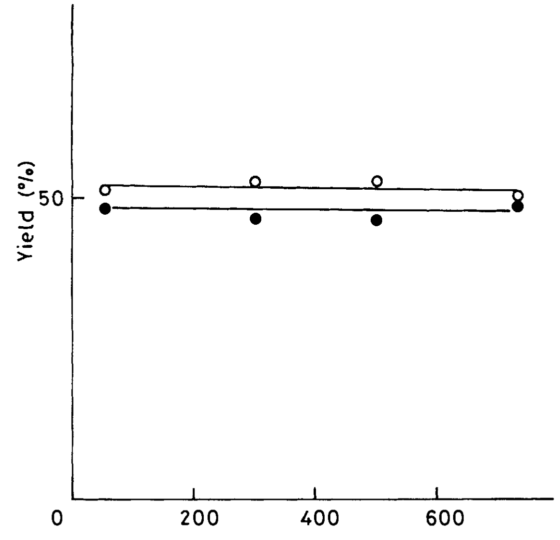


Figure 11. Relative yields of isomeric isopropylthiophenes (**12**) and (**13**) from i-$C_3H_7^+$ ion attack on thiophene (**4**) as a function of the total pressure [$P(C_3H_8)$] of the system, in the absence of NMe_3: ○, 2-isopropylthiophene (**12**); ●, 3-isopropylthiophene (**13**)

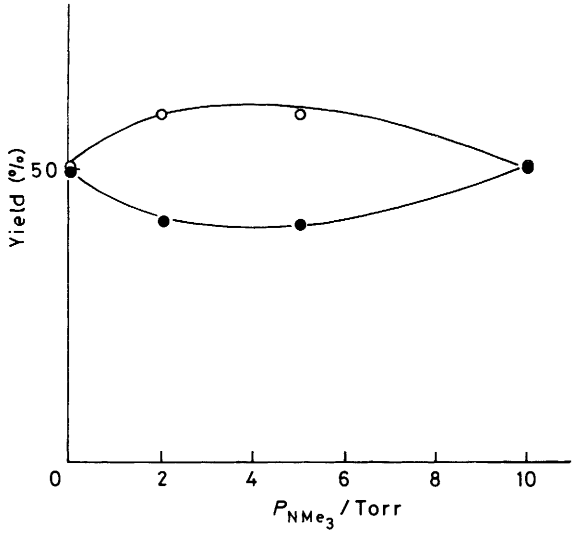


Figure 12. Relative yields of isomeric isopropylthiophenes (**12**) and (**13**) from i-$C_3H_7^+$ ion attack on thiophene (**4**), at 760 Torr, as a function of the partial pressure of NMe_3 [$P(NMe_3)$]: ○, 2-isopropylthiophene (**12**); ●, 3-isopropylthiophene (**13**)

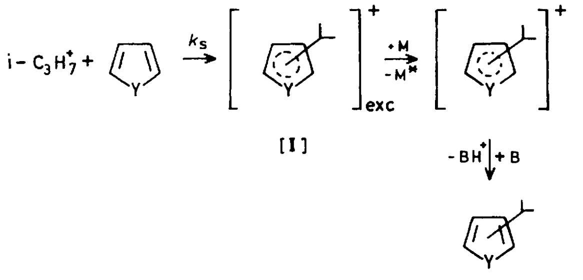
Discussion

Nature and Properties of the Alkylating Reagent.—Extensive studies on the radiolysis and the related ionic chemistry of gaseous C_3H_8 indicate that, in the pressure range of interest to the present work, i-$C_3H_7^+$ represents by far the most significant ionic species, formed in high yields (G value *ca.* 3)[2,6] either directly from C_3H_8 or *via* hydride-ion transfer to its fragment ions, *e.g.* $C_2H_5^+$ or $C_3H_5^+$. Any conceivable n-$C_3H_7^+$ or c-$C_3H_7^+$ isomeric species is found to be converted readily into the most stable secondary i-$C_3H_7^+$ structure, as suggested by independent gas-phase studies,[4-7] and confirmed by the recovery of only minor yields of n-propylated heteroaromatics in the present radiolytic mixtures.

The presence of an effective scavenger (O_2) ensures that thermal radicals do not contribute to the formation of the observed products, while the ionic nature of the alkylation process is confirmed by the sharp decrease of the absolute yields caused by increasing concentrations of NMe_3, an effective interceptor of the i-$C_3H_7^+$ reagent (Figure 2). Use of a large excess (over 100:1) of C_3H_8 over the aromatic substrate can be reasonably expected to deactivate excited i-$C_3H_7^+$ from the radiolysis, owing to the large number of unreactive collisions with the alkane precursor undergone by the alkyl cation before attacking the aromatic substrate.

Thermal i-$C_3H_7^+$ ion may act as a Lewis or as a Brönsted acid which efficiently attacks both n- and π-type substrates. Both protonation and alkylation of the chosen aromatic compounds by i-$C_3H_7^+$ are energetically allowed.* Since the final products from protonation cannot be detected with the analytical techniques employed in the present investigation, it must be explicitly pointed out, when comparing the i-$C_3H_7^+$ attack on different substrates, that the selectivity measured in this work concerns exclusively the alkylation channel, rather than the overall electrophilic reactivity of the cation, and that variations of the substrate selectivity associated with changes of the reaction environment may also reflect alterations of the alkylation pathways, in addition to changes in the absolute rate of isopropylation process.

The Alkylation and Isomerization Processes.—Several exothermic reaction channels are open to the i-$C_3H_7^+$ cation in its attack on the heteroaromatic substrates. In particular, the addition process (1) is characterized by significant exothermicity, the relevant $\Delta H°$ values amounting to *ca.* -53 for (**1**), -66 for (**2**), -38 for (**3**) and -42 kcal mol^{-1} for (**4**).† Process (1) is accompanied by the corresponding exothermic



(1)

process for benzene ($\Delta H°$ -27 kcal mol^{-1}) in the competition experiments. The excited ionic intermediates [I] undergo collisional deactivation with the batch gas molecules (M = C_3H_8) prior to neutralization by proton transfer to a gaseous base B, such as NMe_3 or the substrate itself. In competition with collisional quenching, the excited arenium ions [I] may undergo several secondary processes, including isomerization to a more stable structure or fragmentation with loss of propene.[1a] The latter process represents an additional route to the protonated heteroaromatic compound, which can be formed by direct

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* The PAs of pyrrole (207.6 kcal mol^{-1}), *N*-methylpyrrole (*ca.* 215 kcal mol^{-1}), furan (192.2 kcal mol^{-1}), thiophene (196.5 kcal mol^{-1}), and benzene (181.3 kcal mol^{-1}), are higher than that of propene (179.5 kcal mol^{-1}). PA values taken from ref. 8.

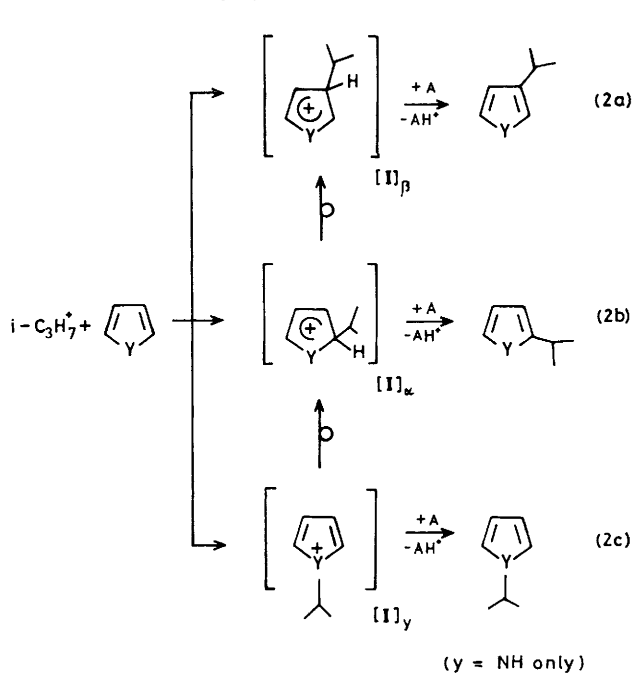
† Values arrived at by estimating the $H°_f$ values of isopropyl-pyrrole, -*N*-methylpyrrole, -furan, and -thiophene from data taken from D. R. Stull, E. F. Westrum, Jr., and G. S. Sinke, 'The Chemical Thermodynamics of Organic Compounds,' Wiley, New York, 1968, and with the further assumption that the PA of the ring position bearing the isopropyl group is only a few kcal mol^{-1} higher than that of the corresponding unsubstituted heteroaromatic compounds.

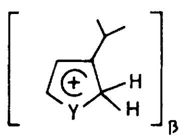
proton transfer from i-$C_3H_7^+$ to the substrate as well. The competition of the direct alkylation channel (1) with the protonation and fragmentation processes is regulated by the density and the nature of the third body (M = C_3H_8). The increase of the apparent k_S/k_B ratios observed by decreasing the sample pressure is in part attributable to the occurrence of an isopropyl-group transfer from the isopropylated benzenium ion to the competing heteroaromatic compound (Figure 3). The intermolecular nature of this exothermic process is supported by the dependence of the apparent ratios upon the [S]/[B] relative concentration. Furthermore, the sensitivity of the isomeric distribution of alkylated heteroaromatic compounds to the [S]/[B] ratio suggests that intermolecular transalkylation between benzene and the heteroaromatic competitor involves, at least in part, a bimolecular mechanism. Owing to their high proton affinity, isopropylated heteroaromatics are the strongest bases present in the gaseous mixtures irradiated without added NMe_3 (PA 225.1 kcal mol^{-1}).[8]

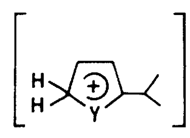
Therefore, deprotonation of the ionic intermediates [I] from the alkylation process (1) may represent a comparatively slow process that allows a long lifetime for the charged intermediates, which thus may undergo extensive fragmentation. On the other hand, the adduct from isopropylation of benzene can be rapidly quenched by efficient exothermic proton transfer to other bases contained in the gaseous mixture, including the heteroaromatic competitor. These conditions explain the apparent increase of the k_S/k_B ratios for pyrroles (1) and (2) by addition of increasing amounts of NMe_3 to the mixtures (Figure 4). Indeed, NMe_3 ensures fast, exothermic deprotonation of all ionic intermediates, including [I], irrespective of the different strengths of their conjugated bases. Their lifetimes are leveled off as well as their extent of decomposition. Instead, with the addition of increasing concentrations of NMe_3, the apparent k_S/k_B ratios for furan (3) and thiophene (4) remain approximately constant or, even, slightly decrease, suggesting that unimolecular fragmentation of the corresponding adducts is negligible at atmospheric pressure. Higher stability levels for the isopropylated adducts from (3) and (4) with respect to pyrroles (1) and (2) are further corroborated by the much higher absolute yields of products estimated at 200 Torr for (3) (82%) and (4) (77%) as compared to those for pyrroles (1) (30%) and (2) (38%). A reasonable explanation for the slight decrease of the apparent k_S/k_B ratio, observed especially for thiophene (4) which increasing NMe_3 concentrations (Figure 4), can be found in the efficient isopropyl-group transfer from the heteroatom of the alkylated adduct to NMe_3, prior to its isomerization to a *C*-alkylated isomer.

In order to account for the isomeric composition of products from each individual heteroarene and its dependence on the reaction environment (Figures 5—12), we suggest that the attack of i-$C_3H_7^+$ ion leads, in the kinetically controlled step of the reaction, to the predominant formation of the β-alkylated derivatives $[\mathbf{I}]_\beta$ of pyrroles (1) (70%) and (2) (61%) and the α-alkylated derivatives $[\mathbf{I}]_\alpha$ of furan (3) (71%). Thiophene (4) is almost equally alkylated at the α- and β-positions [equation (2)]. This conclusion can be inferred from the relevant isomeric distribution of the isopropylated products obtained at atmospheric pressure and at the highest [NMe_3] concentration (Figures 6, 8, 10, and 12), with the restrictive assumption that under such conditions secondary fragmentation and isomerization of isopropylated adducts is minimized by their efficient collisional quenching and fast neutralization by the added base.

Unless deprotonated by the base NMe_3, the intermediates [I] tend to isomerize to a thermodynamically more favoured isomer that, according to the substituent effect on positional basicity and in agreement with previous evidence on related species,[1] is expected to be the β-alkylated structure $[\mathbf{II}]_\beta$. Isomer $[\mathbf{II}]_\beta$ is not necessarily the thermodynamically most stable structure accessible to the intermediates [I]. A plausible candidate could as well be structure $[\mathbf{II}]_\alpha$, whose formation however requires multiple 1,2-alkyl-group and hydrogen-atom transfers within [I] species and is, therefore, efficiently prevented under the present high-pressure conditions by collisional quenching.




$[\mathbf{II}]_\beta$


$[\mathbf{II}]_\alpha$

On the other hand, each step of the $[\mathbf{I}]_y \longrightarrow [\mathbf{I}]_\alpha \longrightarrow [\mathbf{I}]_\beta \longrightarrow [\mathbf{II}]_\beta$ sequence requires only few 1,2 hydrogen- or alkyl-group migrations, whose extent is determined by the specific reaction environment. This is suggested by the dependence of the isomeric composition of the alkylated products on the reaction conditions. Inspection of Figures 5—8 suggests that the relative distribution of the isomeric isopropyl pyrroles (5)—(7) from (1) and (8) and (9) from (2) is mainly determined by competition between the isomerization process and the deprotonation step of equation (2) (whose rate is controlled by the A = NMe_3 concentration) (Figures 6 and 8). Collisional deactivation of the excited isopropylated adducts may play a role as well in determining their isomeric distribution, as shown in Figures 5 and 7. Here, however, a slight increase of the relative yield of the α-alkylated products to the exclusive expenses of the β-alkylated ones is observed at low pressures. This effect cannot be attributed to collisional quenching of the isomerization sequence $[\mathbf{I}]_y \longrightarrow [\mathbf{I}]_\alpha \longrightarrow [\mathbf{I}]_\beta \longrightarrow [\mathbf{II}]_\beta$, since, at least at variance with the results from pyrrole (1) (Figure 5), depletion of the *N*-isopropylpyrrole (5) yield should be observed at low pressures. Rather, a plausible explanation can be found in a different stability of the isomeric alkylated heteroarenium ions toward unimolecular fragmentation, under the same conditions of pressure. On these grounds, we conclude that, after i-$C_3H_7^+$ attack on pyrroles (1) and (2), the fast isomerization sequence $[\mathbf{I}] \longrightarrow [\mathbf{II}]_\beta$ takes place, which is characterized by a comparatively limited activation energy. Furthermore, increase of the yield of the β-isopropyl derivative

(7) of (1), observed by decreasing the NMe_3 concentration (Figure 6), apparently takes place at the expense of the α-isomers (6) without any concomitant decrease of the nitrogen isomer (5), thus suggesting that the first step of the isomerization sequence ($[I]_y \longrightarrow [I]_\alpha$) is substantially slower than the following one ($[I]_\alpha \longrightarrow [I]_\beta$).[1b]

A reaction pattern, similar to that of equation (2), is valid for $i\text{-}C_3H_7^+$ ion attack on furan (3) and thiophene (4) as well. Accordingly, the initial population of the *C*-alkylated intermediates $[I]_\alpha$ and $[I]_\beta$ emerges directly from the isomeric distribution of the neutral derivatives as measured under kinetically controlled conditions, namely at atmospheric pressure and in the presence of 10 Torr NMe_3. Under such conditions, secondary fragmentation and isomerization of excited [I] are minimized. However, the initial populaton of Y-alkylated intermediates $[I]_y$, accompanying formation of the corresponding *C*-alkylated isomers $[I]_\alpha$ and $[I]_\beta$ [equation (2)], cannot be directly determined. In contrast with $[I]_\alpha$ and $[I]_\beta$, intermediates $[I]_y$ cannot generate isolable alkylated products without preliminary isomerization to a *C*-alkylated intermediate, a route prevented under kinetically controlled conditions. Nevertheless, a rough estimate of the relative abundance of $[I]_y$, formed in the kinetically significant step of equation (2), can be inferred from a comparative analysis of Figures 9 and 10 for furan (3) and of the corresponding ones for thiophene (4) (Figures 11 and 12). In the case of furan, the (10):(11) 2.45 ratio, measured under kinetically controlled conditions (Figure 10), increases to 3.17 at $P(NMe_3)$ 5 Torr and 3.35 at $P(NMe_3)$ 2 Torr, and finally drops to 2.12 when the irradiation is carried out at 760 Torr and without any added NMe_3. As the total pressure is lowered (Figure 9), this ratio further decreases to reach 1.38 at $P(C_3H_8)$ 50 Torr. Qualitatively similar trends are observed for thiophene (Figures 11 and 12). Such behaviour is again accounted for by an isomerization sequence $[I]_y \longrightarrow [I]_\alpha \longrightarrow [I]_\beta \longrightarrow [II]_\beta$, whose first step ($[I]_y \longrightarrow [I]_\alpha$) proceeds nearly to completion, even at atmospheric pressures and in the presence of limited concentrations of NMe_3 [$P(NMe_3)$ 2—5 Torr]. The subsequent step ($[I]_\alpha \longrightarrow [I]_\beta$) appears to be inhibited by collisional quenching and by the presence of an added base. It can be, therefore, concluded, by analogy with the behaviour of the intermediates [I] from pyrroles (1) and (2), that the excited isopropylated adducts from furan (3) and thiophene (4) tend to isomerize to a more favoured isomer, which according to the experimental evidence, is the β-alkylated structure $[II]_\beta$. The relative abundance of the intermediates $[I]_y$ from equation (2c) can be estimated from a comparison of the α:β isomeric distribution of the isopropylated products when the irradiation is carried out at different NMe_3 concentrations (Figures 10 and 12). With the reasonable assumption that at least at 760 Torr and in the presence of NMe_3, the isomerization sequence $[I] \longrightarrow [II]_\beta$ takes place essentially *via* an intramolecular mechanism,[4,9] the relevant α:β ratios increase to an extent that would reflect approximately the contribution by the fast $[I]_y \longrightarrow [I]_\alpha$ step of the isomerization sequence to the population of the intermediates $[I]_\alpha$ and, therefore, the relative abundance of the corresponding species $[I]_y$, or at least its lower limit.* On this basis, we can roughly estimate the relative extent of direct $i\text{-}C_3H_7^+$ ion attack on the heteroatom of furan ($\geq 26\%$) and of thiophene ($\geq 22\%$). Accordingly, we can evaluate the intrinsic positional selectivity of $i\text{-}C_3H_7^+$ toward furan (3) and thiophene (4). The relevant figures, together with those concerning pyrroles (1) and (2), are shown in Figure 13.

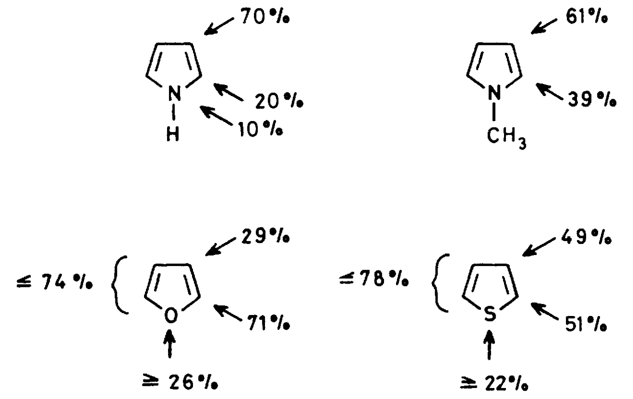


Figure 13. Positional selectivity of gaseous $i\text{-}C_3H_7^+$ ion towards simple heteroaromatic compounds

Substrate and Positional Selectivity.—Owing to the multiplicity of reaction channels in the gas-phase attack of $i\text{-}C_3H_7^+$ on the heteroaromatics substrates (1)—(4), and to the occurrence of secondary fragmentation and isomerization, using the experimental k_S/k_B ratios and isomeric composition of products as a basis for comparing the reactivity and selectivity of gaseous $i\text{-}C_3H_7^+$ cation is open to question. Nevertheless, restricting comparison to the alkylation processes and referring exclusively to the results obtained at the highest C_3H_8 pressures and NMe_3 concentration, *i.e.* under conditions where effective deactivation and deprotonation minimize secondary processes, assessment of the intrinsic substrate and positional selectivity of $i\text{-}C_3H_7^+$ ions toward the chosen heteroaromatic compounds is possible.

The values of the k_S/k_B ratios for gas-phase isopropylation of (1) (k_S/k_B 0.7) and (2) (k_S/k_B 0.8) in the presence of benzene, measured under kinetically controlled conditions (Figure 4), clearly indicates no distinct preference of the ionic electrophile toward benzene and the selected pyrroles. Concerning the substrate selectivity of $i\text{-}C_3H_7^+$ ion towards furan (3) and thiophene (4), it should be considered that a significant fraction ($\geq 26\%$ for furan, $\geq 22\%$ for thiophene) of the $i\text{-}C_3H_7^+$ ion attacks the heteroatom of the substrate, giving rise to the corresponding intermediate $[I]_y$, whose isomerization to a *C*-alkylated isomer and eventually to a neutral alkylated product is hindered by the presence of the NMe_3 interceptor.

This effect is visualized in Figure 4 by the slight decrease of the apparent k_S/k_B ratios with increasing $[NMe_3]$, exclusively observed for (3) and (4). Correction of the apparent k_S/k_B ratios, measured under kinetically controlled conditions. *i.e.* 0.3 for (3) and 0.8 for (4), by factor of 1.4 for (3) and 1.3 for (4) accounts for this fraction and provides the actual reactivity ratios, *i.e.* k_S/k_B 0.5 for (3), 1.1 for (4), on which to base any discussion on heteroaromatic reactivity. On these grounds, it is found that simple five-membered heteroaromatic compounds (1)—(4), as well as benzene, react with gaseous $i\text{-}C_3H_7^+$ ion at rates falling within the same order of magnitude, in substantial agreement with the limited substrate discrimination shown by $i\text{-}C_3H_7^+$ in related gas-phase aromatic substitutions[4] and by other gaseous alkylating reactants towards the same heteroaromatic substrates investigated in the present study.[1]

The intrinsic directive properties of the selected heteroaromatics (1)—(4) towards gas-phase $i\text{-}C_3H_7^+$ ion attack are shown in Figure 13. The reported figures demonstrate, in complete agreement with the conclusions reached in independent gas-phase investigations,[1] the tendency of pyrroles (1) and (2) to direct the ionic electrophile towards the C_β centres [70% (1); 61% (2)], *i.e.* the ring carbons with the highest values of the negative net charge.[10] These results are well accounted for by a theoretical model, based upon the molecular electrostatic

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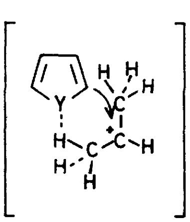
* We cannot exclude *a priori* that partial $[I]_\alpha \longrightarrow [I]_\beta$ isomerization occurs even at $P(NMe_3)$ 2 Torr and at 760 Torr C_3H_8. Furthermore, it should be taken into account that isomerization may take place in part *via* an intermolecular mechanism, allowing direct $[I]_y \longrightarrow [I]_\beta$ transfer.

potential induced around an isolated heteroaromatic molecule by the interaction with a positive point charge,[11] which predicts the C_β sites of (**1**) and (**2**) as the preferred ones for electrophilic attack, while substitution at the other strongly attractive centre (the nitrogen atoms) is inhibited by the presence of relatively acidic[12] hydrogens (NH or NCH_3). Such hindrance is expected to be more pronounced for (**2**) than for (**1**).[13] Accordingly, no evidence of nitrogen substitution is observed for (**2**), whereas only a limited nitrogen attack (10%) is measured for unsubstituted pyrrole (**1**).

The molecular electrostatic potential model may also account for the site selectivity shown by i-$C_3H_7^+$ ion in its attack on furan (**3**) and thiophene (**4**).

In this view, the intrinsic directive properties of furan toward gaseous i-$C_3H_7^+$ can be considered as determined by the combined effects of the static electronic charge distribution of the isolated substrate, which would favour electrophilic attack on the O and C_β atoms, and the dynamic response of the electronic structure of the reactants in the heteroatom–electrophile interaction, which would increase the probability of α-attack.[1,11] In the case of i-$C_3H_7^+$, the latter effect may be magnified by the recognized 'chelating' properties of the electrophile, which would produce the electrostatic adduct [**III**] by attack on a bidentate substrate, such as (**3**).[4c,9] A similar rationale was employed to account for the extensive α-substitution observed in the gas-phase t-$C_4H_9^+$ and $CH_3FCH_3^+$ ion attack on furan.[1] As expected, the significance of such adducts and, hence, the relative extent of substitution is determined by the intensity of the 'hydrogen-bond-like' interaction between the partially charged hydrogens of the electrophile and the *n*-electrons of the heteroatom. Accordingly, when an intense interaction is established, as in the adduct [**III**], with Y = O, α-substitution takes place to an extent exceeding that predicted exclusively on the grounds of the electronic charge distribution in the substrate.[14] When, instead, electrostatic interaction between the heteroatom and the electrophile is much less significant, as in the case of thiophene,[15] the resulting positional selectivity is largely determined by the charge density of the reaction centres in the unperturbed molecule, *i.e.* α > β > S.[16]


[**III**]

In conclusion, the present gas-phase results confirm the previous gas-phase electrophilic heteroaromatic substitution model governed mainly by attractive electrostatic interactions between the ionic reagent and the negatively charged sites of the heteroaromatic molecule.[1] By analogy with the behaviour of related bidentate alkylating electrophiles,[1] isopropylation of simple heteroaromatic compounds is characterized by relatively small substrate selectivity, accompanied by an appreciable positional discrimination favouring direct β-attack in pyrroles and α-substitution in furan and thiophene, the latter favoured by preliminary electrostatic interaction between the *n*-electrons of the heteroatom and the acidic hydrogens of the ionic electrophile.

Comparison with Related Gas- and Condensed-phase Studies.—The results outlined in the previous sections provide a definitive answer to the question concerning the substrate and positional selectivity of ionic alkylating electrophiles in heteroaromatic substitution carried out in the dilute gas state, where the intrinsic reactivity properties of the reactants are not affected by extraneous and variable environmental factors. The conclusions reached for the intrinsic heteroaromatic reactivity of alkylating ions are confirmed by the present study.[1]

The contrast between low substrate discrimination and significant positional selectivity observed in the gas-phase heteroaromatic substitution by $CH_3FCH_3^+$,[1a–c] t-$C_4H_9^+$,[1d] and $^3HeT^+$ ions,[1e] is outlined by the results of i-$C_3H_7^+$ attack as well. Restricting comparison to the available gas-phase alkylation data, i-$C_3H_7^+$ ions, as well as $CH_3FCH_3^+$ and t-$C_4H_9^+$ ions, display a substrate selectivity in the gas phase which is exceedingly low by the reactivity standards normally measured in the most common electrophilic substitutions in solution.[10a–c,17] Nevertheless, the i-$C_3H_7^+$ electrophile exhibits an intrinsic substrate selectivity toward (**1**)—(**4**), covering only *ca.* 2 units on the relative reactivity scale, compared with the *ca.* 3 and 5 units covered by the milder $CH_3FCH_3^+$ and t-$C_4H_9^+$ electrophiles. Although significant analogies are observed in regard to the orienting properties of pyrroles (**1**) and (**2**), furan (**3**), and thiophene (**4**) toward gaseous bidentate electrophiles, such as i-$C_3H_7^+$, t-$C_4H_9^+$, and $CH_3FCH_3^+$, nevertheless appreciable differences in the relevant site selectivities can be pointed out, which can be related to the reactivity and structural features of the ionic reactant. Thus, while the β:α ratios measured in i-$C_3H_7^+$, t-$C_4H_9^+$, and $CH_3FCH_3^+$ alkylation of pyrroles are qualitatively similar for all three alkylating reactants (1.1 < β:α < 3.5), a significant difference is acknowledged as regards the C:N selectivity ratios measured for (**1**). Carbon *versus* nitrogen alkylation ratios, in fact, increase from *ca.* 1.9 for $CH_3FCH_3^+$ to 9.0 for i-$C_3H_7^+$ and to *ca.* 13.3 for t-$C_4H_9^+$. A more pronounced repulsive interaction between the partially charged hydrogens of the 'bulky' t-$C_4H_9^+$ cation and the acidic N–H moiety of (**1**) may be responsible for the low extent of nitrogen attack, compared with that displayed by the less encumbered i-$C_3H_7^+$ and $CH_3FCH_3^+$ ions. The comparatively high extent of nitrogen substitution, exhibited by the latter electrophile, may be related to its distinct affinity for highly localized electrons (the nitrogen centre of the nucleophilic substrate).[9b,c,18] A similar argument applies for the relative extent of O attack observed for furan (**3**) as well. Here, the mildest electrophile investigated, *i.e.* the t-$C_4H_9^+$ cation, displays the most pronounced α *versus* β site selectivity (91:9), whereas it substantially decreases for the relatively stronger i-$C_3H_7^+$ (71:29) and $CH_3FCH_3^+$ (55:45) electrophiles. A similar trend is observed in the case of thiophene (**4**), where the α *versus* β site selectivity decreases from 80:20 (t-$C_4H_9^+$) to 51:49 (i-$C_3H_7^+$) and 53:47 ($CH_3FCH_3^+$).

Comparison of the available gas-phase data with those concerning the corresponding reactions occurring in solution is prevented by the lack of kinetic data concerning the reactivity of the simple heteroaromatics (**1**)—(**4**) toward electrophilic substitution in solution. In fact, meaningful kinetic measurements involving the selected heteroaromatics are complicated by their high sensitivity to acidic media and by their tendency to undergo extensive polymerization.[19] All these factors may significantly alter the very nature of the heteroaromatic substrate, thus preventing the kinetic study of its nucleophilic reactivity. In conclusion, perhaps it is not unwarranted to claim that the results of this series of gas-phase studies[1] represent the only available kinetic data concerning the inter- and intra-molecular selectivity of the electrophilic attack on simple heteroarenes, irrespective of the particular reaction environment.

References

1 (*a*) M. Speranza, *J. Chem. Soc., Chem. Commun.*, 1981, 1177; (*b*) G. Angelini, C. Sparapani, and M. Speranza, *J. Am. Chem. Soc.*, 1982, **104**, 7084; (*c*) G. Angelini, G. Lilla, and M. Speranza, *ibid.*, p. 7091;

(*d*) A. Margonelli and M. Speranza, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1491; (*e*) G. Angelini, G. Laguzzi, C, Sparapani, and M. Speranza, *J. Am. Chem. Soc.*, 1984, **106**, 37.

2 (*a*) P. Ausloos, in 'Ion–Molecule Reactions,' ed. J. L. Franklin, Plenum Press, New York, 1970; (*b*) P. Ausloos and S. G. Lias, *J. Chem. Phys.*, 1962, **36**, 3163; (*c*) S. G. Lias and P. Ausloos, *ibid.*, 1962, **37**, 877.

3 (*a*) H. Heaney and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1973, 499; (*b*) G. P. Bean, *J. Org. Chem.*, 1967, **32**, 228; (*c*) H. Gilman, N. O. Calloway, and R. R. Burtner, *J. Am. Chem. Soc.*, 1935, **57**, 906; (*d*) H. Gilman and N. O. Calloway, *ibid.*, 1933, **55**, 4197; (*e*) H. Pines, B. Kvetinskas, and J. A. Vesely, *ibid.*, 1950, **72**, 1568.

4 (*a*) F. Cacace and E. Possagno, *J. Am. Chem. Soc.*, 1973, **95**, 3397; (*b*) M. Attinà, F. Cacace, G. Ciranni, and P. Giacomello, *ibid.*, 1977, **99**, 2611; (*c*) M. Attinà and P. Giacomello, *ibid.*, 1979, **101**, 6040.

5 (*a*) S. G. Lias and P. Ausloos, *J. Chem. Phys.*, 1965, **43**, 2748; (*b*) G. J. Collin, *Can. J. Chem.*, 1976, **54**, 3050.

6 (*a*) I. B. Sandoval and P. Ausloos, *J. Chem. Phys.*, 1963, **38**, 2452; (*b*) G. R. Freeman, *Radiat. Res. Rev.*, 1968, **1**, 1.

7 (*a*) S. G. Lias, R. E. Rebbert, and P. Ausloos, *J. Am. Chem. Soc.*, 1970, **92**, 6430; (*b*) D. J. McAdoo, F. W. Lafferty, and P. F. Bente III, *ibid.*, 1972, **94**, 2024.

8 S. G. Lias, J. F. Liebman, and R. D. Levin, *J. Phys. Chem. Ref. Data*, 1984, **13**, 695.

9 (*a*) M. Attinà, F. Cacace, G. Ciranni, and P. Giacomello, *J. Chem. Soc., Perkin Trans.* 2, 1979, 891; (*b*) M. Attinà and F. Cacace, *J. Am. Chem. Soc.*, 1983, **105**, 1122; (*c*) M. Attinà, F. Cacace, and G. De Petris, *ibid.*, 1985, **107**, 1556.

10 (*a*) I. A. Abronin, L. I. Belenkii, and Ya. L. Gol'dfarb, in 'New Trends in Heterocyclic Chemistry,' Elsevier, Amsterdam, 1979; (*b*) J. Ridd, *Phys. Methods Heterocycl. Chem.*, 1971, **4**, 55; (*c*) R. A. Jones and G. P. Bean, in 'The Chemistry of Pyrroles,' Academic Press, New York, 1977; (*d*) J. Catalan and M. Yanez, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1672; (*e*) M. H. Palmer and A. G. Gaskell, *Theor. Chim. Acta*, 1971, **23**, 52; (*f*) R. W. Kramling and E. L. Wagner, *ibid.*, 1969, **15**, 43.

11 (*a*) P. Politzer and H. Weinstein, *Tetrahedron*, 1975, **31**, 915; (*b*) D. Chou and H. Weinstein, *ibid.*, 1978, **34**, 275; (*c*) P. Politzer, R. A. Donelly, and K. C. Daiker, *J. Chem. Soc., Chem. Commun.*, 1973, 617; (*d*) G. Bertheir, R. Bonaccorsi, E. Scrocco, and J. Tomasi, *Theor. Chim. Acta*, 1972, **26**, 101.

12 J. E. Bartmess, J. A. Scott, and R. T. McIver, Jr., *J. Am. Chem. Soc.*, 1979, **101**, 6046.

13 D. W. Scott, *J. Mol. Spectrosc.*, 1971, **37**, 77.

14 (*a*) R. B. Hermann, *Int. J. Quantum Chem.*, 1968, **2**, 165; (*b*) H. J. T. Preston and J. J. Kaufman, *Int. J. Quantum Chem. Symp.*, 1973, **7**, 207; (*c*) J. J. Kaufman, H. J. T. Preston, E. Kerman, and L. C. Cusachs, *ibid.*, p. 249.

15 (*a*) P. Schuster, G. Zundel, and C. Sandorfy, in 'The Hydrogen Bond,' North-Holland, Amsterdam, 1976; (*b*) P. J. Desmueles and L. C. Allen, *J. Chem. Phys.*, 1980, **72**, 4731; (*c*) R. C. Kerns and L. C. Allen, *J. Am. Chem. Soc.*, 1978, **100**, 6587; (*d*) K. F. Purcell and R. S. Drago, *ibid.*, 1967, **89**, 2874; (*e*) T. B. Vishnyakova, V. V. Lobanov, and V. K. Pogorelyi, *Eksp. Khim.*, 1980, **16**, 534.

16 (*a*) V. Gelius, B. Roos, and P. Siegbahn, *Theor. Chim. Acta*, 1972, **27**, 171; (*b*) F. Bernardi, A. Bottoni, and A. Mangini, *Gazz. Chim. Ital.*, 1977, **101**, 55.

17 (*a*) G. Marino, *Adv. Heterocyclic. Chem.*, 1971, **13**, 235; (*b*) A. R. Katritzky and J. M. Lagowsky, in 'The Principles of Heterocyclic Chemistry,' Academic Press, New York, 1968; (*c*) A. Albert, in 'Heterocyclic Chemistry,' Oxford Univ. Press, New York, 1968; (*d*) R. A. Jones, *Adv. Heterocycl. Chem.*, 1970, **11**, 383.

18 N. Pepe and M. Speranza, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1430.

19 R. Nicoletti and C. Germani, *Ric. Sci.*, 1966, **36**, 1343.

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