

Gas-phase Heteroaromatic Substitution. Part 4.¹ Electrophilic Attack of *t*-Butyl Cation on Pyrrole, *N*-Methylpyrrole, Furan, and Thiophene

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t-Butyl cation, obtained in the gas state from the γ -radiolysis of neopentane has been allowed to react with pyrrole (1), *N*-methylpyrrole (2), furan (3), and thiophene (4). Experiments have been carried out in the pressure range 50–760 Torr and in the presence of variable concentrations of a gaseous base (NMe_3). The reactivity of simple heteroaromatic compounds relative to toluene in competition experiments is found to depend markedly upon the composition of the gaseous reaction environment. The apparent k_s/k_T ratios decrease slightly with increasing pressure. At atmospheric pressure, these ratios increase with the NMe_3 concentration levelling off to a value of 1.0 (1), 2.2 (2), 2.6 (3), and 0.6 (4), at the highest base concentration ($P_{\text{NMe}_3} = 10$ Torr). Under the same conditions, predominant β substitution occurs in the pyrroles [$\beta : \alpha : \text{N} = 72 : 21 : 7$ from (1) and $\beta : \alpha = 53 : 47$, from (2)], whereas α -attack is favoured in the case of furan ($\beta : \alpha = 9 : 91$) and thiophene ($\beta : \alpha = 20 : 80$). The gaseous electrophile appears rather unselective between the n - and the π -type centres of furan (O:ring = 50:50) and thiophene (S:ring = 40:60), while it displays no [in the case of (2)] or very limited substitution [7% for (1)] on the heteroatom of the pyrroles. A mechanism based upon reversible addition of the *t*-butyl cation to the heteroaromatic nucleus, involving preliminary formation of an electrostatic adduct, is used to account for the formation of the *t*-butylated products and their isomeric composition. It is concluded that the gas-phase *t*-butyl alkylation of simple five-membered heteroaromatic compounds is regulated by electrostatic interactions established within the encounter pair. A close correspondence exists between this rationalization of the present gas-phase results and recent theoretical and experimental evidence concerning related alkylation processes.

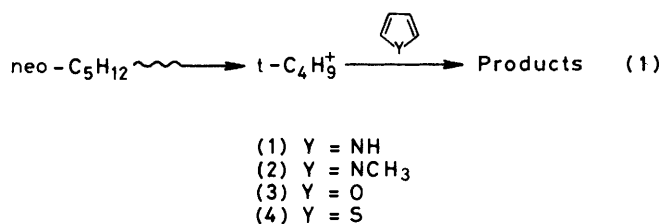
Few kinetic data are available on the electrophilic substitution of heteroaromatic compounds in the gas phase, *i.e.* in a reaction environment entirely free from the complicated effects of solvation and ion pairing. A comprehensive study of the gas-phase methylation of simple five-membered heteroaromatic compounds by radiolytic $\text{CH}_3\text{XCH}_3^+$ ($\text{X} = \text{F}$ or Cl) ions has been recently reported by us.¹ The relevant data demonstrated little substrate discrimination for the chosen electrophiles, accompanied by an appreciable positional selectivity towards those substrate positions with the highest negative net charge (the β -carbons and the nitrogen atom of pyrrole, the oxygen of furan, and the α -carbons of thiophene).

From the limited data, it could not be decided whether the unexpected behaviour of $\text{CH}_3\text{XCH}_3^+$ ions towards simple heteroatomics was due to the specific nature of the reactants.

To gain further insight into the factors regulating gas-phase heteroaromatic alkylation, we have now extended the investigation to a milder alkylating electrophile, the *t*-butyl cation, which can be conveniently generated in the gas phase by γ -radiolysis of neopentane.²

Experimental

Materials.—Neopentane, oxygen, and trimethylamine were research grade gases from Matheson Co., with a minimum purity of 99.99 mol%. Toluene, pyrrole, *N*-methylpyrrole, furan, and thiophene, (research grade chemicals from Fluka AG) were analysed by g.l.c. to check for the absence of alkylated products. Isomeric *t*-butylpyrroles, *t*-butyl-*N*-methylpyrroles, *t*-butylthiophenes, and 3-*t*-butyltoluene, required as g.l.c. standards, were prepared according to established procedures.³ 4-*t*-Butyltoluene was commercial (Aldrich Chemical Co). 2-*t*-Butylfuran was prepared by HgCl_2 -catalysed decarboxylation⁴ of the 5-*t*-butyl-2-furoic acid.⁵ Catalytic isomerization of 2-*t*-butylfuran on H_3PO_4 -Keiselhur afforded 3-*t*-butylfuran in low yields (<20%).⁶ These *t*-butyl derivatives, required as g.l.c. standards for the analysis



of the irradiated samples, were 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 unit, on the same columns employed for the analysis of the reaction mixtures, and their identity verified by conventional n.m.r. spectroscopy.

Procedure.—The general procedure used for the preparation of the samples and their irradiation have been described in detail elsewhere.⁷ Typical experimental conditions were: neopentane, 50–760 Torr; heteroaromatic substrate, 0.3–4.5 Torr; O_2 , 4 Torr; NMe_3 , 0–10 Torr. The radiation dose, as measured with a neopentane dosimeter,^{2b,8} was 3.3 Mrad, delivered at the rate of 0.22 Mrad h^{-1} at 37.5 °C, in a ^{60}Co γ -cell (Atomic Energy Canada Ltd.). Control experiments carried out at higher doses showed that the relative yields of products and their isomeric composition are largely independent of the dose, at least up to *ca.* 14 Mrad.

Product Analysis.—The analysis of the products was performed by injecting measured portions of the homogeneous reaction mixture into a Perkin-Elmer model Sigma 1 gas chromatograph, equipped with a flame ionization detection unit. In order to prevent selective losses of the reaction products by adsorption on the glass of the reaction bulb (and to obtain reproducible and meaningful reaction yields) the

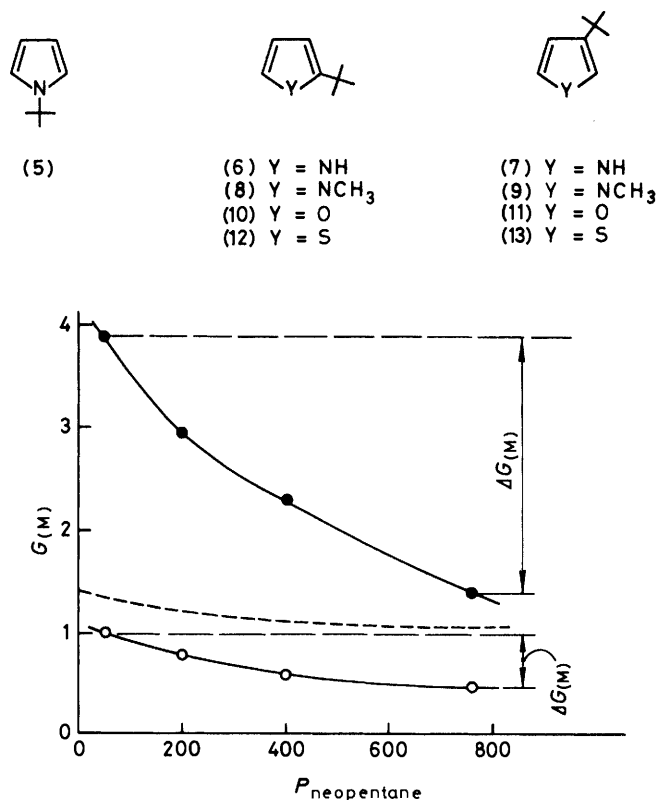


Figure 1. Dependence of the overall absolute yields of t-butyl derivatives of simple heteroaromatics upon the total pressure of the irradiated system ($P_{\text{neopentane}}$): ●, t-butylfurans (10), (11); ○, t-butylthiophenes (12), (13); broken line: t-butylpyrroles (5)–(7) and t-butyl-N-methylpyrroles (8), (9).

analysis was repeated after careful washing of the bulb walls with freshly purified ethyl acetate. Satisfactory agreement between the results of the gaseous mixture and the ethyl acetate solution analysis was found in all runs. The products were identified by comparison of their retention volumes with those of the authentic standard compounds. Appropriate calibration curves for the detector response were employed to measure the yields of each product. The identity of the products was further confirmed by g.l.c.–m.s., using a Micromass VG 7070 mass spectrometer. The same instrument operated in the chemical ionization (CI) mode, was employed for the CI experiments. The reagent gas (neopentane) pressure in the source was directly measured using a Bourdon gauge, inserted in place of the direct introduction probe.

Results

Gas-phase attack of t-butyl ions, generated by γ -radiolysis of neopentane, on pyrroles (1) and (2), furan (3), and thiophene (4) yields the corresponding alkylated derivatives; (5)–(7) from (1); (8) and (9) from (2); (10) and (11) from (3); (12) and (13) from (4). Their absolute yields ($G_{(M)}$ values), expressed as the number of molecules M produced per 100 eV of energy absorbed by the gaseous mixture are found to be markedly dependent upon the experimental conditions. 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 character of the t-butylation process. In addition, comparison of the overall absolute yield

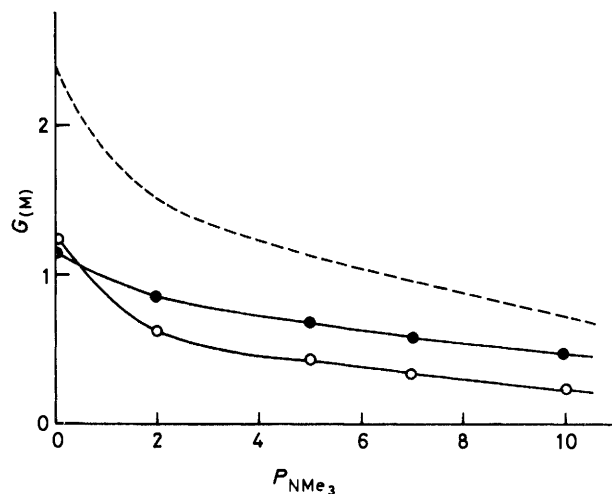


Figure 2. Reaction of neo- C_5H_{12} (740–760 Torr), *N*-methylpyrrole (2) (0.9–1.2 Torr), toluene (1.0–1.5 Torr), and O_2 (4 Torr). Dependence of the $G_{(M)}$ values on the partial pressure of NMe_3 (P_{NMe_3}): ●, t-butyl-N-methylpyrroles (8), (9); ○, 3- and 4-t-butyl-toluenes. The broken line reports the total yield of products. Similar curves were obtained for pyrrole (1), furan (3), and thiophene (4)

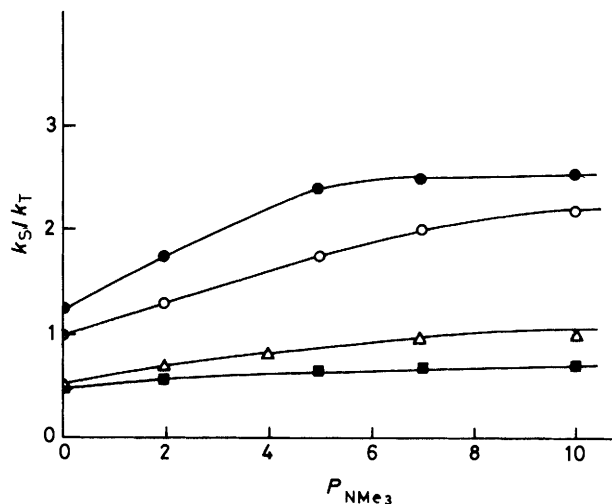


Figure 3. Dependence of the apparent k_s/k_T ratio (see text) on the partial pressure of NMe_3 (P_{NMe_3}) at a total pressure of 760 Torr: Δ, pyrrole (1)-toluene; ○, *N*-methylpyrrole (2)-toluene; ●, furan (3)-toluene; ■, thiophene (4)-toluene

of the t-butylated products recovered at 200 Torr with the known $G_{(t-\text{C}_4\text{H}_9^+)}$ values which approach 3.2 at the same pressure² demonstrates that condensation between the alkylating reactant and the heteroaromatic compound is a highly efficient process [87% for (1); 76% for (2); 90% for (3); 42% for (4)]. This is further confirmed by the neopentane-CI mass spectra of the chosen heteroaromatic compounds (0.1 mol%), recorded at pressures ranging from 0.1 to 1.0 Torr and at the ion-source temperature of 200 °C. At the highest pressures the $[M + 57]^+$ species and the $[M + 1]^+$ protonation fragment are major ions.

The apparent ratios of the specific rate constants, k_s/k_T , measured from the radiolytic competition experiments, are reported in Figure 3 as a function of the NMe_3 concentration. A regular increase of the k_s/k_T values with $[\text{NMe}_3]$ is observed.

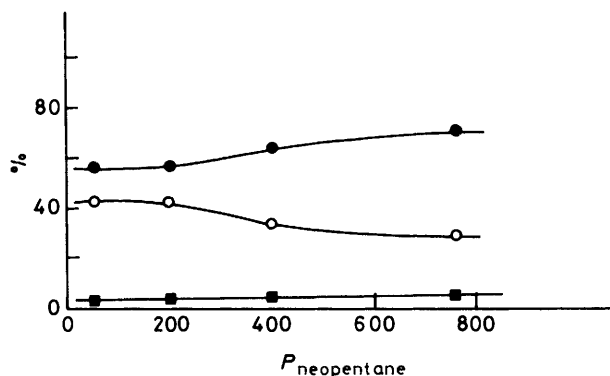


Figure 4. Relative yields of isomeric t-butylpyrroles (5)–(7) from $t\text{-C}_4\text{H}_9^+$ ion attack on pyrrole (1) as a function of the total pressure [$P_{\text{neopentane}}$] of the system in the absence of NMe_3 : ■, *N*-t-butylpyrrole (5); ○, 2-t-butylpyrrole (6); ●, 3-t-butylpyrrole (7)

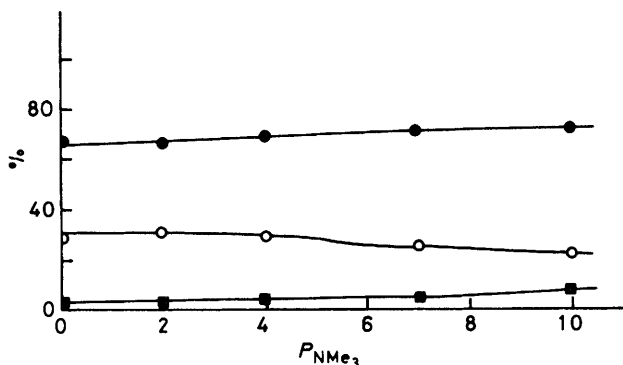


Figure 5. Relative yields of isomeric t-butylpyrroles (5)–(7) from the $t\text{-C}_4\text{H}_9^+$ ion attack on pyrrole (1), at 760 Torr, as a function of the partial pressure of NMe_3 (P_{NMe_3}): ■, *N*-t-butylpyrrole (5); ○, 2-t-butylpyrrole (6); ●, 3-t-butylpyrrole (7)

An appreciable dependence of the k_s/k_T ratios is also found as a function of the heteroaromatic *versus* toluene concentration ratio ($[\text{S}]/[\text{T}]$) at atmospheric pressure.

The gas-phase t-butylation of pyrrole (1) and *N*-methylpyrrole (2) gives rise to the corresponding isomeric derivatives (5)–(9),* whose relative distribution is affected by the pressure of the system and the NMe_3 concentration. It should be noted that the most conspicuous variation of the isomeric distribution from (1) is obtained by varying the total pressure of the system (from $\beta : \alpha : \text{N} = 56.3 : 41.2 : 2.5$ at 50 Torr to $69.1 : 28.1 : 2.8$ at 760 Torr) (*cf.* Figures 4 and 5). In contrast, the isomeric distribution of products from (2) appears most affected by the presence and concentration of NMe_3 (from $\beta : \alpha = 60.1 : 33.9$ in the absence of NMe_3 to $\beta : \alpha = 53.2 : 46.8$ at 10 Torr of NMe_3) (Figure 6). The relative distribution of the isomeric t-butyl derivatives of furan (3) and thiophene (4) [(10)–(13)] is instead largely independent of the pressure of the system and the NMe_3 concentration. The α -substituted derivatives are formed predominantly under all conditions, their relative yield tending to increase slightly at low pressures and in the absence of base [91.4–96.0% for (10); 80.2–82.8% for (12)]. In the competition experiments, the presence

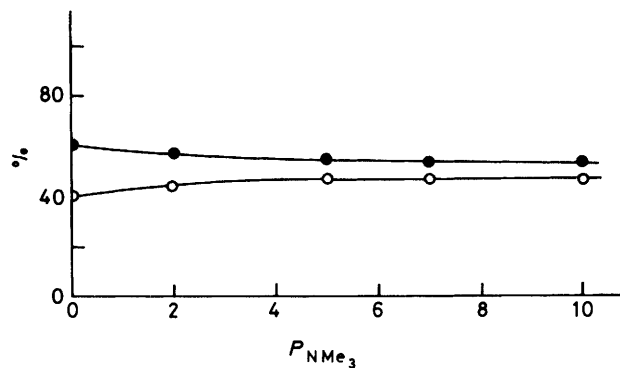


Figure 6. Relative yields of isomeric t-butyl-*N*-methylpyrroles (8), (9) from $t\text{-C}_4\text{H}_9^+$ ion attack on *N*-methylpyrrole (2) at 760 Torr, as a function of the partial pressure of NMe_3 (P_{NMe_3}): ○, 2-t-butyl-*N*-methylpyrrole (8); ●, 3-t-butyl-*N*-methylpyrrole (9)

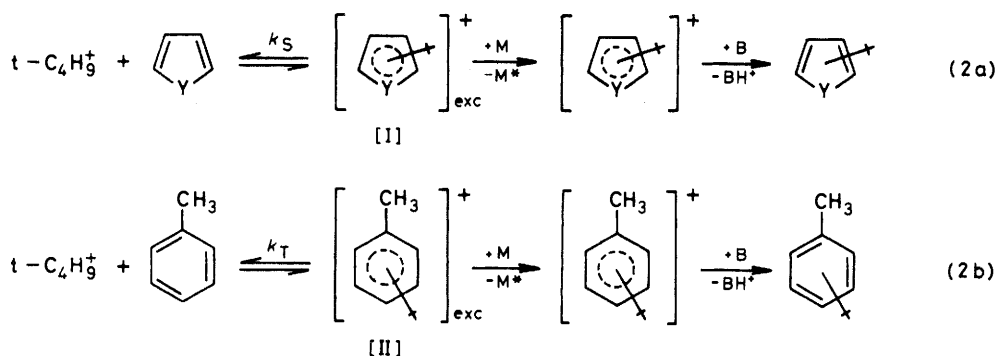
and the concentration of the toluene competitor do not appreciably influence the isomeric distribution of the t-butylation of the heteroaromatics under all conditions used. As expected,^{7a} only *meta*- and *para*-substitution occurs on toluene at rates depending exclusively upon the pressure [*meta* : *para* = 1 : 20 (760 Torr); 1 : 4 (50 Torr)] and NMe_3 concentration. The distribution of the isomeric t-butyltoluenes does not seem to be appreciably influenced by the presence of limited concentrations of the heteroaromatic substrate.

In conclusion, the major features of the gas-phase t-butylation of the simple heteroaromatic compounds (1)–(4) can be summarized as follows. (i) Pyrroles (1) and (2), furan (3), and thiophene (4), as well as toluene, are efficiently alkylated by the $t\text{-C}_4\text{H}_9^+$ cation in the gas phase. (ii) The increase of the apparent k_s/k_T values with $[\text{NMe}_3]$ indicates that alkylation can be accompanied by secondary processes (*e.g.* protonation, fragmentation, transalkylation, *etc.*), whose extent can be inhibited by addition of suitable amounts of the base in the gaseous mixture. (iii) Gas-phase $t\text{-C}_4\text{H}_9^+$ attack on the simple pyrroles (1) and (2) leads to predominant β -substitution under all conditions. Only very minor yields of *N*-t-butylated pyrrole (5) are formed from (1) (relative yield <2.8%). No evidence for $t\text{-C}_4\text{H}_9^+$ ion attack on the heteroatom of (2) is found. (iv) The relative distribution of (5)–(7) from (1) is mostly dependent upon the total pressure of the mixture. The (8) : (9) ratio from (2) is, instead, mostly affected by $[\text{NMe}_3]$. (v) t-Butyl alkylation of (3) and (4) in the gas phase mostly gives the α -substituted derivative, whose relative yield slightly increases at the lowest pressures used. (vi) In the competition experiments, no evident effect of the presence and concentration of toluene on the distribution of the t-butylation of heteroaromatic compounds is observed.

Discussion

The Reagent.—The electrophile used in the present study is the gaseous $t\text{-C}_4\text{H}_9^+$ ion, formed in high yields from the γ -radiolysis of the neopentane and thermolysed by a large number of unreactive collisions with the parent molecules, as discussed in detail in previous studies.^{7,9} Thermal $t\text{-C}_4\text{H}_9^+$ ion may act as a Lewis or as a Brønsted acid which efficiently attacks both *n*- and π -type substrates. Both protonation and alkylation of the chosen heteroaromatic compounds by $t\text{-C}_4\text{H}_9^+$ are energetically allowed, while the reactivity of the alkyl cation toward toluene is restricted to the alkylation channel, owing to the higher proton affinity (PA) of isobutene

* The yield of other conceivable methyl-t-butylpyrroles, whose formation involves migration of the methyl group originally bonded to the nitrogen atom of (2), was below the detection limit ($G_{(M)} < 1 \times 10^{-4}$).



Scheme 1.

with respect to toluene.* Hence, the reactivity ratios established by the competition experiments of Figure 3 refer exclusively to the t-butylation channel, and clearly provide only the lower limit for the overall nucleophilic reactivity of (1)—(4) toward $t\text{-C}_4\text{H}_9^+$. However, the relatively high t-butylation yields measured in the irradiated systems indicate that such limit is very close to the actual overall nucleophilicity of the heteroaromatic compounds with respect to toluene.

The Alkylation Process.—The experimental features of gas-phase t-butylation of the selected pyrroles arising from both the radiolytic and CI mass spectrometric experiments are consistent with the alkylation pattern outlined in Scheme 1. This involves primary attack of $t\text{-C}_4\text{H}_9^+$ on the heteroaromatic compound, accompanied by the corresponding process for toluene in the competition experiments.

Owing to the exothermicity of their formation [ΔH° ca. -43 (Y = NH); -50 (Y = NCH₃); -25 (Y = O or S); -18 kcal mol⁻¹ (toluene)],† the resulting ionic intermediates [I] and [II] are vibrationally excited. Collisional stabilization of the excited intermediates [I] and [II], followed by proton transfer to a gaseous base B (e.g. NMe₃, or the substrate itself), provides a direct route to the neutral alkylated products [equations (2a,b)]. Alternatively the excited intermediates [I] and [II] may undergo several secondary processes, including isomerization to a more stable structure or fragmentation with loss of isobutene. The latter process represents an additional route to the protonated heteroaromatic, which can be formed by direct proton transfer from $t\text{-C}_4\text{H}_9^+$ to the substrate as well. The competition of the direct alkylation channel (2) with the protonation and fragmentation processes

(and with other conceivable minor pathways not leading to isolable products, e.g. ring-opening, polymerization, etc.), appears regulated by changes of the reaction environment. The increase of the apparent k_S/k_T ratios observed by decreasing the system pressure is in part attributable to the occurrence of a t-butyl group transfer from intermediate [II] to the competing heteroaromatic compound. The intermolecular nature of this process is supported by the dependence of the apparent reactivity ratios upon the [S]/[T] relative concentration. Furthermore, the insensitivity of the isomeric distribution of products to both [S] and [S]/[T] suggests that any intermolecular transalkylation involving intermediates [I] or [II] may follow a unimolecular mechanism and that, therefore, the first step of equations (2) may have a certain character of reversibility.

The appreciable increase of the apparent k_S/k_T values by successive addition of the base NMe₃ at atmospheric pressure (Figure 3) is consistent with this conclusion, since fast deprotonation of [I] by NMe₃ (PA 229 kcal mol⁻¹) can be expected to prevent dealkylation, thus increasing the yield of the isomeric t-butyl heteroaromatic compounds. In contrast, extensive dealkylation of the arenium ion [II] can be efficiently inhibited, even in the absence of NMe₃, by any base present in the system, including the competing heteroaromatic substrate itself.

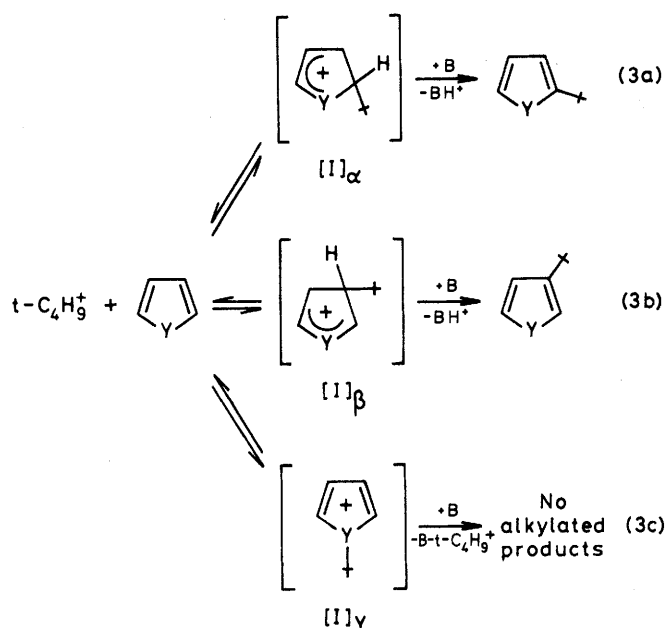
The curves of Figure 1 represent the pressure dependence of the overall $G_{(M)}$ value of the t-butylated derivatives of the chosen heteroaromatic compounds, recovered in experiments carried out in the absence of toluene. A remarkable increase of the $G_{(M)}$ values of the alkylated products of furan (3) and thiophene (4) is observed, which contrasts with the limited pressure dependence of the absolute yield of the products from pyrroles (1) and (2). This effect can be attributed to the reversible $t\text{-C}_4\text{H}_9^+$ group transfer from the heteroatom of furan and thiophene to their ring carbons, a process which is favoured at low pressure and in the absence of added bases, namely under thermodynamically controlled conditions [equation (3)]. A similar isomerization in pyrroles (1) and (2) is much less extensive on account of the limited effect of the total pressure of the systems upon the $G_{(M)}$ values of their alkylated derivatives.‡

Given this model, a rough estimate of the relative abundance of intermediates [I]_Y (Y = O or S), formed in the kinetically significant step of sequence (2a), can be inferred from the curves of Figure 1. With the restrictive assumption that reversible dealkylation of [I]_Y is minimized at atmospheric pressure by its efficient collisional quenching, the relative

* The PAs of pyrrole (213 kcal mol⁻¹), N-methylpyrrole (220 kcal mol⁻¹) (J. L. Devlin III, J. F. Wolf, R. W. Taft, W. J. Hehre, R. T. McIver, Jr., J. A. Pople, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1974, **96**, 7162; D. H. Aue, H. M. Webb, and M. T. Bowers, *ibid.*, 1972, **94**, 4762), furan and thiophene (195.9 kcal mol⁻¹) (R. Houriet, H. Schwarz, W. Zummack, J. G. Andrade, and P. v. R. Schleyer, *Now. J. Chim.*, 1981, **5**, 505), are higher than that of isobutene (193 kcal mol⁻¹),¹⁰ which is in turn higher than that of toluene (189.9 kcal mol⁻¹) (R. Yamdagni and P. Kebarle, *J. Am. Chem. Soc.*, 1976, **98**, 7452). Hydride-ion transfer from the side chain of toluene to the $t\text{-C}_4\text{H}_9^+$ cation is estimated to be endothermic by several kcal mol⁻¹.

† Values arrived at by estimating the H_F value of t-butylpyrrole, t-butyl-N-methylpyrrole, and t-butyltoluene 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 t-butyl group is only a few kcal mol⁻¹ higher than that of the corresponding unsubstituted aromatic compound.

‡ In the case of (1), attack on the nitrogen is not only rather limited (7%), but the ensuing N-alkylated intermediate may also undergo deprotonation giving the corresponding neutral product (5).

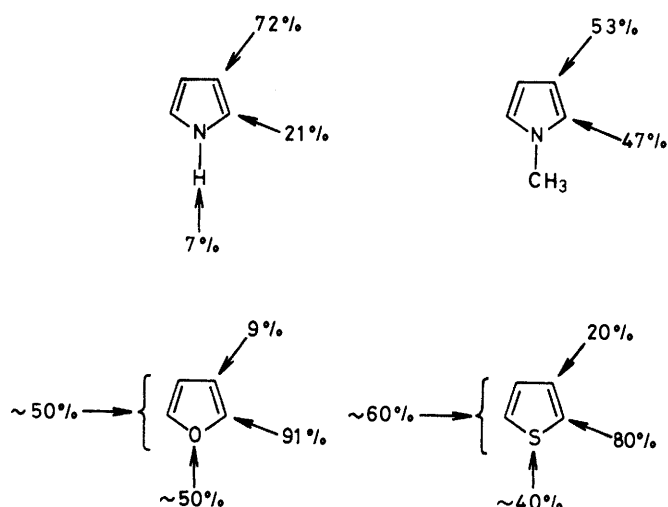


yield of intermediate [I]_γ from channel (3c) arises directly from the ratio between the $G_{(M)}$ decrease ($\Delta G_{(M)}$), observed by increasing the pressure from 50 to 760 Torr, and the maximum $G_{(M)}$ value measured under thermodynamically controlled conditions (total pressure ≤ 50 Torr), where complete isomerization of [I]_γ to the more stable C-alkylated isomers is expected to occur. On these grounds, we can calculate the relative extent of t-C₄H₉⁺ ion attack on the heteroatom of furan (3) and thiophene (4), which ranges around ca. 50% and ca. 40%, respectively.

The initial population of the C-alkylated intermediates [I]_α, [I]_β, and [I]_γ emerges directly from the k_s/k_T ratio and the isomeric distribution of the neutral alkylated products, measured under kinetically controlled conditions (at atmospheric pressure and in the presence of $P_{NNe_3} = 10$ Torr), where reversible dealkylation as well as other conceivable side processes (fragmentation, etc.) involving the t-butylated intermediates are efficiently prevented. Thus, the relative ratio of the C-alkylated intermediates [I]_α and [I]_β, produced in the kinetically significant step of sequence (1a), is ca. 0.29 for pyrrole, 0.85 for N-methylpyrrole, 10.7 for furan, and 4.0 for thiophene. These ratios, coupled with the measured extent of nitrogen-attack in (1) and the estimated relative abundance of [I]_γ from (3) and (4), provide the complete distributions of the isomeric intermediates [I] reported in Scheme 3, which reflect the intrinsic positional selectivity of t-C₄H₉⁺ cations toward the chosen simple heteroaromatic compounds.

Positional and Substrate Selectivity.—The values of the k_s/k_T ratios for gas-phase t-butylation of (1) and (2) [1.0 (1); 2.2 (2)] in the presence of toluene, measured under kinetically controlled conditions, clearly indicates a slight preference of the ionic electrophile toward the most activated pyrrole.

Concerning the substrate selectivity of t-C₄H₉⁺ cations towards furan (3) and thiophene (4), it should be considered that a large fraction (ca. 50% for furan, ca. 40% for thiophene) of the t-C₄H₉⁺ ions attacks the heteroaromatic substrate on the heteroatom giving rise to the corresponding intermediate [I]_γ, which does not evolve further to neutral alkylated products, under kinetically controlled conditions.



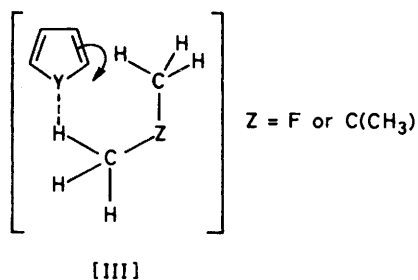
Scheme 3. Positional selectivity of gaseous t-C₄H₉⁺ towards simple heteroaromatic compounds

$k_{rel}(t-C_4H_9^+)$	5.2	2.2	1.0	1.0	1.0
$k_{rel}(CH_3FCH_3^+)$	1.7	1.4	1.1	1.0	~0.6

Scheme 4. Relative reactivity of simple five-membered heteroaromatic compounds towards gaseous alkylating reactants

Correction of the relevant k_s/k_T ratios [2.6 for (3) and 0.6 for (4); Figure 3] by factor of 2.0 for (3) and 1.7 for (4) gives account of this fraction and provides the actual reactivity ratios [$k_s/k_T = 5.2$ (3); 1.0 (4)] on which to base any discussion on heteroaromatic reactivity. On these grounds, the intrinsic substrate selectivity of t-C₄H₉⁺ cations toward simple heteroaromatic compounds is given in Scheme 4, and compared with that concerning the gas-phase methylation of the same substrates by CH₃FCH₃⁺ ions.¹ The reported figures indicate that simple five-membered heteroaromatic compounds, as well as toluene, react with gaseous ionic electrophiles at rates falling within the same order of magnitude, in substantial agreement with the limited substrate discrimination observed in related gas-phase aromatic substitutions and with the available mass spectrometric data.

The intrinsic directive properties of pyrroles (1) and (2) toward gas-phase t-C₄H₉⁺ ion attack demonstrate the tendency of the heteroaromatic molecule to direct the electrophile toward the ring carbons with the highest value of the negative net charge (the C_β centres) [72% (1); 54% (2)].^{11,12} These results well agree with the positional selectivity of CH₃FCH₃⁺ ions toward simple pyrroles¹ and find a theoretical justification in recent semiempirical calculations of the molecular electrostatic potentials, induced around an isolated (1) [or (2)] molecule by the interaction with a positive point charge.¹³ The C_β sites of (1) and (2) are predicted to be preferred for attack by a positively charged electrophile, while substitution on the nitrogen atom (the other centre with strongly attractive electrostatic potential) is inhibited by the presence of relatively acidic¹⁴ hydrogens (NH or NCH₃). Such hindrance is expected to be more pronounced for (2)¹⁵ and appears to be particularly significant for a 'bulky'



electrophile, such as $t\text{-C}_4\text{H}_9^+$. In fact, only 7% substitution by $t\text{-C}_4\text{H}_9^+$ takes place on the nitrogen atom of (1), whereas ca. 35% alkylation by $\text{CH}_3\text{FCH}_3^+$ on the same centre is observed under comparable experimental conditions.¹ A more pronounced repulsive interaction between the partially charged hydrogens of the 'bulky' $t\text{-C}_4\text{H}_9^+$ cation and the acidic N-H moiety may be responsible for this difference.

Accordingly, the intrinsic directive properties of furan (3), shown in Scheme 3, demonstrate the distinct tendency of the substrate to direct the electrophile predominantly towards the heteroatom, *i.e.* the ring site with the maximum value of the net negative charge.^{11,12} In addition, an exceedingly high extent of α -substitution is observed, which however cannot be explained in terms of charge density on the corresponding carbons, which are a minimum in the case of furan.¹⁶

Similar behaviour was observed in the gas-phase $\text{CH}_3\text{-FCH}_3^+$ methylation of the same substrate ($\text{O} : \alpha : \beta = 36 : 35 : 29$). In this case, the relatively high extent of α -substitution was ascribed to the establishment of an intense attractive region around the heteroatom of the substrate, electrostatically interacting with the positive ion, which may increase the probability of α -attack, *via* the formation of the electrostatic adduct [III; $\text{Z} = \text{F}$].^{9,17} The same rationale can explain the extensive α -substitution observed in the *t*-butylation of furan. Here, the significance of adduct [III; $\text{Z} = \text{CCH}_3$] is increased by the relatively hard character of the electrophile, which is expected to favour establishment of an intense 'hydrogen-bond-like' interaction between the partially charged hydrogens of $t\text{-C}_4\text{H}_9^+$ and the 'hard' site (the n -electrons) of the bidentate heteroaromatic substrate.*

In conclusion, the present gas-phase results confirm the view that electrophilic alkylation of simple heteroaromatic compounds is mainly governed by attractive electrostatic interactions between the ionic reagent and the negatively charged sites of the heteroaromatic molecule. In general, alkylation of simple heteroaromatic compounds is characterized by relatively small reactant discrimination, accompanied by an appreciable positional selectivity.

Comparison with Solution Chemistry Data.—The gas-phase results do not show any correspondence with those available from solution-chemistry studies concerning related alkylations on simple heteroaromatic compounds. Although in qualitative agreement with the most accepted theories of substituent effects,^{11,19} the substrate selectivity of the gas-phase *t*-butylation is nevertheless exceedingly low by the reactivity standards of the most common electrophilic substitutions in solution.^{11,19} A similar discrepancy is found with regard to the positional selectivity of the alkylating electrophile as well. The preferred β -substitution characterizing gas-phase alkylation of simple pyrroles contrasts remarkably with the general

predominance of α -attack observed for electrophilic substitution in the condensed phase. In particular, aluminium chloride-catalysed *t*-butylation of pyrrole at -80°C gives low yields of a (6) : (7) = 1.0 : 0.8 mixture, accompanied by considerable polymerization,²⁰ whereas the same reaction carried out in the gas phase leads to high yields of a (5) : (6) : (7) = 7 : 21 : 72 mixture.

From these considerations and in agreement with earlier conclusions from related gas-phase investigations,¹ we point at the specific interactions between a simple heteroaromatic molecule and the reaction medium (solvent, counterion, 'catalyst', *etc.*) as mostly responsible for the 'classical' reactivity and selectivity features of the heteroaromatic compound observed in condensed phase. In the absence of specific environmental effects, in fact, the intrinsic reactivity of a free carbocation toward an unsolvated heteroaromatic molecule appears to be governed by factors strictly related to direct electrostatic interactions between the ionic reactant and the negatively charged sites of the substrate.

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* A similar correlation between the 'hard' character of a gaseous ionic electrophile and its affinity toward the n -centre and the *ortho*-ring positions of a bidentate aromatic substrate, such as aniline, has been recently observed.¹⁸

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