Gas-Phase Heteroaromatic Substitution. 7.[1] Methylation of Five-Membered Heteroaromatic Rings by Free Methyl Cations

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Abstract: The results of a study of the reactions of a powerful alkylating electrophile, the CT_3^+ ion from the β-decay of CT_4, with gaseous pyrrole, *N*-methylpyrrole, furan, and thiophene are reported. In all the systems investigated, two major categories of labeled products are recovered: the methylated and the tritiated substrates. The nature and the yields of the methylated products, as well as their isomeric composition, suggest that the gas-phase alkylation reaction of simple heteroaromatics by the CT_3^+ cation is regulated by factors related to electron mixing between the HOMO of the substrate and the LUMO of the electrophile in the transition state, a behavior that ranks CT_3^+ as a "soft" Lewis acid. For "harder" alkylating species, such as $CH_3FCH_3^+$, the orienting properties of the heteroaromatic substrates are mainly determined by electrostatic interactions established within the encounter pair. Furan and thiophene give, although for different reasons, similar product distributions with both "hard" and "soft" alkylating cations.

Simple five-membered heteroaromatics such as pyrrole and furan are prominent members of that very special category of aromatic compounds with a HOMO electron density distribution opposite to the total π-electron and charge-density ones.[2] The HOMO orbital of such compounds is characterized by a high π-electron density at the α-carbons, while the total net negative charge is located predominantly on the β-carbons and the heteroatom. Thus, in principle, these compounds may be conveniently used for assaying the electronic properties and the reactivity of virtually all electrophilic reactants. In the framework of the frontier molecular orbital theory for chemical reactivity,[3] a distinct preference for the β-carbons and the heteroatom of the above heteroaromatics is expected for "hard" electrophiles, whose reactivity is essentially controlled by electrostatic interactions.[4] "Soft" electrophiles are, instead, characterized by their tendency to accept partial electron transfer from the HOMO orbital of the substrate in the transition state, thus interacting preferentially with the α-carbons of the heteroaromatic molecule.

It follows that an experimental probe for the orbital configuration of a variety of electrophiles may be provided by the determination of their site selectivity toward simple heteroarenes in the dilute gaseous state. Under such conditions the intrinsic orienting properties of the substrate[2] and the actual reactivity features of the electrophilic reactant[4] are not affected by extraneous and variable phenomena, such as solvation, ion pairing, and catalyst–substrate interactions, which are invariably superimposed upon the intrinsic factors determining the activation energy barrier in electrophilic heteroaromatic substitutions in solution.

In recent years the first experimental insight into the behavior of five-membered heteroaromatics toward charged alkylating electrophiles (e.g., $CH_3FCH_3^+$,[5] t-$C_4H_9^+$,[6] and i-$C_3H_7^+$ ions[1]) in the gas phase was given by the application of the radiolytic technique,[7] which, unlike most conventional mass spectrometric approaches, provides direct information about the site of attack of the ionic reactant on the heteroaromatic ring and the structural features of the resulting ionic intermediate(s). The relevant results are consistent with a reactivity pattern dominated by attractive electrostatic interactions between the negatively charged sites of the heteroaromatic molecule (i.e., the β-carbons and the heteroatom of pyrroles) and the gaseous alkylating ions, which therefore behave as typical "hard" electrophiles.

From these limited data it could not be decided whether the electrostatic control of the electrophilic attack of alkylating ions on heteroaromatics is a general feature of gas-phase heteroaromatic substitutions, or whether other factors related to the frontier-orbital perturbation of the reaction partners may intervene.

We now report an extension of the study to the gas-phase alkylation of simple five-membered heteroaromatics by the simplest alkylating ionic electrophile, the methyl cation CT_3^+, which is conveniently generated in the gas phase by spontaneous β-decay in multitritiated methane (eq 1).[8] The investigation has been primarily undertaken to bring into discussion the possibility of frontier-orbital control in ion–heteroaromatic molecule reactions in the gas phase, the methyl cation being considered among the softest charged electrophiles.[3] A close comparison between the selectivities of two gaseous methylating reactants, namely the CH_3^+ and $CH_3FCH_3^+$ cations, may help in elucidating the effect on the HOMO orbital energy of CH_3^+ when it is bonded to a CH_3F moiety.

(1)

Y = NH (1), NMe, (2), O (3), S (4)

Experimental Section

Materials. Multitritiated methane, used as a precursor of the labeled methyl cations, was prepared according to established procedures.[9] The isotopic composition was measured by radio gas chromatography and mass spectrometry and corresponded to 60% CT_4, 30% CHT_3, 8% CH_2T_2, and 2% CH_3T, with an uncertainty level of ±1%.

The heteroaromatic substrates and the gaseous additives used for the preparation of the decay mixtures were research grade chemicals from Fluka AG and Matheson Co. and were used without further purification. 2-Methylfuran and isomeric methylthiophenes, used as carriers or as standards in the radio gas chromatographic analyses, were obtained from ICN Pharmaceutical, Inc., and Fluka AG. 3-Methylfuran as well as

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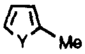
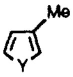
Table I. Tritiated Products from the Attack of CT_3^+ Decay Ions on Gaseous Heteroarenes (T = 100 °C)

	system composition[a] (Torr)				relative yields of products[b] (%)				
substrate	CH_4	O_2	NH_3	NMe_3					total absolute yield[c] (%)
1, 150	3.7	-	-	-	61.2	27.7 (72)	9.4 (24)	1.7 (4)	99
1, 150	4.1	4.5	-	-	56.7	29.1 (67)	11.0 (25)	3.2 (7)	98
1, 150	5.1	4.5	21.3	-	56.8	31.5 (73)	9.5 (22)	2.2 (5)	90
1, 150	4.6	4.5	-	21.3	55.6	32.0 (72)	9.8 (22)	2.6 (6)	88
2, 150	5.1	-	-	-	59.7	23.8 (59)	16.5 (41)	-	99
2, 150	4.8	4.5	-	-	59.3	24.4 (60)	16.3 (40)	-	97
2, 150	5.1	4.5	21.3	-	58.8	26.0 (63)	15.2 (37)	-	89
2, 150	4.5	4.5	-	21.3	57.4	26.0 (61)	16.6 (39)	-	88
3, 150	4.0	-	-	-	63.0	24.0 (65)	13.0 (35)	-	39
3, 150	3.7	4.5	-	-	63.6	24.4 (67)	12.0 (33)	-	37
3, 150	5.1	4.5	21.3	-	62.8	25.7 (69)	11.6 (31)	-	32
3, 150	4.9	4.5	-	21.3	61.2	26.4 (68)	12.4 (32)	-	30
4, 150	3.7	-	-	-	54.5	25.0 (55)	20.5 (45)	-	58
4, 150	3.7	4.5	-	-	44.5	31.7 (57)	23.8 (43)	-	61
4, 150	5.1	4.5	21.3	-	48.2	29.5 (57)	22.3 (43)	-	34
4, 150	4.3	4.5	-	21.3	47.6	29.0 (55)	23.4 (45)	-	38

[a] All systems contained ca. 1.5–2.0 mCi CT_4, diluted with CH_4 to a specific activity of 18.7 Ci mol^{-1}. [b] Ratio of the activity of each product to the combined activity of all products identified. Relative composition of methylated products given in parentheses. Each value is the average of several determinations, with an uncertainty level of ca. 5%. [c] Absolute yields expressed as the percent ratio of the total activity of all identified products to the activity originally contained in the nuclear-decay formed CT_3^+ reactant.

isomeric methyl- and dimethylpyrroles were prepared according to established procedures.[10]

Procedure. The gaseous samples were prepared by introducing multitritiated methane (1.5–2.0 mCi), diluted with CH_4 to a specific activity of 18.7 Ci mol^{-1}, into evacuated and carefully outgassed 0.5-L Pyrex vessels, containing a measured amount of the heteroaromatic substrate, together with O_2, used as a radical scavenger, and ion trapping gases (NH_3 or NMe_3), when required. The vessels were then sealed off and stored in a thermostatic oven at 100 °C for 4–6 months.

After the storage period, the ampules were opened, and their content analyzed by radio gas chromatographic (GLC) and radio high-performance liquid chromatographic (HPLC) procedures. A C. Erba Fractovap 4200 gas chromatograph equipped with a high-sensitivity hot-wire detector in series with a 10-mL internal-flow Berthold proportional counter, heated at 180 °C, was used for the radio gas chromatographic analyses. A Varian Vista 5500 high-pressure liquid chromatograph equipped with a 254-nm UV detector in series with a Berthold LB 503 HS flow liquid scintillation counter was used for the radio high-performance liquid chromatographic analyses.

The identity of the tritiated products was established by coincidence of their retention volumes with those of authentic reference compounds on the following columns: (i) GLC, 3 m × $^1/_8$ in. stainless steel column packed with 10% Carbowax 20M/1% KOH on Chromosorb W, operated between 85 and 110 °C; (ii) GLC, 9 m × $^1/_8$ in. stainless steel column packed with 20% E 301 on Chromosorb W, operated at 70 °C; (iii) HPLC, 25 cm × 5 mm Alltech Rosil C-18 HL from Alltech, Italy, using $MeOH/H_2O$ 3:2. The absolute yields of the tritiated products correspond to the ratio of their activity to the activity of the labeled decay ions formed during the storage period in the reaction mixtures from the β-decay of multitritiated methane.

Results

The absolute and relative yields of the tritiated products from the attack of CT_3^+ decay ions on pyrrole (**1**), *N*-methylpyrrole (**2**), furan (**3**), and thiophene (**4**) and the isomeric composition of the methylated derivatives are given in Table I. The absolute yields, defined by the ratio of the activity of the products to the total activity of the CT_3^+ ions formed within the system, can be calculated from the initial activity and the isotopic composition of tritiated methane, the decay rate of tritium, the abundance (82%) of the methyl ions among the decay fragments,[11] and the absolute counting efficiency of the detector employed.

From the data of Table I, it is apparent that the combined activity of the reaction products identified, while essentially matching (>88%) the theoretical activity of the CT_3^+ reagent in the runs with pyrroles **1** and **2**, does not exceed 61% in thiophene **4** runs and 39% in the furan **3** ones. Radio gas chromatographic analysis showed that low-boiling fragmentation products accounts for only a limited fraction of the missing activity (1–10%). We therefore proceeded in the quantitative measurement of the total activity of the crude reaction mixtures as well as of that of the inner surface of the relevant reaction vessels by liquid scintillation counting. We observed that, while the first essentially matches the combined activity of the identified products in all systems investigated, the latter is negligible (<5%) for pyrroles **1** and **2**, while it amounts to 20–30% for furan **3** and thiophene **4**. It is concluded that the activity balance is mostly accounted for by labeled-polymerization products, not detectable by radio-GLC and radio-HPLC, accompanied by minor yields of low-boiling fragmentation products.

The largely different effects of the additives, i.e., O_2, NH_3, and NMe_3, on the yield and the relative composition of the labeled products emerge clearly from inspection of Table I. In fact, while the presence of ca. 3 mol % of a powerful thermal radical scavenger, such as O_2, does not alter the product pattern from all systems, addition of ca. 10 mol % of a strong base, such as NMe_3 or NH_3, leads to a significant decrease (from 10 to 44%) of the absolute yields of the tritiated products. It is noteworthy that such a decrease is not accompanied by an appreciable change in the product pattern and in the relative distribution of the methylated products, where predominance of the α-isomer (55–73%) is invariably observed.

Discussion

Nature of the Reagent. The formation of tritiated methyl cation from the decay of multitritiated methane has been discussed in detail elsewhere.[8,11] The methyl cation, formed in its electronic ground state for more than 82% of the decay events, is characterized by a certain excess of internal energy due inter alia to the relaxation from its original tetrahedral structure, reminiscent of the parent methane, to the vibrationally most stable trigonal geometry.[12] In the extreme hypothesis of an overall adiabatic process for the formation of CT_3^+ ion from the nuclear transition shown in the first step of eq 1, theoretical calculations set an upper

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(10) (a) Shell, P. S.; Bean, G. P. *J. Am. Chem. Soc.* **1962**, *84*, 4655. (b) Hinman, R. L.; Theodoropulos, S. *J. Org. Chem.* **1963**, *28*, 3052. (c) Sherman, E.; Amstutz, E. D. *J. Am. Chem. Soc.* **1950**, *72*, 2195. (d) Franklin, R. B.; Statham, C. N.; Boyd, M. R. *J. Labelled Compd. Radiopharm.* **1978**, *15*, 569.

(11) (a) Snell, A. H.; Pleasonton, F. *J. Phys. Chem.* **1958**, *62*, 1377. (b) Cantwell, M. *Phys. Rev.* **1956**, *101*, 1747. (c) Ikuta, S.; Okuno, K.; Yoshihara, K.; Shiokawa, T. *Radiochem. Radioanal. Lett.* **1975**, *23*, 213.

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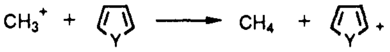
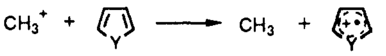
Table II. Energetics of Several Relevant Reactions of CT_3^+ with Heteroaromatic Compounds[a]

	process	ΔH° (kcal mol⁻¹); Y = NH (**1**)	NMe (**2**)	O (**3**)	S (**4**)
(2)	 **5**	−111	−118	−97	−97
(3)	 **6**		−27[b]		
(4)	 **7**	−37	−43	−21	−22
(5)	 (singlet) **8**	−1	−7	+15	+10

[a] The formation enthalpies of the ions and the neutrals used for these calculations have been taken from the following: (i) Lias, S. G.; Liebman, J. F.; Levin, R. D. *J. Phys. Chem. Ref. Data* **1984**, *13*, 695. (ii) Stull, D. R.; Westrum, E. F., Jr.; Sinke, G. C. *The Chemical Thermodynamics of Organic Compounds*; Wiley: New York, 1969. (iii) Eland, J. H. D. *Int. J. Mass Spectros. Ion Phys.* **1969**, *2*, 471. (iv) Shavitt, I. *Tetrahedron* **1985**, *41*, 1531. An estimate of the $H_f°$ values of **5** can be arrived at by assuming that the proton affinities of the ipso position of methylated heteroatomics is equal to that of the corresponding unsubstituted substrates, taken ref i. [b] Roughly estimated by assuming an hydride-ion affinity for **6** equal to that of phenylium ion ($Y = C_2H_2$).

limit of ca. 32 kcal mol⁻¹ to the vibrational excitation energy of the decay CT_3^+ ion.[12,13]

Concerning the fate of the energetic β-particle released in the decay transition, it should be considered that the reaction conditions have been specifically selected to make entirely negligible any contribution to the products of Table I from β-radiolytic processes. In fact, the very low activity employed in the experiments and concentrated in the molecules of multitritiated methane, highly diluted into the system (ca. 5×10^{-4} mol %), makes the probability of β-particle-induced processes, such as direct radiolysis of labeled methane as well as combination of reactive species from radiolysis of **1**–**4** with labeled methane, vanishingly small. Furthermore, any thermal radical component to products formation is expected to be cut off by the presence of an effective radical scavenger, such as O_2. These circumstances as well as the effects of the additives on the absolute yields of the products of Table I allow the conclusion that ground-state methyl cations are the primary species responsible for the formation of the labeled products of Table I, with only minor contributions from other reactive fragments released in the decay event.

Several exothermic reaction channels are available to the methyl cation in its attack on the heteroaromatic substrates **1**–**4**, as illustrated in Table II, where the approximate ΔH° values for the relevant gas-phase processes are given. The enthalpy changes have been calculated from the $\Delta H_f°$ value of the gaseous CH_3^+ ion in its vibrational ground state (261.2 kcal mol⁻¹).[14] If an allowance is made for a certain excess of vibrational energy in the decay CT_3^+ ion, the actual enthalpy changes of reactions 2–5 (Table II) may be further lowered by up to 32 kcal mol⁻¹. In this view, while the exothermic process 2 is recognized as the main source of the labeled methylated products of Table I, there are at least two "blind" (i.e., not leading to labeled products other than the starting methane) exothermic reaction channels, i.e. eqs 3 and 4, which could account for the activity loss observed especially in the furan and thiophene systems. Reaction 4 would lead to the inactive molecular ion of the heteroarene and to tritiated methyl radical, whose contribution, if any, to the identified products is negligible on account of the lack of any appreciable effect of O_2 on the product yield. Further evidence against path 4 as a significant source of methylated products is provided by the equally high yields of labeled products recovered from pyrroles **1** and **2**. In view of the well-documented ability of radicals to efficiently abstract a hydrogen atom from the methyl moiety of **2**, giving methane and 1-pyrrolyl methyl radicals,[15] this result argues against the involvement of free methyl radicals. Pathway 4 may nevertheless represent a conceivable route to tritiated **1**–**4**, provided that the charge-exchange process takes place via a complex mechanism involving extensive hydrogen-atom scrambling within the ion–molecule adduct. Additional sources of tritiated **1**–**4** may be identified in partial fragmentation of the excited intermediates **5** from eq 2 and in the direct triton transfer, eq 5 (Table II), between CT_3^+ and the substrate. In these cases, however, labeled methylene is expected to be formed that would attack the heteroarene ring inducing, inter alia, its rupture and/or enlargement.[16] While, in principle, ring rupture of **3** and **4** may account in part for the formation of labeled polymerization products in these systems, the absence of the same type of products as well as of labeled pyridine derivatives in the samples with **1** and **2** argues against reaction 5 (as well as against fragmentation of **5** from eq 2) as significant routes to the tritiated starting substrates. A more likely path to tritiated **1**–**4** may arise from extensive hydrogen scrambling within the collision complex between vibrationally excited CT_3^+ and **1**–**4**, which reversibly decomposes to the labeled neutral substrate and a quenched CHT_2^+ cation, eventually trapped by another heteroaromatic molecule.

Methylation Reaction. The evidence reported in Table I is consistent with a reaction sequence, initiated by the highly exothermic attack of the CT_3^+ cation upon the nucleophilic centers of the heteroaromatic substrate, yielding the corresponding excited heteroarenium ions **5** (eq 2, Table II). Intermediate **5**, if not stabilized by collision with the gaseous components of the mixture, may decompose into smaller fragments or rearrange to a more stable isomeric structure. The stabilized heteroarenium ions **5** eventually lose a proton to a suitable acceptor (the substrate itself or an added base), giving rise directly to the methylated end products. Within the reasonable assumption that the yields of the recovered methylated products reflect the fraction of the excited **5** escaping fragmentation, the results confirm and extend earlier observations on the stability of arenium intermediates from gas-phase attack of CT_3^+ on aromatic compounds. The absolute yields of the methylated products of Table I ranging from 13 to 42% are comparable with those of the methylated derivatives of toluene (22–29%)[17] and halobenzenes (15–30%),[18] measured under milder conditions.

As pointed out in related gas-phase studies,[1,5b,6,19] the comparatively low yields observed in the case of furan **3** (13%, Table

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(13) Williams, J. E., Jr.; Buss, V.; Allen, L. C.; Schleyer, P. v. R.; Lathan, W. A.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 6867.

(14) Traeger, J. C.; McMoughlin, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 3647.

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(17) Cacace, F.; Giacomello, P. *J. Chem. Soc., Perkin Trans. 2* **1978**, 652.

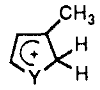
(18) Giacomello, P. *Radiochim. Acta* **1979**, *26*, 185.

(19) Angelini, G.; Laguzzi, G.; Sparapani, C.; Speranza, M. *J. Am. Chem. Soc.* **1984**, *106*, 37.

I) may be attributed, apart from occurrence of the parasitic processes 3–5, to the presence of the *n*-electron pair of oxygen which competes efficiently with the π-system for the gaseous electrophile. Such competition may increase the extent of CT_3^+-consuming processes, such as ring opening, ending with polymeric products. Similar paths appear much less pronounced in the case of thiophene (**4**) and totally absent in the case of pyrroles **1** and **2**, as demonstrated by the higher absolute yields of the corresponding methylated derivatives.

Recovery of significant amounts of the tritiated starting substrate from the decay systems under all conditions (Table I) can be attributed to any of several processes. Apart from those introduced in the previous section (in particular hydrogen exchange in the reversible attack of CT_3^+ on **1–4**), an additional route to tritiated substrates may involve reactive species other than CT_3^+. A minor fraction (ca. 18%) of the decay events in CT_4 produces daughter ions with very large excitation energies (up to 60 eV), which lead to decomposition into reactive fragments, such as T^+ and $^3HeT^+$, which can act as tritonating agents toward **1–4**.[11] In the presence of NH_3 or NMe_3 (21.3 Torr), part of these fragments as well as of CT_3^+ may be intercepted by the base.

The conceivable occurrence of residual fragmentation and isomerization of the intermediates **5** from eq 2 undoubtedly complicates the evaluation of the positional selectivity of the methyl cation toward **1–4**. A further source of uncertainty arises from the possibility of transalkylation processes between the primary intermediates **5** from eq 2 and the neutral substrate, yielding secondary arenium ions **5**, with an isomeric distribution that does not necessarily coincide with that of their primary precursors. This latter possibility seems excluded on the grounds of the evident insensitivity of the isomeric composition upon the presence and the nature of the added bases (Table I), one of them (NMe_3) being basic enough (PA: 225.1 kcal mol^{-1}) to rapidly neutralize any intermediate **5**. Partial fragmentation or intramolecular isomerization of **5** would favor formation of the thermodynamically more stable structure **9**,[5] which is the precursor of the β-substituted neutral product.



9

As a consequence the positional selectivity of the methyl cation toward **1–4**, expressed by the α- over β-methylated product yield ratios measured in the presence of NMe_3 (Table I), must be regarded as a lower limit.

A pronounced preference of the free methyl cation for the α-positions of pyrroles **1** and **2** clearly emerges, which contrasts with the directive properties of the same substrates toward other gaseous ionic electrophiles.[1,5,6,19] Furan (**3**) and thiophene (**4**) seem to undergo preferential α-substitution from all gaseous alkylating electrophiles investigated,[1,5,6] including methyl cation.

The different behavior of methyl cation with respect to other gaseous alkylating species, such as *tert*-butyl,[6] isopropyl,[1] and dimethylfluoronium ions[5] can be explained in terms of the energy gap between the HOMO of the pyrroles and the LUMO of the ionic alkylating electrophile.[3] The energy level of the LUMO orbital of a carbocation is directly related to the net positive charge located at its sp^2 center and to the extent of delocalization of the orbital over the entire molecule. These factors account for the reported $CH_3^+ < C_2H_5^+ < i\text{-}C_3H_7^+ < t\text{-}C_4H_9^+$ "hardness" order,[20] which is strictly related to their increasing LUMO energy. Within the framework of the charge and frontier orbital control concept,[21] the energy gap between the HOMO of the heteroaromatic substrates and the LUMO of a "hard" electrophile, such as $t\text{-}C_4H_9^+$ or $i\text{-}C_3H_7^+$, is relatively large. The total perturbation energy in the orbital interaction is primarily determined by electrostatic interactions (a "charge-controlled" reaction), favoring attack of the ionic electrophile on the ring sites of the heteroarene with the highest negative net charge (the β-positions of **1** and **2**, the heteroatom of **3**, and the α-positons of **4**). As the energy level of the LUMO of the electrophile is lowered, as in the case of the "soft" methyl cation, the total perturbation energy in the orbital interaction is determined by extensive mixing between the HOMO of the donor and the LUMO of the acceptor (a "frontier-controlled" reaction). In this case, the exchange mainly involves the frontier π-electrons of **1–4**, which are predominantly located at the α-carbons of the heteroaromatic ring.

The same model explains the different orienting properties of pyrroles **1** and **2** toward naked methyl cation and $CH_3FCH_3^+$, which may be regarded as a CH_3F-solvated methyl cation.[22] Here orbital delocalization over the entire $CH_3FCH_3^+$ moiety is reflected in a LUMO energy higher than that of CH_3^+, which results to be "soft" relative to $CH_3FCH_3^+$. This condition induces unsolvated methyl cation to attack predominantly the α-positions of **1** and **2**, while $CH_3FCH_3^+$ is preferentially oriented toward the β- and N-sites of the same substrates.[5a]

Conclusions

The essential features of an electrophilic substitution on simple five-membered heteroaromatics are exhibited in the gas phase by the attack of CT_3^+ ions from β-decay of CT_4 on pyrrole (**1**), *N*-methylpyrrole (**2**), furan (**3**), and thiophene (**4**). The intrinsic directive properties of **1–4** toward gaseous carbocations are controlled by electrostatic interactions in the encounter complex, when the "hard" electrophiles $t\text{-}C_4H_9^+$, $i\text{-}C_3H_7^+$, and $CH_3FCH_3^+$ are employed as opposed to extensive frontier electron mixing between the HOMO of **1–4** and the LUMO of the electrophile, when the "soft" CT_3^+ ion is used. While **1** and **2** are preferentially alkylated at their β- and heteroatom centers by "hard" carbocations, they undergo predominant α-substitution by the "soft" CT_3^+ cation. Thiophene (**4**) displays preferential attack at the α-sites in all cases, since its net negative charge distribution is qualitatively similar to the π-electron density of its HOMO orbital. Furan (**3**) exhibits predominant formation of the α-substituted product with almost all alkylating reagents either "hard", i.e. $t\text{-}C_4H_9^+$, or "soft", i.e. CT_3^+. A "hard" electrophile, such as $t\text{-}C_4H_9^+$, is electrostatically directed toward the negative center of **3**, i.e. the oxygen atom, yielding a "chelate" adduct, favoring subsequent attack at the adjacent α-center by proximity effect.[17] A "soft" electrophile, such as CT_3^+, is instead directly oriented toward the most populated α-centers of the frontier π-orbital.

Registry No. 1, 109-97-7; **2**, 96-54-8; **3**, 110-00-9; **4**, 110-02-1; $(CPh_3)_3C^+$, 125685-47-4.

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