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Gas-phase Alkylation of 2-Methylfuran under Chemical Ionization Conditions

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In the gas phase, under chemical ionization conditions, the sites of attachment of $[CH_3]^+$ and $[C_2H_5]^+$ to 2-methylfuran have been studied by tandem mass spectrometry. Spontaneous metastable and collision-induced fragmentations have been compared to those observed for the protonated alkylfuran isomers. The results obtained show that alkylation occurs preferentially at the β-position.

INTRODUCTION

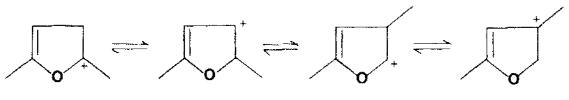
For a number of years systematic studies have been performed to determine the sites of protonation and alkylation for organic molecules in the gas phase. These reactions have in particular been studied by ion cyclotron resonance (ICR), by radiolytic techniques and by mass spectrometry. In the first case, which involves equilibrium conditions, thermodynamic control characterizes the reactions and many proton affinity measurements have been carried out with this method,[1] e.g. for furan[2] and for methylfurans.[3] With the use of radiolytic techniques, Speranza *et al.* have shown that protonation of furan[5] as well as alkylation of furan, thiophene and pyrrole[6] depend on the experimental conditions which can be chosen to favour kinetic control or thermodynamic control.

The alkylation of many aromatic compounds has been studied by mass spectrometry under chemical ionization (CI) conditions: alkylbenzenes,[8–10] anilines,[11–13] phenols[12–14] and nitrogen heterocycles.[11] Cooks *et al.*[12] have concluded that these reactions are under thermodynamic control, whereas Harrison[13] considers that, in some cases, the control may be kinetic. The alkylation of 2-methylfuran under CI conditions has, for this reason, been studied in this work to obtain more insight into this problem.

In solution, the attack of a cation on furan occurs specifically at the α-position.[15] It has been shown (by ICR) that protonation in the gas phase also occurs at α-position for furan[2] and methylfurans.[3] However, results obtained by radiolysis led Speranza *et al.* to conclude that protonation is not specific[5] and that alkylation by $[CH_3{-}F{-}CH_3]^+$ leads to a mixture of 2- and 3-substituted derivatives.[7] However, under these conditions, the alkylation of pyrrole[6] occurs selectively at the β-position, whereas the reaction of furan is more likely to give the α-substituted product.[7]

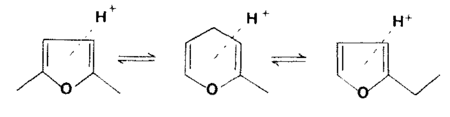
Ethylation of furans is conveniently carried out under CI conditions where adduct ions $[\text{furan} + C_2H_5 \text{ or } C_2D_5)]^+$ can be prepared when CH_4 (or CD_4) is used as the reagent gas in the source of a mass spectrometer. The adduct ions can be characterized by their subsequent fragmentations in the 2nd field-free region (2nd FFR). However, the mass-analysed ion kinetic energy (MIKE) and MIKE–collision-induced dissociation (MIKE–CID) spectra of protonated 2- and 3-ethylfurans are almost identical and attempts to determine the structures of the adducts by this method were not successful,[16] since protonated alkylfurans and isomeric adducts rearrange before dissociation. Two competing pathways have been observed for protonated methylfurans[16–18] and for protonated xylenes:[19]

(i) fast 1,2-migration of hydrogen or methyl groups (Scheme 1);



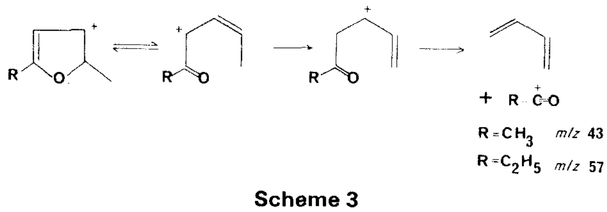
Scheme 1

(ii) ring expansion and ring contraction reactions (Scheme 2).



Scheme 2

These conclusions were reached through isotope labelling studies on the formation of the $[CH_3CO]^+$ fragment ion. This is formed by ring opening and fragmentation of 2,5-disubstituted furans as shown in Scheme 3.[17] Using this last assumption, $[\text{2-methylfuran} + CH_3]^+$, $[\text{2-methylfuran} + C_2H_5]^+$ and $[\text{2-ethylfuran} + CH_3]^+$ adduct ions have been studied in this work. The conclusions based on the experimental data have been correlated with MNDO calculations.



Scheme 3

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Table 1. MIKE spectra of ions 1 to 4

		43	55	67	69	79
1	(CH_4)	29	9	6	16	40
2	(C_4H_{10})	25	10	4	12	49
	(CH_4)	29	8	5	13	45
3	(CH_4)	23	11	4	14	48
4	(CH_4)	17	14	5	16	47

Table 2. Shifts of the *m*/*z* 43 peak in the MIKE spectra of labelled analogues of 1 and 2

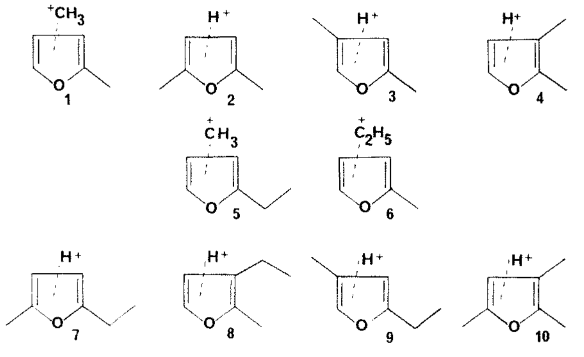
	Furan	Cation	43	44
1a	2-$^{13}CH_3$	$\overset{+}{C}H_3$	60	40
1b	2-CH_3	$^{13}\overset{+}{C}H_3$	66	34
2a	2-$^{13}CH_3$, 5-CH_3	H^+	58	42

EXPERIMENTAL

All experiments were performed on a reversed-geometry VG ZAB.2F double-focusing mass spectrometer with a collision cell in the 2nd FFR. Typical ion source conditions were 100 eV electron energy, 150 °C source temperature, the pressure in the source being 10^{-4} mbar.

The adduct ion [2-methylfuran + CH_3]$^+$ (1)

(i) The adduct ion [2-methylfuran + CH_3]$^+$ (**1**) is shown in Scheme 4 without specific indication of the structure. It has been produced in the source of the mass spectrometer by the action of methyl iodide on 2-methylfuran. The MIKE spectrum of the adduct ion is similar to those of the protonated dimethylfuran isomers **2**, **3** and **4** (Scheme 4, Table 1). The MIKE–CID spectra of ions **1**–**4** are also similar and these results have not allowed us to determine the structure of ion **1**. However, the similarity of the decompositions of metastable ions **1**–**4** allow us to conclude that $CH_3{}^+$ is in fact attached directly to the furan ring: the adduct **1** is not a weakly bonded ion–molecule complex.



Scheme 4

The results also show that if the maximal internal energy of ion **1** (formed by the action of CH_3I) and of the ions **2**, **3** and **4** prepared by the action of $[C_2H_5]^+$ or $[C_4H_9]^+$ (Table 1) is different, then this parameter does not determine the course of the fragmentation processes.

(ii) A comparison of the behaviour of the adducts [2-$^{13}CH_3$-furan + CH_3]$^+$ (**1a**) and [2-CH_3-furan + $^{13}CH_3$]$^+$ (**1b**) with the [2-$^{13}CH_3$, 5-CH_3-furan + H]$^+$ (**2a**) provide conclusive evidence with regard to the site of attack of the alkylating agent. The metastable ion **2a** yields *m*/*z* 43 $[CH_3CO]^+$ and *m*/*z* 44 $[^{13}C^{12}CH_3O]^+$ fragment ions in a 58:42 abundance ratio (Table 2). This is slightly different from the 1:1 ratio expected if there were only direct fragmentation (Scheme 3); however, dissociation takes place in competition with reversible isomerization, as shown in Scheme 2.[16–18]

If $[CH_3]^+$ attack on 2-methylfuran leads exclusively to 2,5-dimethylfuran (**2**), then the behaviour of the adduct ion **1a** should be similar to **1b** as well as to that of ion **2a**. However, the results show that the incorporation of ^{13}C in the fragment ion $[CH_3CO]^+$ is not the same for these three ions. Differences in internal energy cannot explain these results, because the ions **1a** and **1b** are formed under the same conditions, while different spontaneous fragmentation reactions are observed. Moreover, differences between the MIKE–CID spectra corroborate these conclusions.

This study of labelled adduct ions **1** indicates that $[CH_3]^+$ is not bonded exclusively to position 5.

The adduct ions [2-ethylfuran + CH_3]$^+$ (5) and [2-methylfuran + C_2H_5]$^+$ (6)

The MIKE spectra of the adduct ions **5**, **6** (formed by the action of $[CH_3]^+$ or $[C_2H_5]^+$) and the protonated alkylfuran isomers **7**–**10** are reported in Table 3. Metastable ions **5**–**10** lead to the same fragmentations but, unlike the higher homologues, the relative abundance of the various fragments varies considerably. In particular, only the protonated 2-methyl-5-ethylfuran (**7**) leads to a single significant fragment ion *m*/*z* 57, $[CH_3CH_2CO]^+$. Deuterium labelling demonstrates that this fragment ion is formed with retention of the atoms of the ethyl group at position 5. Hence, the origin is the direct fragmentation shown in Scheme 3. This fragment ion is characteristic of 2,5-disubstituted furans.

First, it emerges from the results in Table 3 that the metastable adduct ions **5** and **6** do not produce the fragment ion $[CH_3CH_2CO]^+$ *m*/*z* 57 in appreciable abundance. Here again the internal energy seems not to play an important role because the adduct ion **6** shows the same behaviour whether it is formed in a methane plasma or by reaction with C_2H_5I.

These results indicate that the adduct ions **5** and **6** do not have only the structure of ion **7**. This is confirmed by the formation of the $[CH_3CO]^+$ fragment ion (*m*/*z* 43) from isotope-labelled ions. It has been shown that different isomerization and dissociation reactions are in competition for each protonated dialkylfurans. For this reason, the degree of incorporation of one atom in the $[CH_3CO]^+$ fragment ion characterizes the initial position of the alkyl substituants.

Table 3. MIKE spectra of ions 5–10

			43	55	57	67	69	81	83	93
5	2-CH_2CH_2	$\overset{+}{CH_3}$	29	6.5	0.5	3	10	2	14	34
6	2-CH_3	$[C_2H_5]^+$ (**a**)	27	8	0.5	5	5	2	22	43.5
		$[C_2H_5]^+$ (**b**)	25	7	2	3	4.5	1.5	11	48
7	2-CH_3, 5-C_2H_5	H^+	34	5	7	3	4	1	10	36
8	2-CH_3, 3-C_2H_5	H^+	26	6	0.5	2	2.5	3	16.5	43.5
9	2-C_2H_5, 4-CH_3	H^+	8	6	0.5	11	6.5	3.5	27.5	37.5
10	2,3,5-$(CH_3)_3$	H^+	19	3.5	0.5	2.5	5	1.5	13.5	54.5

To specify the degree of incorporation of deuterium in this fragment ion, two parameters have been used to analyse the experimental results:

(i) the heavy atoms total degree of incorporation p for each position is defined by $P = 3[46] + 2[45] + [44]$, where the numbers in brackets correspond to the normalized abundance of the fragments ($[43] + [44] + [45] + [46] = 100$);

(ii) p is the degree of incorporation of only one of these atoms ($p = P/3$ for a CD_3 group).

The MIKE results are given in Table 4. The results obtained from MIKE–CID spectra lead to the same conclusions:

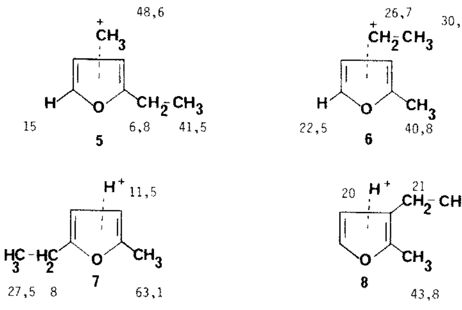
(i) Ion **7** is characterized by a very different degree of incorporation of the two methyl groups. The $[CH_3CO]^+$ fragment ion is formed with a high participation of the hydrogens of the methyl group in position 2 ($p = 63.1$) while the p value for the other methyl group is significantly lower ($p = 27.5$): since ion **7** is substituted in positions 2 and 5, $[CH_3CO]^+$ is formed either by a direct dissociation (Scheme 3) or, but only partly, after isomerization and hydrogen exchanges (Scheme 2).

For the same reason, the hydrogen exchanges are not important and the p values for the secondary hydrogens ($p = 8$) and for the protonating hydrogen ($p = 11.5$) are low.

(ii) The fragmentation reactions for **8** are very different from those observed for **7**: not only is the abundance of the fragment ion m/z 57 $[CH_3CH_2CO]^+$ different (Table 3), but the degree of incorporation of the various atoms in the fragment ion m/z 43 also varies.

The degree of incorporation of hydrogens of the methyl group in position 2 is more important in ion **7** ($p = 63.1$) than in ion **8** ($p = 43.9$). For the secondary hydrogens in the ethyl group, this degree of incorporation is lower for ion **7** ($p = 8$) than for ion **8** ($p = 21$). These data are explained if we consider that ion **7** reacts partly by direct fragmentation to give the fragment ion $[CH_3CO]^+$, while exchange of hydrogens and isomerization processes are more important for ion **8**.

(iii) In [2-ethylfuran + $CH_3]^+$ (**5**) the ethyl group is fixed on position 2 before methylation: the incorporation of the secondary hydrogen of the ethyl group in the fragment ion is nearly the same as that for ion **7** (Table 4, Scheme 5). However, the p values associated



Scheme 5. p values.

Table 4. Shifts of the fragment $[C(H,D)_3\text{-}CO]^+$ in the MIKE spectra of the deuterated compounds 5–8: (x) generated by the action of alkyl iodide; (xx) generated in a methane plasma

	Furan	Cation	m/z 43	m/z 44	m/z 45	m/z 46	P	p
5a	2-CH_2CH_3, 5-*d*	$[CH_3]^+$ xx	85	15	–	–	15	15
5b	2-CD_2CH_3	$[CH_3]^+$ xx	90	6.5	3.5	–	13.5	6.8
5c	2-CH_2CD_3	$[CH_3]^+$ xx	52	6.5	6.5	3.5	124.5	41.5
5d	2-CH_2CH_3	$[CD_3]^+$ xx	41	10.5	10	38.5	146	48.6
6a	2-CH_3, 5-*d*	$[C_2H_5]^+$ x	77.5	22.5	–	–	22.5	22.5
6b	2-CH_3	$[CD_2{-}CH_3]^+$ xx	57.5	31.5	11	–	53.5	26.7
6c	2-CH_3	$[CH_2{-}CD_3]^+$ xx	46.5	26	21	7.5	90.5	30.2
6d	2-CH_3	$[CD_2{-}CD_3]^+$ xx	29.5	21	16	33.5	153.5	–
6e	2-CD_3	$[C_2H_5]^+$ x	47.5	13	9	30.5	122.5	40.8
7a	2-CH_3, 5-CH_2CH_3	D^+ x	88.5	11.5	–	–	11.5	11.5
7b	2-CH_3, 5-CD_2CH_3	H^+ xx	87.5	9	3.5	–	16	8
7c	2-CH_3, 5-CH_2CD_3	H^+ xx	68	5	3.5	23.5	82.5	27.5
7d	2-CD_3, 5-CH_2CH_3	H^+ xx	32	5.5	3.5	59	189.5	63.1
8a	2-CH_3, 3-CH_2CH_3	D^+ x	80	20	–	–	20	20
8b	2-CH_3, 3-CD_2CH_3	H^+ xx	67.5	23	9.5	–	42	21
8c	2-CD_3, 3-CH_2CH_3	H^+ xx	49	7.5	6.5	37	131.5	43.8

with the two methyl groups are approximately the same: $p = 41.5$ and $p = 48.6$ as for the adduct ion **5** and they are considerably different from that observed for ion **7**. This difference shows that the adduct ion **5** is not formed only with structure **7**.

(iv) The difference between the behaviour of the adduct ions **5** and **6** indicates that alkylation at position 5 is less important, since their behaviour should be similar if alkylation occurs on position 5. It is convenient to observe that the p value corresponding to hydrogens of the added methyl group in adduct ion **5** ($p = 48.6$) is somewhat higher than for the methyl group of the $[C_2H_5]^+$ in adduct ion **6** ($p = 30.2$) (Scheme 5). Conclusive evidence is obtained from comparison of the deuterium-labelled adduct ions, **5b** and **6b**. These have been formed by alkylation with CH_3I and CH_3CD_2I so their internal energy is quite similar. Alkylation in position 5 should lead in both cases to the same ion **7b**, but the degree of incorporation of the secondary hydrogens is 6.8 for ion **5b** and 26.7 for ion **6b** (Table 4, Scheme 5). This difference between **5** and **6** indicates that alkylation on position 5 in 2-methyl- or 2-ethylfuran is of marginal importance. This is confirmed by the comparison of the adduct ion **6** with ions **7** and **8**.

(v) The results in Table 4 show that the behaviour of adduct ion **6** is completely different from that of ion **7** but similar to that of ion **8**: the degree of participation of the secondary hydrogens and of the ring hydrogens are high for **6** and **8** and low for **7**; the p values corresponding to the hydrogens of the methyl group in position 2 are similar for ion **6** ($p = 40.8$) and ion **8** ($p = 43.8$). This value is considerably higher for ion **7** ($p = 63.1$).

It is not possible to conclude from these data whether alkylation occurs at position 3 or 4, but our results show without ambiguity that alkylation occurs predominantly at the β-position.

DISCUSSION

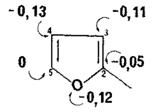
The experimental results show that alkylation occurs predominantly at the β-position. To study if these reactions are under kinetic or thermodynamic control, we have calculated the following properties:

(i) the charge distribution in the 2-methylfuran before attack of the carbocation R^+;
(ii) the enthalpies of the adduct ions formed by the initial attack of R^+;
(iii) the enthalpies of the possible final products.

Charge distribution in 2-methylfuran

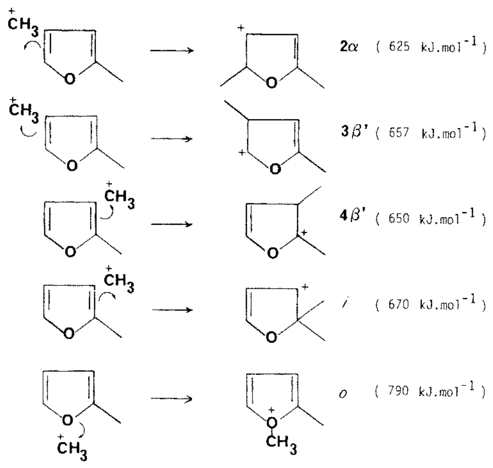
Several authors have rationalized the course of addition of cations to aromatic heterocycles with the aid of charge densities and molecular electrostatic potentials for the molecules in their ground state, based on the premise that a high electron density will exert an attractive influence on an electrophilic reagent. With regard to furan, the calculated charge densities show that the oxygen and the β-carbons are nucleophilic. The curves of molecular electrostatic potential illustrate in particular the nucleophilic character of the oxygen.[20]

In this work, the charge distribution has been determined by MNDO calculation for 2-methylfuran (Scheme 6). The charge densities are, respectively, -0.11 and -0.13 for C(3) and C(4) and -0.12 for the oxygen. The charge density of C(2) is lower (-0.05); a yet lower value is calculated for C(5).



Scheme 6. Charge densities.

According to this kinetic criterion, the first attack of $[CH_3]^+$ on 2-methylfuran should lead to a mixture of β-methyl forms and to the oxonium ion o (Scheme 7).



Scheme 7

Three lines of evidence show that it is highly probable that ion o does not exist in the 2nd FFR:

(i) Results obtained by radiolysis have shown that O-alkylated furans rearrange rapidly to give α-substituted isomers. However, reactions under these conditions are in general very rapid (10^{-9} s^{-1}), compared to reactions in the mass spectrometer FFR (10^{-5} s^{-1}). Furthermore, the MIKE–CID and MIKE spectra of the adduct ions and of their labelled derivatives are not very different from those observed for protonated alkylfurans.

(ii) Moreover, Maquestiau *et al.*[11] did not observe any protonated N-ethylpyrrole in the 2nd FFR after reaction of $[C_2H_5]^+$ with pyrrole under CI conditions.

Thus, ion o appears to be an unstable intermediate in agreement with the enthalpy values.

Enthalpies of the five adduct ions 2α, 3β′, 4β′, *i* and *o* (Scheme 7)

In order to determine which forms are the more stable, the enthaply calculations[3] were extended to the $\Delta H_f{}^\circ$ values of the protonated 2,3-dimethylfurans and the $\Delta H_f{}^\circ$ values of the ipso and O-alkylated forms, i and o.

These results lead to the following conclusion: if the course of the alkylation reactions were determined by the stability of the first adduct formed, the reaction product would be a 2,5-dialkylfuran: this is not in agreement with the experimental data.

Since ΔH_f° for ion *o* is very high, rapid isomerization to the more stable isomer **2α** can occur as suggested by Speranza.[7] Ion **2α** then rearranges to 2,3- and 2,4-disubstituted forms; this is supported by the lower ΔH_f° for the different protonated forms.

Calculation of the more stable forms

ΔH_f° values for the protonated form of all the dimethylfurans are reported (Scheme 8):

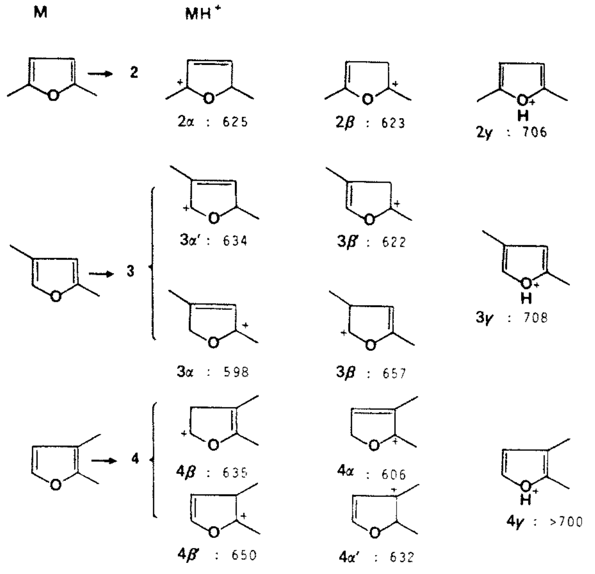
(i) the ΔH_f° values of the more stable 2,5-disubstituted forms (**2α** and **2β**) are 623 and 625 kJ mol^{-1};

(ii) the ΔH_f° of the more stable 2,4-disubstituted isomer (**3α**, 598 kJ mol^{-1}) and the more stable 2,3-disubstituted isomer (**4α**, 606 kJ mol^{-1}) are considerably lower.

Comparison of the results of calculation with the experimental data suggests that alkylation of 2-alkylfurans under CI conditions is thermodynamically controlled.

CONCLUSION

The experimental study of the adduct ions [2-alkylfuran, CH_3 or C_2H_5]$^+$ and their isomers shows that under CI conditions alkylation of 2-methylfuran occurs preferentially at the *β*-position. The conclusion that these reactions are under thermodynamic control is supported by MNDO calculations. Work is in progress to determine if alkylation occurs preferentially on position 3 or 4. Another unanswered question is whether the initial adduct ions evolve only through unimolecular processes to give the most stable forms or if successive reactions take place in the source; indeed, the formation of protonated furan has been observed by the reaction of CH_3I with 2-methylfuran.



Scheme 8. ΔH_f°, kJ mol^{-1}.

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