Acetyl Exchange between Acetyl Chloride and Sterically Hindered Aryl Ketones under Friedel–Crafts Conditions

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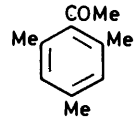
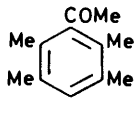
The kinetics of acetyl exchange between acetylmesitylene, or acetyldurene, and ^{14}C-labelled acetyl chloride have been measured in nitromethane solution in the presence of aluminium chloride. Mechanistic studies using acetyl[3,5-$^{2}H_2$]mesitylene as substrate show conclusively that acetyl exchange proceeds, not by acylation–deacylation or deacylation–acylation, but *via* a synchronous reaction involving an *ipso*-complex. Theoretical calculations (MNDO) indicate that of three possible synchronous pathways, two are energetically feasible.

KINETICS of acetyl exchange have been determined for the aluminium-chloride-catalysed reaction between acetylmesitylene (1) and ^{14}C-labelled acetyl chloride in nitromethane solution.[1] The criteria for this novel reaction appear to be a ketone whose acetyl function is attached to an electronically activated position flanked by two methyl groups and a solvent which prevents significant diacetylation.

We have sought other examples of this reaction in order to assess their relevance to the problem [2] of the reversibility of Friedel–Crafts acylations. The kinetic data for the ketones examined, by the method given previously,[1] are summarised in Tables 1 and 2.



(1)



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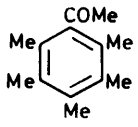

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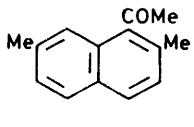

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For most of these systems problems were encountered with the rate measurements. Acetyldurene (2) proved not to be stable under the acetylation conditions beyond *ca.* 10% reaction. For molar proportions of ketone : acetic anhydride : aluminium chloride = 1 : 1 : 4 on a *ca.* 0.2 mol dm^{-3} scale in nitromethane solution at 35 °C it was found that *ca.* 5% of durene was present after 6 h (*cf.* ref. 3); after 30 h <50% of the ketone (2) remained. Therefore, only those kinetic runs which were carried out at low temperatures, and which give a monotonic increase in rate constant with temperature, could be used (Table 1). For these runs only 4—15% of exchange reaction was observed. The precision of the rate measurements decreased with increasing reaction temperature (Table 1, footnotes), and in consequence the activation parameters (Table 2) given for acetyldurene (2) are not very reliable.

Exchange of acetyl function with acetylpentamethylbenzene (3) occurred very slowly; only 3.5% of reaction was observed after 8 h at 50 °C. At this temperature side reactions take place, as gauged by g.l.c. analysis and as observed in previous work.[4] This permits us to quote only an approximate rate constant. This restriction is also true for 1-acetyl-2,7-dimethylnaphthalene (4), where in a steric sense a *peri*-hydrogen atom substitutes for a second *ortho*-methyl group; at 25 °C only 1% reaction

TABLE 1

Rate constants of the reaction between ketones and ^{14}C-labelled acetyl chloride in anhydrous nitromethane, catalysed by aluminium chloride

Substrate					
Ketone	Conc. (mol dm^{-3})	Acetyl chloride (mol dm^{-3})	T/K	$t_{\frac{1}{2}}$/min	$10^{6}k_2$/dm^3 mol^{-1} s^{-1}
Acetylmesitylene (1)	0.204	0.204	293.2	4 660	6.09
	0.204	0.204	298.6	3 420	8.27
	0.204	0.204	302.8	2 730	10.4
	0.204	0.204	305.5	2 100	13.5
	0.204	0.408	305.5	1 430	13.2
	0.408	0.204	305.5	1 360	13.8
	0.204	0.204	308.6	1 540	18.4
Acetyldurene (2)	0.204	0.204	283.1	4 000	1.2 [a]
	0.204	0.204	288.1		1.7 [b]
	0.204	0.204	293.1		7.0 [c]
	0.204	0.204	298.1		7.9 [d]
Acetylpentamethylbenzene (3)	0.204	0.204	323.1	~4 000	~7
1-Acetyl-2,7-dimethylnaphthalene (4)	0.204	0.204	298.2	~3 300	~9
1,3-Diacetyl-2,4,6-trimethylbenzene [e] (5)	0.0280	0.2080	308.2	~110,000	~1.8

95% Confidence limits: [a] $\pm 0.3 \times 10^{-6}$. [b] $\pm 0.6 \times 10^{-6}$. [c] $\pm 1.8 \times 10^{-6}$. [d] $\pm 1.9 \times 10^{-6}$. [e] Solvent: 1,2-dichloroethane.

was observed after 22 h, and although no rearrangement could be detected by g.l.c. analysis, the solution gradually became dark green and a solid slowly deposited.

An attempt at accurately measuring the rate of acetyl exchange with 1,3-diacetyl-2,4,6-trimethylbenzene (5) was frustrated by the low solubility of the ketone–catalyst

TABLE 2

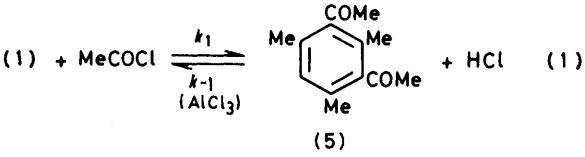
Computed rate constants and activation parameters for the reactions of acetylmesitylene or acetyldurene with [1-^{14}C]acetyl chloride in anhydrous nitromethane, catalysed by aluminium chloride

	Ketone	
Parameter	Acetylmesitylene (1)	Acetyldurene (2)
k_2 (298.1 K, computed)/ dm^3 mol^{-1} s^{-1}	8.24×10^{-6}	1.0×10^{-5}
Correlation coefficient	0.987	0.973
$\Delta H^{\ddagger}$/kJ mol^{-1}	49.9	98
$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	−175	−47
$\Delta G^{\ddagger}$/kJ mol^{-1}	102.0	112

complex in the preferred solvent,[5a] 1,2-dichloroethane. Again, only an approximate value can be quoted for the rate constant, merely *ca.* 7% reaction having taken place after 8 days at 35 °C.

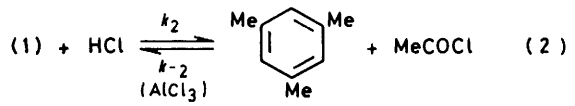
The data given in Table 1 show that all the acetyl exchange reactions studied are quite slow. The rate constant for acetylmesitylene (1), extrapolated to 50 °C, is 4.4×10^{-5} dm^3 mol^{-1} s^{-1}, which is *ca.* 6 times as great as that of acetylpentamethylbenzene (3). From data obtained earlier[5a] a rate constant (k_2 at 40°) for the Friedel–Crafts acetylation of mesitylene in nitromethane solution can be estimated to be *ca.* 6.5×10^{-3} dm^3 mol^{-1} s^{-1}, which is *ca.* 300 times as fast as the acetyl exchange reaction under the same conditions. For acetyldurene (2) the corresponding ratio is *ca.* 250. Clearly, acetyl exchange is not a major factor during the Friedel–Crafts acetylations of these hydrocarbon systems.

The question must be asked, ' Do these results provide experimental proof of the reversibility of Friedel–Crafts acetylation reactions? '. It is tempting to assume that acetyl exchange occurs, in the presence of the acetylating reagent acetyl chloride–aluminium chloride, by an initial acylation, followed by protiodeacylation [mechanism (1)]. In fact a yield of *ca.* 0.34% of diketone (5) could be determined in a reaction carried



(5)

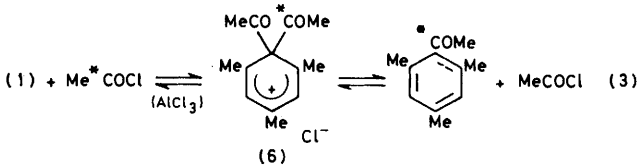
out under the conditions of the exchange reaction for 5.8 half-lives. This result could mean that exchange proceeds by mechanism (1), with the deacylation stage (k_{-1}) being predominantly responsible for the overall rate, and an equilibrium constant for the acetylation reaction in nitromethane, $K = (0.34/99.7)^2 = 1.2 \times 10^{-5}$. On the other hand, the presence of diketone (5) could instead be due to a side-reaction not connected with the acetyl exchange; in this event the amount of diketone (5) estimated need not represent its equilibrium



concentration. In this case, also, the formation of the diketone would be very slow, with a rate constant, assuming it to be a forward reaction only, k at 25 °C = *ca.* 1.4×10^{-8} dm^3 mol^{-1} s^{-1}.

Acetyl exchange could take place by another mechanism (2), involving initial deacylation (k_2) followed by re-acylation (k_{-2}). Protiodeacylation of acetylmesitylene (1) and related ketones has recently been observed in nitromethane solution under Friedel–Crafts conditions.[4] Whether such deacetylations can be important in the presence of added acetylating agent is another matter. Mesitylene could not be detected in the reaction mixture, which did afford a trace of the diketone (5).

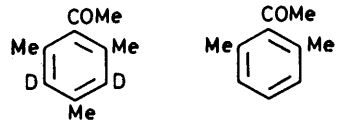
Acetyl exchange proceeding either *via* mechanism (1) or (2) would provide strong evidence of reversibility of Friedel–Crafts acetylations. There is a third possibility, however, that the acetyl exchange proceeds synchronously without the involvement of any stable reaction intermediate [mechanism (3)]. The reaction would here proceed through the intermediacy of an *ipso*-complex (6).



(6)

In previous work,[5a] involving competition between acyl groups in the acylation of mesitylene, mechanism (1) was considered the most likely, and mechanism (3) the least likely.

It was considered feasible to distinguish between the three possible modes of acetyl exchange if deuteriated acetylmesitylene (7) were treated during an acetyl-exchange reaction with an excess of hydrogen chloride. By mechanism (1) 50% of the D-label would be replaced during the acetyl exchange of 1 mol of ketone (7). If the *meta*-positions of acetylmesitylene rapidly undergo hydrogen exchange, the D-content of the product from an acetyl exchange of ketone (7) would then be sub-



(7) (8)

stantially <50%. Acetyl exchange *via* mechanism (2) would be dominated by H–D exchange, depending on the relative rates of hydrogen exchange and acetylation

of the intermediate mesitylene. At most 67.3% of the D-label present in ketone (7) could be retained after acetyl exchange, allowing for an isotope effect k_H/k_D of 1.06 for Friedel–Crafts acylation [5b] (the only such published ratio which can be considered relevant to the present system). Only in a favourable case could a distinction be achieved between mechanisms (1) and (2) by this method.

However, should the acetyl exchange proceed *via* the *ipso*-complex (6) [mechanism (3)], the *meta*-positions would not be involved at all, and the D-label of ketone (7) would be retained completely.

Deuterium-labelling Experiments.—A first attempt to prepare ketone (7) was made by reacting ketone (1) with CF_3COOD–D_2SO_4–D_2O, a medium not sufficiently acidic to cause appreciable protiodeacetylation, which moderately concentrated aqueous sulphuric acid does.[6,7] Incorporation of deuterium occurred solely in the acetyl side-chain. The inertness of the *meta*-positions encouraged us in the belief that labelled acetylmesitylene (7) could survive the acidic conditions obtaining during the work-up of this ketone prepared by a Friedel–Crafts reaction.

On careful acetylation of *e.g.* 95.6% trideuteriated mesitylene a labelled ketone was obtained, which was *ca.* 73—76% dideuterio-labelled (by ^1H n.m.r.), confirming that under these conditions hydrogen exchange occurs rapidly with the nuclear positions of mesitylene, and that there is a consequent loss of label prior to acetylation. The labelled ketone [mainly (7)] was, however, suitable for the acetyl exchange experiments. The results of three such experiments are given in Table 3.

TABLE 3

Acetyl-exchange experiments using 2′,4′,6′-trimethyl-[3,5-$^2H_2$]acetophenone (0.204 mol dm^{-3}), acetic anhydride (0.204 mol dm^{-3}), aluminium chloride (0.816 mol dm^{-3}), and hydrogen chloride, in nitromethane solution at 35.5 °C

Expt.	[HCl]/mol dm^{-3}	No. of half-lives	D : H in 3,5-positions [a,b]	Retention of label (%)
A	2.04	1	2.94	98.7
B	2.04	10	3.37	102
C	20.4	1	3.39	102

[a] Ratio calculated from the integration of aromatic signal/methyl signals in ^1H n.m.r. spectrum. [b] D : H in starting ketone = 3.10 (D% 75.6).

The results indicate effectively complete retention of the deuterium label in the aromatic hydrogen positions of acetylmesitylene (7), when reacted with 10 molar proportions of hydrogen chloride for up to 10 half-lives, or with 100 molar proportions for one half-life. If mechanisms (1) or (2) had been important one would have expected, for reactions *B* and *C* (Table 3) a more substantial loss of deuterium label than for reaction *A*. Since the deuterium content of the ketone was measured only indirectly by the n.m.r. method, a complementary method of estimation was used in addition.

A sample of deuterium-labelled acetylmesitylene (1.51 D atoms per molecule, by ^1H n.m.r.) was subjected to repeated ion-current scans (low resolution m.s.) to determine the proportions of di-labelled ($^2H_2$), mono-labelled ($^2H_1$), and unlabelled species ($^2H_0$). Although the precision of the method is only moderate, it is clear (Table 4) that the deuterium-labelling of the starting material closely follows the statistical distribution pattern. The total content of D-label (73.8%) was found to be only slightly lower than that determined by ^1H n.m.r.

After acetyl exchange for one half-life with 10 molar proportions of hydrogen chloride (Table 3, reaction *A*) the product showed a 10% reduction in overall D-label. The proportions of labelled species $^2H_2$ and $^2H_1$ are also close to those of the starting material. It is not possible to conclude that any significant change had occurred in the composition of the ketone mixture.

TABLE 4

Properties of ^2H-labelled acetylmesitylene species

Mixture	$^2H_0$	$^2H_1$	$^2H_2$
Reactant [a]	7.6	37.3	55.1
Statistical (based on 1.51 D atoms per molecule [b])	6.0	36.9	57.2
Statistical (based on 1.48 D atoms per molecule [c])	6.9	38.7	54.4
Product [a]	16.6	33.9	49.5
Statistical (based on 1.33 D atoms per molecule [c])	11.3	44.6	44.2
D-label randomised with 10 mol equiv. HCl	76.9	21.6	1.5

[a] From ion-current scans. [b] D-content, as found by ^1H n.m.r. [c] D-content, as found by m.s.

The two methods of analysis agree: the acetyl exchange with acetylmesitylene proceeds predominantly, and perhaps exclusively, by the synchronous mechanism (3).

Molecular Orbital Calculations.—In view of the novelty of the acetyl-exchange reaction it was thought desirable to explore the details of the mechanism by means of quantum mechanical calculations using the recent MNDO technique.[8] For this purpose the equilibrium geometry and charge distribution were first calculated for the reacting species, and potential surfaces were then plotted for their interaction, by the mechanism (3) now established.

Structure of the acetylium ion. It proved necessary to assume that the electrophilic attacking species is the acetylium cation. It is recognised [9] that the acylating reagent is, in kinetic terms, more likely to be the acyl halide–catalyst addition complex $CH_3C(Cl)=O,AlCl_3$, or the ion-pair $[CH_3CO^+][AlCl_4^-]$, but as the reaction proceeds the actual process will be a transfer of an acetyl cationic species from the ' reagent ' to the substrate at the point of substitution. The CH_3CO^+ species will serve for this purpose, especially when, as below, the energies of different pathways using the same reactants are being compared. The equilibrium geometry of the acetylium ion as calculated is given in Figure 1. The central atom (C_R) is shown to carry nearly half the positive charge, with the hydrogen-atoms sharing most of the remaining charge, an example of hyperconjugation. The LUMO of this species involves a very large atomic

orbital coefficient for the $2p_y$ orbital on C_R, consistent with nucleophilic attack occurring at this point. The CCO framework of the ion is linear. The total energy of the isolated cation was calculated as $E_{tot} = -611.687\ 57$ eV.

Equilibrium geometry and E_{tot} *of acetylmesitylene and 2,6-dimethylacetophenone.* MNDO calculations on acetylmesitylene (1) and 2,6-dimethylacetophenone (8) were carried out, allowing the acetyl group and *ortho*-methyl groups to ' relax ', *i.e.* permitting the molecule to achieve optimum geometric parameters (bond lengths, bond angles) in terms of minimising the total energy of the system. The significant bond lengths and charge distributions thus obtained are given in Table 5. It is noteworthy that in both ketone molecules all ring atoms bear negative charges, and at C-1, the position at which acetyl exchange occurs, this is relatively high. The acetyl group is calculated to be nearly orthogonal to the aromatic plane, whereas various physicochemical measurements [10] on acetylmesitylene (1) in solution suggested a dihedral angle of $\gtrsim 75°$.

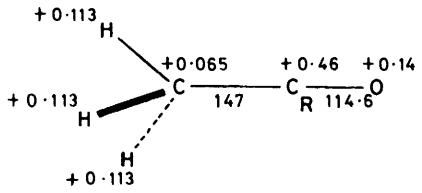


FIGURE 1 Calculated charge distribution (units of e) and bond distances (pm) of the isolated acetylium cation

TABLE 5

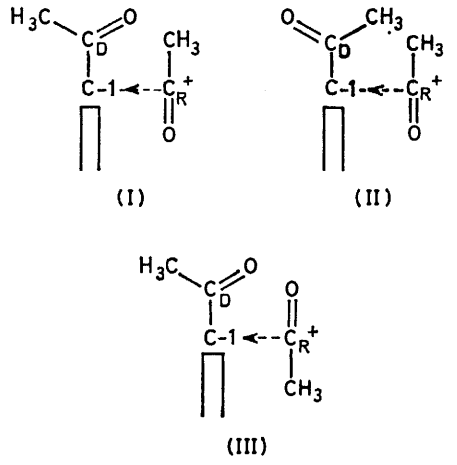
Bond lengths, electronic charges, dipole moments, and total energies calculated (MNDO) for acetylmesitylene and 2,6-dimethylacetophenone

Property	Acetylmesitylene (1)	2,6-Dimethylacetophenone (8)
Bond length (pm)		
C-1–C-2 (C-1–C-6)	140.1	140.1
C-1–CO	150.8	150.8
CH_3–CO	153.6	153.6
CH_3–C-2 (CH_3–C-6)	153.7	154.0
C–O	122.6	122.7
Charge (10^3e)		
C-1	−92	−90
C-2 (C-6)	−74	−74
C-3 (C-5)	−30	−38
C-4	−98	−46
2(6)-CH_3	+66	+69
$COCH_3$	+6	+5
C–O	+262	+247
O	−280	−283
Dipole moment		
10^{30} C_m/D	8.25 (2.503)	8.27 (2.478)
E_{tot}/eV	−1 925.831 09	−1 769.359 88

Three theoretical models of the acetyl exchange reaction. As a result of the asymmetry of an acetyl group in ketones (1) or (8), with respect to the plane of the aromatic ring, different modes of attack by an incoming acetylium ion are possible. The three different reaction co-ordinates to be considered involve an initial close approach of (I) the methyl end of the reagent to the carbonyl oxygen of the ketone, or (II) the methyl end of the reagent to the methyl group of the ketone, or (III) the carbonyl end of the reagent to the carbonyl oxygen of the ketone.

Each of these reaction profiles was studied initially for ketone (8), which is sterically analogous to acetylmesitylene (1), and which was within the capacity of the computer program when first available.

The starting point is the reactants, ketone (8) and the acetylium ion, an infinite distance apart, with a combined energy, $E_{tot} = -2\ 381.047\ 45$ eV. The two reactants are next brought together in a series of steps,



setting the central atom (C_R) of the reagent at a fixed distance from the C-1 atom of the benzene ring, at which substitution will take place. Apart from the tetrahedral angles of the methyl groups (which were held constant) all the geometric parameters for the incoming and outgoing acetyl groups, the *ortho*-methyl groups, and the *ortho*-carbon positions adjacent to the site of attack, were optimised for each chosen C-1–C_R distance. After the position of the energy maximum, corresponding to the transition state, had been located, the C-1–C_R distance was also ' relaxed ', in order to allow the optimised structure and energy of the σ-complex intermediate to be obtained.

The plots of total energy *versus* C-1–C_R distance (Figure 2) are typical for aromatic substitutions, and their symmetry is as expected for reactions in which the forward and reverse processes are identical. The heats of formation of the critical structures (maxima and minima) are given in Table 6. From these data it can be seen that for 2,6-dimethylacetophenone, acetyl exchange *via* pathways (I) and (III) are very similar energetically, involving enthalpies of activation $\Delta H^{\ddagger} = 89.71$ and 90.15 kJ mol^{-1}, respectively, whilst pathway (II) with a transition state of much higher energy, and $\Delta H^{\ddagger} = 121.06$ kJ mol^{-1}, is much less probable. A dissection of the total energy into its electronic and core–core repulsion terms indicates that it is the magnitude of the former which principally differentiates the transition state of pathway (II) from those of the other two.

The energy levels of the σ-complexes are very similar in the three cases. The stabilisation energies of the three σ-complexes are 43.34, 70.35, and 42.73 kJ mol^{-1}, respectively, for pathways (I)—(III). The σ-complex if

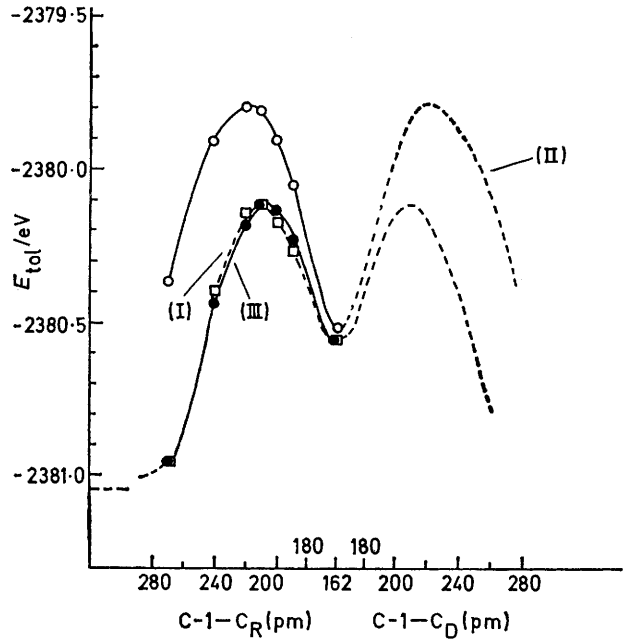


FIGURE 2 Calculated reaction co-ordinate for pathways (I)—(III)

formed by pathway (II) would have to be considered as quite a stable intermediate.

The two most likely reaction paths (I) and (III) were then examined for reactant acetylmesitylene (1), using an extended MNDO program, with the transition states and σ-complexes assumed to occur at the same values of C-1–C_R as for ketone (8). From the data presented in Table 6 it is apparent that the $\Delta H^{\ddagger}$ values for the two

TABLE 6

Heats of formation of critical structures along the potential surface of the reaction between acetylium ion and 2′,6′-dimethylacetophenone and acetylmesitylene, calculated by MNDO

C-1–C_R distance (pm)	Heat of formation (kJ mol^{-1}) 2′,6′-Dimethylacetophenone Pathway			Acetylmesitylene	
	(I)	(II)	(III)	(I)	(III)
∞ [a]	701.477	701.477	701.477	679.374	679.374
210 [b]	791.189		791.628	764.500	764.117
220 [b]		822.537			
162 [c]	747.850	752.289	748.895	718.648	718.677

[a] Corresponds to the initial state, *i.e.* reactants an infinite distance apart. [b] Corresponds to the energy maximum, *i.e.* the transition state. [c] Corresponds to the energy minimum, *i.e.* of the σ-complex intermediate.

reaction paths are again closely similar, *viz.* 85.13 and 84.74 kJ mol^{-1} for pathways (I) and (III), respectively. Thus, the extra methyl group lowers $\Delta H^{\ddagger}$ by *ca.* 5 kJ mol^{-1}. The σ-complex stabilisation energies are increased slightly, to 45.85 and 45.44 kJ mol^{-1}, respectively. For either ketone it is difficult to distinguish between the two favourable pathways (I) and (III).

The values of the activation enthalpies thus obtained are encouragingly low. While these calculations must be regarded as approximate in that the modelling of the reagent is over-simplistic, and that problems of solvation are not considered, they nevertheless strongly suggest that acetyl exchange at a sterically hindered site is perfectly feasible for two reaction pathways.

These routes involve quite complex and subtle series of synchronous motions of the attacking and departing acetyl groups and of the *ortho*-methyl groups. To illustrate what the calculations reveal one may describe pathway (I) in some detail. As the acetylium ion approaches the reaction site (at C-1), with the methyl end of the reagent coming in close to the oxygen-side of the ketone, the departing acetyl group is rapidly displaced out of the plane of the ring, and simultaneously rotated away from its near-orthogonal orientation. This motion is facilitated by a large rotation of the *ortho*-methyl group contiguous to the methyl fragment of the departing acetyl group in a counterclockwise sense, as if the

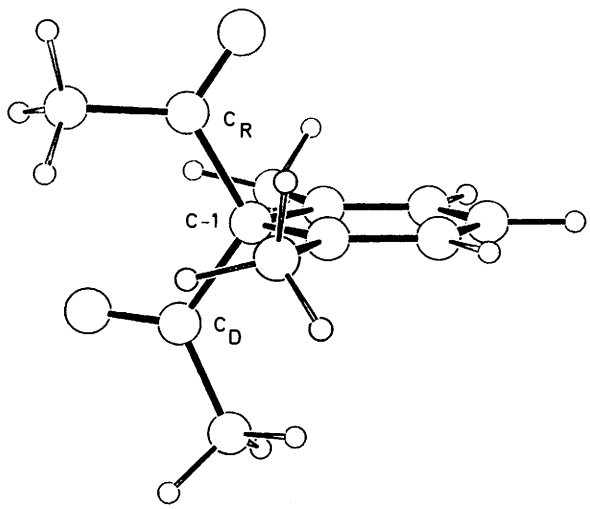


FIGURE 3 Transition state for pathway (I)

groups were 'meshing' or 'gearing' (*cf.* the 'gear effect'[11]). At the same time the ring methyl groups flex out-of-plane and backwards by *ca.* 7°. During this process the incoming acetyl is rotating about its incipient C-1–C_R bond, in the opposite sense to the departing group. The computed orientations for the transition state (energy maximum) are shown in Figure 3. The bond-lengths from C-1 to the attacking and departing acetyl groups are still unequal at this point, C-1–C_R = 210 and C-1–C_D = 154 pm, respectively. As the local energy minimum on the reaction co-ordinate, corresponding to the σ-complex, is approached, the two aromatic bonds adjacent to the site of attack, C-1–C-2 and C-1–C-6, lengthen rapidly and the bond angles

C-1–C-2–C-3 (=C-1–C-6–C-5) increase from 120 to *ca.* 129°. In the σ-complex the two bond lengths C-1–C_R = C-1–C_D = 160 pm, and the two acetyl groups become equivalent (Figure 4). Subsequent loss of an acetylium

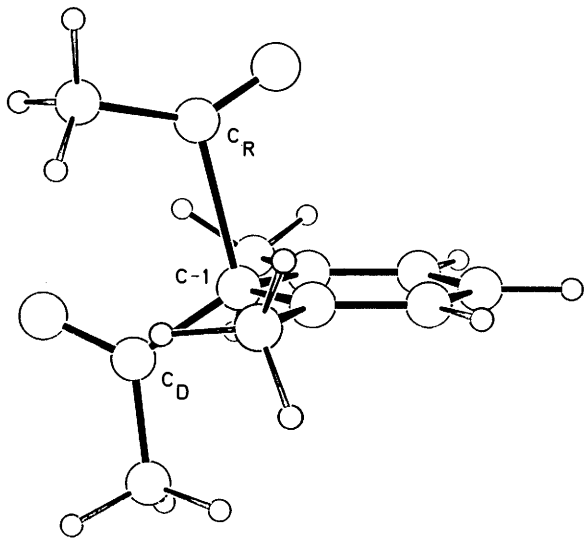


FIGURE 4 σ-Complex for pathway (I)

ion retraces the geometric and energy changes which have given rise to the σ-complex.

Pathways (II) and (III) are characterised by very similar complex motions of the substituent groups, as

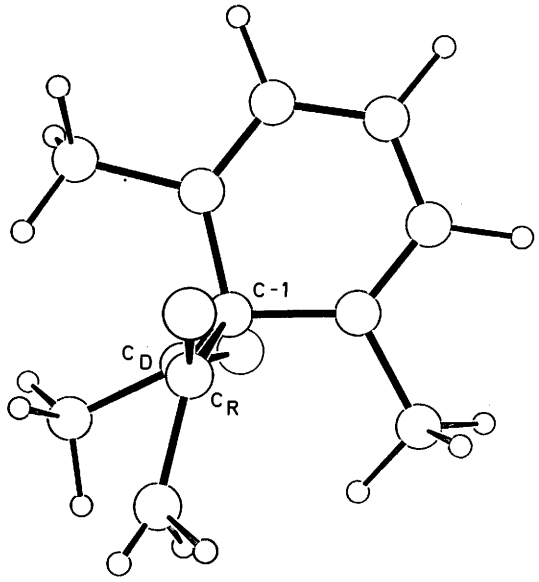


FIGURE 5 σ-Complex for pathway (II)

just described. In each case, however, the σ-complex (Figures 5 and 6) has a C_2 symmetry axis passing through C-1 and C-4, as required by the principle of microreversibility. Pathway (II) involves two rather bulky methyls on the acetyl groups sliding through the constricted region between the two *ortho*-methyl groups, a situation in which the degree of steric hindrance becomes maximised.

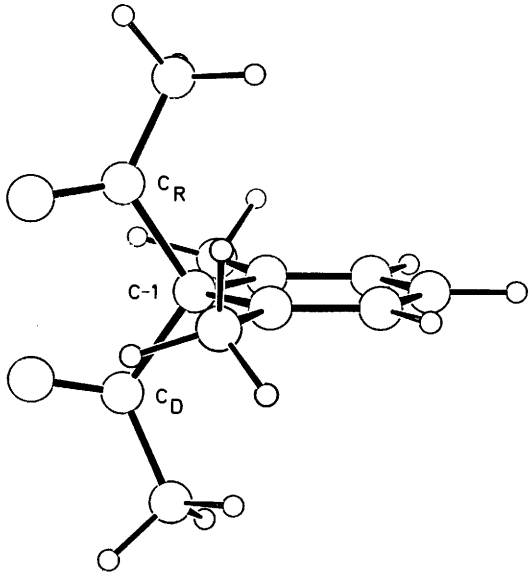


FIGURE 6 σ-Complex for pathway (III)

EXPERIMENTAL

Materials.—2′,4′,6′-Trimethylacetophenone,[5] 2′,3′,5′,6′-tetramethylacetophenone,[3] 2′,3′,4′,5′,6′-pentamethylacetophenone,[4] and 1,3-diacetyl-2,4,6-trimethylbenzene [5] were obtained in earlier work.

1-*Acetyl*-2,7-*dimethylnaphthalene.*—A Friedel–Crafts acetylation of 2,7-dimethylnaphthalene [12] gave a product, b.p. 122—126 °C at 0.8 mmHg, which g.l.c. showed contained 91% of the desired isomer. The picrate was prepared, and recrystallised, having m.p. 62—62.5 °C, $\nu_{max.}$ (KBr) 1 702 (C=O), 1 560 (NO_2), 1 345 (NO_2), and 1 120 cm^{-1} (OH). 1-Acetyl-2,7-dimethylnaphthalene was obtained (99.6% pure, by g.l.c.) from the picrate in the usual way, b.p. 111—112 °C at 0.15 mmHg (lit.,[12] 114—116 °C at 0.14 mmHg), $\nu_{max.}$ (film) 1 690 cm^{-1} (C=O); τ ($CDCl_3$) 2.81 (d, 3-*H*), 2.33 (m, 4- and 5-*H*), 2.74 (dd, 6-*H*), 2.65br (8-*H*), 7.41 (s, $COCH_3$), 7.53 (s, 2-CH_3), and 7.61 (s, 7-CH_3); $J_{3,4}$ 8.4, $J_{5,6}$ 8.3, $J_{6,8}$ 1.8 Hz (the reported [12] ^{1}H n.m.r. spectrum is closely similar).

^{2}H-*Labelling of* 2′,4′,6′-*Trimethylacetophenone.*—(1)Trifluoroacetic [^{2}H]acid (4 ml) was mixed with 2′,4′,6′-trimethylacetophenone (1 ml), and to the dark solution [$^2H_2$]sulphuric acid (1 ml) and [$^2H_2$]water (0.05 ml) were added. The mixture was set aside for 3 days, then diluted with water (25 ml), and the ketone extracted into chloroform. The recovered ketone was 2′,4′,6′-trimethyl [2,2,2-$^2H_3$]acetophenone (77%), τ ($CDCl_3$) 7.79 (s, 2′- and 6′-CH_3), 7.73 (s, 4′-CH_3), and 3.17 (s, 3′- and 5′-*H*).

(2) This was carried out as in (1) with a duration of 21 days. The product was mesitylene, with 12% ^{2}H-label on the aromatic positions, τ ($CDCl_3$) 2.9 (s, arom-*H*, integration 7.5 mm) and 7.7 (s, CH_3, integration 37.5 mm).

(3) 1,3,5-*Trimethyl*[2,4,6-$^2H_3$]*benzene.*—A mixture of trifluoroacetic acid (8 ml), [$^2H_2$]water (4 ml), and [$^2H_2$]sulphuric acid (1 drop) was added to mesitylene (4 ml). The

pale brown mixture was shaken for 48 h, and the product isolated in the usual way. Partly deuteriated mesitylene (3.6 ml, 90%) was obtained, containing 80.6% [$^2H_3$]-mesitylene [by ^1H n.m.r.; *cf.* (2) above]. This product was treated again, with a mixture of trifluoroacetic anhydride (7.4 ml), [$^2H_2$]water (5.0 ml) and [$^2H_2$]sulphuric acid (1 drop), for 3 h at 75 °C. Isolated in the usual way one obtained 1,3,5-trimethyl[2,4,6-$^2H_3$]benzene (95.6% $^2H_3$, by ^1H n.m.r. analysis).

Acetylation of 1,3,5-*Trimethyl*[2,4,6-$^2H_3$]*benzene*.—To a mixture of aluminium chloride (4.45 g) and acetyl chloride (2.62 g) in chloroform (115 ml) was added a solution of 1,3,5-trimethyl[2,4,6-$^2H_3$]benzene (3.64 g) in chloroform (10 ml). The mixture was set aside for 100 h, then worked up in the usual way. The product was 2′,4′,6′-trimethylacetophenone (4.06 g, 83%), b.p. 121—122 °C at 12 mmHg. The ^2H-content by ^1H n.m.r. analysis was 73.5% (integration of C*H*$_3$ signals 99.7 mm, of arom-*H* signal = 4.4 mm); low resolving power spectrum conditions (m.s.): ion source at 250 °C, electron energy 70—20 eV, trap current 300—30 μA, using heated inlet, *m/z* (20 eV) (relative peak heights, and standard deviation from seven scans, in parentheses 162 (4.7, 0.12), 163 (23.6, 0.58), 164 (36.08, 0.42), 165 (4.4, 0.19), and 166 (0.4); hence $^2H_0$ = 4.7, $^2H_1$ 23.0, $^2H_2$ = 34.0, $^2H_3$ = 0.1, giving composition: $^2H_0$ = 7.6%, $^2H_1$ = 37.3%, $^2H_2$ = 55.1%; total content by m.s. = 1.475 D-atoms per molecule.

The product from an acetyl-exchange experiment (see below) using the above labelled ketone was 73.8% acetyl-[$^2H_2$]mesitylene (by ^1H n.m.r.). It gave *m/z* 162 (12.5, 1.6), 163 (27.0, 3.3), 164 (40.4, 4.5), 165 (5.0, 0.6), and 166 (0.4); hence $^2H_0$ = 12.5, $^2H_1$ = 25.5, $^2H_2$ = 37.2, $^2H_3$ = 0.3, giving composition: $^2H_0$ = 16.6%, $^2H_1$ = 33.9%, $^2H_2$ = 49.5%; total content by m.s. = 1.329 D-atoms per molecule.

Exchange Reactions using Isotropically Labelled Acetic Anhydride.—Reactions were carried out between an inactive ketone and [1-^{14}C]acetic anhydride in the following way: aluminium chloride (4 mol. equiv.) and labelled acetic anhydride (1 mol. equiv.) were added to nitromethane, to give concentrations of 0.816 and 0.204 mol dm^{-3}, respectively. To start the reaction the ketone was added, at the selected temperature, over 5 s, so as to give 0.204 mol dm^{-3} of the substrate. The mixture was maintained at the appropriate temperature (±0.1°) using a thermostatically controlled water-bath. Portions (5 ml) were taken at intervals, and were separately added to ice and concentrated hydrochloric acid. The organic layer was separated and to it added the ether extract of the aqueous layer. The combined extract was washed with water, 0.02M-sodium carbonate solution, again with water, and dried (Na_2SO_4). The solvent was then evaporated and the oily residue made up with methanol (or ethanol), usually to 5 ml. Portions (1 ml) were then added to a borosilicate glass vial containing liquid scintillator (TTP/3–toluene) (9 or 14 ml) and thoroughly mixed. The vial was placed in the refrigeration unit of the scintillation counter for at least 1 h, prior to counting for 4—10 min, usually three times. The chemical yield of each sample was calculated from the u.v. light absorption, using a Beer-Lambert plot.

The results of a typical kinetic run are shown in Table 7. A plot of log(1 − *F*) *versus* time, where *F* = fraction exchange (see Table 7) is a good straight line. The $T_{\frac{1}{2}}$ is determined by a least-squares method, and rate *R* is then calculated, using a modification [13] of the exchange-rate equation (4) of McKay [14] where *a* and *b* are total concentrations (in mol dm^{-3}) of (labelled + unlabelled) acetyl

$$R = k_2ab = ab/(a + b) \times (\ln 2/T_{\frac{1}{2}}) \qquad (4)$$

species, and (labelled + unlabelled) ketone, respectively. For the kinetic run described in Table 7, $a = b = 0.204$ mol dm^{-3}, and hence $T_{\frac{1}{2}} = 4\,658$ min, $k_2 = 6.085 \times 10^{-6}$ dm^3 mol^{-1} s^{-1}.

Activation parameters were calculated in the usual way, using a computer program.

TABLE 7

Reaction between 2′,4′,6′-trimethylacetophenone (0.204 mol dm^{-3}) and labelled acetyl chloride (0.204 mol dm^{-3}) in anhydrous nitromethane at 293.2 K

Time interval (h)	Count rate (min^{-1})	Yield (%)	Corrected count rate (X) (min^{-1}) [a]	$(1-F)$ [b]
1.0	384	57.0	674	0.980
4.0	1 183	63.4	1 866	0.946
52.5	3 988	73.1	5 455	0.842
60.0	5 417	82.8	6 540	0.810
70.0	4 514	56.3	8 014	0.767
113.8	5 417	48.6	11 447	0.677
120.0	5 387	45.9	11 725	0.660
130.0	5 612	42.2	13 302	0.614

[a] Calculated X_∞ = 34 458 min^{-1}. [b] F = fraction exchange = X/X_∞.

Experiments on Chemical Stability of Ketone under Acetyl-exchange Conditions.—(1) 2′,4′,6′-*Trimethylacetophenone* (*acetylmesitylene*). A reaction was carried out using acetylmesitylene (1 mol equiv.), acetic anhydride (1 mol equiv.), and aluminium chloride (4 mol equiv.) in nitromethane for 14 days at *ca.* 20 °C. Careful analysis of the product by g.l.c. (3% OV17 on 60—80 mesh, acid-washed, silanised Diatomite C; N_2; 150 °C) revealed the absence of mesitylene, and the presence of diacetylmesitylene (corrected for mass response, 0.34 ± 0.04% w/w).

(2) 2′,3′,5′,6′-*Tetramethylacetophenone* (*acetyldurene*). A reaction carried out with acetyldurene, acetic anhydride, and aluminium chloride (mol equiv. 1 : 1 : 4), on a 0.204 mol dm^{-3} scale, for 6 h at 35 °C, showed the presence of durene (5.4%) in the product. A similar experiment (duration 30 h), gave on g.l.c. analysis: durene (18%), isodurene (5.5%), pentamethylbenzene (7.4%), acetylmesitylene (0.5%), two isomeric trimethylacetophenones (11 and 5.8%, respectively), residual acetyldurene (48%), and 2′,3′,4′,5′-tetramethylacetophenone (3.1%).

The Action of Aluminium Chloride on Acetic Anhydride in Nitromethane Solution.—A mixture of anhydrous aluminium chloride (3.92 g) and acetic anhydride (0.75 g) in nitromethane (34 ml) was connected to a gas trap and set aside at 20 °C for 7 days. Dry nitrogen was then bubbled through the reaction flask for 36 h, the issuing gases (containing acetyl chloride) being scrubbed by water in collecting bottles connected in series. The total acid in the traps was estimated by titration with dilute NaOH. The amount of acetyl chloride thus estimated was 0.920 mol per mol of acetic anhydride. To the residue in the reaction flask (containing $AcOAlCl_2$; *cf.* ref. 15) 0.5M-H_2SO_4 (90 ml) was added, the mixture heated over steam under reflux for 3.5 h, then filtered, cooled, and made up to 250 ml with distilled water. Portions were then titrated potentiometrically against 0.1M-NaOH, giving a titre (by difference) corresponding to 1.23 mol acetic acid per mol of acetic anhydride.

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