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# Aromatic Substitution. XXII.[1a] Acetylation of Benzene, Alkylbenzenes, and Halobenzenes with Methyloxocarbonium (Acetylium) Hexafluoro- and Hexachloroantimonate

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Competitive acetylation of benzene with alkylbenzenes and halobenzenes using methyloxocarbonium (acetylium) hexahaloantimonate complexes was investigated in nitromethane and nitrobenzene solution at 25°. The high selectivity reactions proceed according to a mechanism involving a $\sigma$-complex type transition state determining both substrate and positional selectivity. The nature of the acetylating agent was investigated and appears to be the solvated ion-pair or donor–acceptor complex, both substantially bulkier than the free $CH_3CO^+$ ion. Investigation of kinetic isotope effects of ring-deuterated toluene and benzene revealed a primary isotope effect in the acetylations with acetylium salts in accordance with a $\sigma$-complex type transition state involved in the rate-determining step. At the same time a secondary isotope effect of side-chain labeled toluene was also observed owing to the decreased conjugative effect of the $CD_3$ group on the benzenonium ion type $\sigma$-complex. The mechanistic aspects are discussed, including correlation between structure and reactivity of the methyloxocarbonium and nitrosonium, but not nitronium, salts.

## Introduction

The isolation of stable alkyloxocarbonium (acylium) salts[2] enabled us to undertake the investigation of the acetylation of benzene and alkylbenzenes with prepared methyloxocarbonium (acetylium) hexafluoroantimonate and hexachloroantimonate.

Using a stable alkyl oxocarbonium salt, the first kinetic step of the Friedel–Crafts type ketone synthesis, *e.g.*, the interaction of the acyl halide reagent with the Lewis acid catalysts, is eliminated. Similarly, as in the previously reported case of nitration of alkylbenzene with nitronium salts,[3] it was hoped that useful information on the mechanism of the acetylation reaction could be obtained.

By eliminating the formation step of the methyloxocarbonium ion, only a two-step mechanism must be considered, composed of the primary interaction of the methyloxocarbonium ion with the aromatic giving an intermediate transition state, which in the second step loses a proton and gives acetophenone.

$$ArH + CH_3CO^+SbF_6^- \longrightarrow [ArHCOCH_3]^+SbF_6^-$$

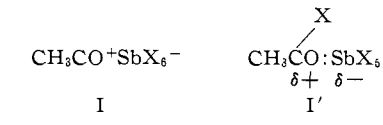
$$[ArHCOCH_3]^+SbF_6^- \longrightarrow ArCOCH_3 + HF + SbF_5$$

If the proton elimination step is of kinetic importance, a kinetic isotope effect must be observed in the acetylation of deuterated or tritiated aromatics. No such observation has been previously reported for Friedel–Crafts acetylations.[4] The general difficulty caused by fast hydrogen exchange in Friedel–Crafts systems containing strong acid catalysts has made the observation of kinetic isotope effects difficult.

Although the acetylation of aromatics with $CH_3CO^+SbF_6^-$ or $CH_3CO^+SbCl_6^-$ represents only a variation of the Perrier modification[5] of the general Friedel–Crafts ketone synthesis, a well-defined oxocarbonium salt reagent is used. Perrier found as early as 1900 that the 1:1 addition compound of acetyl chloride–aluminum chloride (and some other metal halide catalysts) is an effective acetylating agent for aromatics. Later work using modern spectroscopic methods[6] showed that the acetyl chloride–aluminum chloride complex is indeed not a pure methyloxocarbonium salt, but a mixture of the oxocarbonium salt and the polarized covalent complex in which the aluminum is coordinated with the carbonyl oxygen atom. Also the complex is difficult to purify and is not sufficiently stable to handle in kinetic work. These properties must have been the reason that no kinetic investigation using the Perrier method of ketone synthesis has been reported yet in the literature.

## Results and Discussion

**Nature of the Acetylating Agent.**—It was shown by previous infrared spectroscopic investigations that in the crystalline state the methyloxocarbonium complexes are present predominantly in the ionic form I.[2] High resolution nuclear magnetic resonance investigations have at the same time proved that in the solvents investigated (liquid sulfur dioxide and hydrogen fluoride) equilibrium of the ion salts with the donor:-acceptor complexes I′ is established.[2]



I I′

Investigation of the $H^1$, $H^2$, and $C^{13}$ nuclear magnetic resonance in $SO_2$ or HF solution of the $CH_3CO^+SbF_6^-$, $CD_3CO^+SbF_6^-$, and $CH_3C^{13}O^+SbF_6^-$ complexes,[2a,2b] as compared with the starting acetyl halides, indicated that the chemical shifts to less shielding of about 2 p.p.m. in the $H^1$ and $H^2$ resonance, and 45 p.p.m. in the $C^{13}$ resonance, are attributable only to a structure of the complexes, in which the positive charge is at least partly localized on the C atom.

$$[CH_3—C\equiv\equiv O]^+SbF_6^-$$

Neither $SO_2$ nor HF is particularly suitable for carrying out homogeneous, kinetic acetylations of benzene and alkylbenzenes with methyloxocarbonium complexes. Scanning available solvents we found nitromethane and nitrobenzene the most suitable for the kinetic investigations. As it is not possible to extrap-

(1) (a) Part XXI: *J. Am. Chem. Soc.*, **86**, 2198 (1964); (b) correspondence should be addressed to Dow Chemical Company, Eastern Research Laboratory, Framingham, Mass.

(2) (a) G. A. Olah, S. J. Kuhn, W. S. Tolgyesi, and E. B. Baker, *ibid.*, **84**, 2733 (1962); (b) G. A. Olah, W. S. Tolgyesi, S. J. Kuhn, M. E. Moffatt, I. J. Bastien, and E. B. Baker, *ibid.*, **85**, 1328 (1963).

(3) G. A. Olah, S. J. Kuhn, and S. H. Flood, *ibid.*, **83**, 4571 (1961).

(4) In a study of the Friedel–Crafts acetylation and sulfonylation reactions, F. R. Jensen (dissertation, Purdue University, 1955) carried out investigation of kinetic isotope effects in some of these reactions, but these results were not published elsewhere.

(5) G. Perrier, *Ber.*, **33**, 815 (1900); *Bull. soc. chim. France*, **131**, 31, 859 (1903); **131**, 859 (1900).

(6) (a) B. P. Susz and J. J. Wuhrmann, *Helv. Chim. Acta*, **40**, 971 (1957); (b) D. Cook, *Can. J. Chem.*, **37**, 48 (1959).

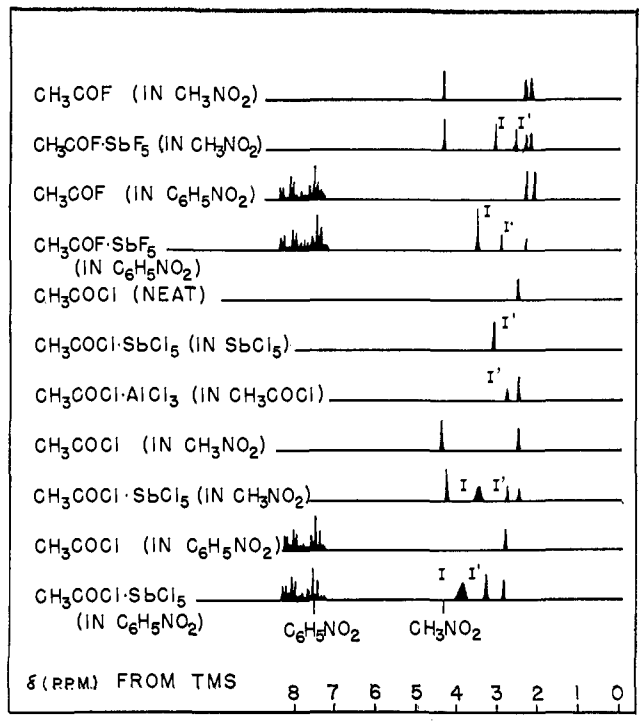



Fig. 1.—$H^1$ magnetic resonance spectra of acetyl halides and acetyl halide–antimony halide complexes in nitromethane and nitrobenzene solutions at 60 Mc.

olate data obtained on carbonium ion complexes in a specific solvent to another solvent system without further consideration, we felt it necessary to investigate the nature of methyloxocarbonium hexafluoro- and hexachloroantimonate in nitromethane and nitrobenzene solution.

The infrared investigations were hindered by solvent interference. High resolution nuclear magnetic proton resonance investigations of the acetyl fluoride–antimony pentafluoride and acetyl chloride–antimony pentachloride systems were, however, carried out both in nitromethane and in nitrobenzene solutions. The spectra summarized in a schematic way in Fig. 1 show that in nitromethane solution equilibration of the ionic complexes with the donor–acceptor complexes takes place and the solutions contain both the methyloxocarbonium ions I and the donor–acceptor complexes I′. In nitrobenzene solution the ionic form alone was detectable in the case of the $CH_3CO^+SbF_6^-$ complex. However, in the case of the chloride complex in nitrobenzene solution both species are present. It should be stressed in connection with these investigations that data obtained on the solution spectra give information only about the spectroscopically detectable species and do not exclude, in those cases where only one of the species was detected, the possibility that a small subspectroscopic concentration of the other form is present in equilibrium.

Although prepared methyloxocarbonium salts were used for the acetylations, their solutions actually contained both oxocarbonium salts and donor–acceptor complexes according to the nuclear magnetic proton resonance investigations.

The nature of the ionic species in the solutions was also investigated by cryoscopic measurements. Although, because of the limited solubility of the methyloxocarbonium salts (less than 5% in nitromethane solution) and the fairly high molecular weights, the accuracy of these measurements was not sufficient to reach final conclusions, the data show negligible, if any, ion separation. Thus in the following treatment it will always be stipulated that the oxocarbonium ion is not present in the "free" form but as part of an ion pair, or as we term it an "oxocarbonium salt." Obviously the ion salt will be substantially solvated in solution, providing a fairly bulky acetylating agent.

**Competitive Acetylation of Benzene and Alkylbenzenes.**—In order to investigate the relative reactivity of benzene and alkylbenzenes with methyloxocarbonium (acetylium) hexafluoroantimonate or hexachloroantimonate, the competitive method of relative rate determination was used. Competitive acetylations of alkylbenzenes were carried out *vs.* benzene with the exception of *o*- and *m*-xylene and mesitylene which were run against toluene (the substantially higher rates in these cases otherwise would cause significant error) and the rates relative to benzene calculated by employing the toluene:benzene relative rate constant. Equimolar quantities of the competing aromatics used in excess were acetylated in nitromethane solution by adding to the well-stirred reaction mixture a solution of $CH_3CO^+SbF_6^-$ or $CH_3CO^+SbCl_6^-$ in nitromethane at 25°. The relative amount of acetophenone and alkylacetophenones and the isomer distribution of the alkylacetophenone isomers were determined by gas–liquid chromatography. Tables I and II summarize the benzene–alkylbenzene data.

TABLE I

COMPETITIVE ACETYLATION OF BENZENE AND ALKYLBENZENES WITH $CH_3CO^+SbF_6^-$ IN NITROMETHANE SOLUTION AT 25°

| Aromatic | $k_{Ar}:k_{benzene}$ | Isomer distribution, % ortho | meta | para |
|---|---|---|---|---|
| Benzene | 1.0 | | | |
| Toluene | 125.0 | 1.4 | 0.9 | 97.7 |
| Ethylbenzene | 116.0 | 0.3 | 0.9 | 98.8 |
| Isopropylbenzene | 90.2 | 0 | 4.5 | 95.5 |
| *t*-Butylbenzene | 74.0 | 0 | 5.7 | 94.3 |
| *o*-Xylene | 1260.0 | 100% 3,4-dimethylacetophenone | | |
| *m*-Xylene | 647.0 | 100% 2,4-dimethylacetophenone | | |
| *p*-Xylene | 23.0 | 100% 2,5-dimethylacetophenone | | |
| Mesitylene | 1100 | 100% 2,4,6-trimethylacetophenone | | |

TABLE II

COMPETITIVE ACETYLATION OF BENZENE AND ALKYLBENZENES WITH $CH_3CO^+SbCl_6^-$ IN NITROMETHANE SOLUTION AT 25°

| Aromatic | $k_{Ar}:k_{benzene}$ | Isomer distribution, % ortho | meta | para |
|---|---|---|---|---|
| Benzene | 1.0 | | | |
| Toluene | 121 | 0.8 | 0.9 | 98.3 |
| Ethylbenzene | 117 | 0.2 | 2.2 | 97.6 |
| *o*-Xylene | 1210 | 100% 3,4-dimethylacetophenone | | |
| *m*-Xylene | 423 | 100% 2,3-dimethylacetophenone | | |
| *p*-Xylene | 21.5 | 100% 2,5-dimethylacetophenone | | |
| Mesitylene | 1020 | 100% 2,4,6-trimethylacetophenone | | |

In comparing the acetylations with $CH_3CO^+SbF_6^-$ and $CH_3CO^+SbCl_6^-$ it is found that in the latter case

there is a somewhat larger steric *ortho* effect, as shown by the amount of *o*-isomers formed and also expressed by the somewhat slower rates of acetylations where the substitution must take place *ortho* to a methyl group (*m*-xylene, *p*-xylene, and mesitylene). However, these effects are less significant than those observed in *t*-butylations.

All the competitive acetylations were found to be first order in aromatics by investigating the variation of concentration of benzene and toluene, respectively, in competitive experiments. Table III shows the result of the variation of concentration in the acetylation of toluene and benzene using $CH_3CO^+SbF_6^-$ and $CH_3CO^+SbCl_6^-$ in nitromethane solution at 25°.

TABLE III

VARIATION OF CONCENTRATION OF BENZENE AND TOLUENE IN COMPETITIVE ACETYLATIONS WITH $CH_3CO^+SbF_6^-$ AND $CH_3CO^+SbCl_6^-$ IN NITROMETHANE SOLUTION AT 25°

| Acetylating agent | Toluene:benzene | | Obsd. rel. rate | $k_{toluene}:k_{benzene}$ |
|---|---|---|---|---|
| $CH_3CO^+SbCl_6^-$ | 1 | 10 | 11.5 | 115 |
| | 1 | 4 | 29 | 116 |
| | 1 | 2 | 60 | 120 |
| | 1 | 1 | 121 | 121 |
| $CH_3CO^+SbF_6^-$ | 1 | 10 | 11.7 | 117 |
| | 1 | 4 | 30 | 120 |
| | 1 | 2 | 62 | 124 |
| | 1 | 1 | 125 | 125 |

In the Friedel–Crafts acetylation it appears possible to modify the steric requirements of the substituting agent and thereby modify the orientation. Baddeley reported[7] that in the absence of added reagents which can unite with the acid chloride–aluminum chloride addition compound, the acylation of naphthalene occurs exclusively in the 1-position. However, in the presence of molecular proportions of added substances, such as nitrobenzene, nitromesitylene, or excess acid chloride, which are presumed to increase the steric requirement by solvation, the extent of acylation in the 2-position increases to as much as 60–70% of the product.

Jensen[8] recently showed that in the acylation of naphthalene factors other than steric are also involved. It was of interest to try to determine whether the solvent used affects the selectivity of acetylations with methyloxocarbonium salts.

Competitive acetylation of benzene and methylbenzenes with methyloxocarbonium salts in various solvents should give an answer to this question since the solutions contain predominantly the solvated ion pairs or salts. However, failure to find suitable solvents other than nitro compounds has so far prohibited a wider scope of investigation.

Using nitrobenzene as solvent in the acetylation of benzene and alkylbenzenes with $CH_3CO^+SbCl_6^-$, the data (Table IV) show no significant differences from those obtained in nitromethane solution. $CH_3CO^+SbF_6^-$ was not sufficiently soluble in nitrobenzene to allow a similar investigation.

The acetylation of benzene and alkylbenzenes with methyloxocarbonium (acetylium) salts in both nitromethane and nitrobenzene solution shows a close resemblance to previous kinetic investigations by Brown, Marino, and Stock of aluminum chloride-catalyzed acetylation with acetyl chloride in ethylene dichloride solution[9] and to our investigations of the $AlCl_3$-catalyzed acetylations with acetyl halides or acetic anhydride in nitromethane solution.[1] That the solvent employed has relatively little effect on the relative rates and isomer distributions was further shown when sulfur dioxide was used at −10° with $CH_3CO^+SbF_6^-$ and $CH_3Co^+SbCl_6^-$ as acetylating agent giving toluene:benzene ratios of 120 and 128, respectively, with isomer distributions practically identical with those obtained in nitromethane or nitrobenzene solutions.

TABLE IV

ACETYLATION OF BENZENE AND ALKYLBENZENES WITH $CH_3CO^+SbCl_6^-$ IN NITROBENZENE SOLUTION AT 25°

| Aromatic | $k_{Ar}:k_{benzene}$ | Isomer distribution, % ortho | meta | para |
|---|---|---|---|---|
| Benzene | 1.0 | | | |
| Toluene | 124 | 0.6 | 1.8 | 97.6 |
| *o*-Xylene | 706 | 100% 3,4-dimethylacetophenone | | |
| *m*-Xylene | 480 | 100% 2,4-dimethylacetophenone | | |
| *p*-Xylene | 19.2 | 100% 2,5-dimethylacetophenone | | |
| Mesitylene | 1173 | 100% 2,4,6-trimethylacetophenone | | |

The similarity of the investigated acetylations with methyloxocarbonium salts in nitromethane and nitrobenzene solutions indicates that in these solvents of comparable dielectric nature the methyloxocarbonium salts are present in a very similar state. If solvents of substantially higher dielectric constant could be used, the solvent effect probably would become more significant.

Competitive acetylation of benzene and halobenzenes with $CH_3CO^+SbF_6^-$ and $CH_3CO^+SbCl_6^-$ in nitromethane solution at 25° gave a very close correspondence (Table V) with the results obtained with acetyl chloride–aluminum chloride in the same solvent.[1] Analysis by gas–liquid chromatography revealed only the *p*-isomers. Thus if even minor amounts of the *m*- and *o*-haloacetophenones could not be excluded, this amount must be less than 0.5%.

TABLE V

ACETYLATION OF BENZENE AND HALOBENZENES WITH $CH_3CO^+SbF_6^-$ AND $CH_3CO^+SbCl_6^-$ IN NITROMETHANE SOLUTION AT 25°

| Aromatic | $CH_3CO^+SbF_6^-$ $k_{Ar}:k_{benzene}$ | $CH_3CO^+SbCl_6^-$ $k_{Ar}:k_{benzene}$ |
|---|---|---|
| Benzene | 1.0 | 1.0 |
| Fluoro- | 0.51 | 0.44 |
| Chloro- | .016 | .02 |
| Bromo- | .01 | .01 |

The solvent effect, although probably more important if solvents with substantially varying structure and dielectric constants were used, was found negligible in the case of nitrobenzene, as shown in Table VI, for the acetylation of benzene and halobenzenes with $CH_3CO^+SbCl_6^-$ ($CH_3CO^+SbF_6^-$ is not sufficiently soluble in nitrobenzene to allow investigations).

(7) G. Baddeley, *J. Chem. Soc.*, S99 (1949).

(8) F. R. Jensen, IXth Reaction Mechanism Conference, Brookhaven, N. Y., Sept., 1962.

(9) H. C. Brown, G. Marino, and L. M. Stock, *J. Am. Chem. Soc.*, **81**, 3310 (1959); H. C. Brown and G. Marino, *ibid.*, **81**, 5611 (1959).

TABLE VI

COMPETITIVE ACETYLATION OF BENZENE AND HALOBENZENES WITH $CH_3CO^+SbCl_6^-$ IN NITROBENZENE SOLUTION AT 25°

| Aromatic | $k_{halobenzene}:k_{benzene}$ |
|---|---|
| Benzene | 1.0 |
| Fluoro- | 0.42 |
| Chloro- | .01 |
| Bromo- | .007 |

That the competitive method of rate determination could be used in the case of acetylation of benzene and halobenzenes with methyloxocarbonium salts was shown in experiments in which the concentration of benzene and halobenzenes was varied. The relative reactivities remained constant when corrected for the molar ratios of the aromatics, thus indicating first-order dependence of the acetylations on the aromatic substrates. Table VII shows the results of concentration variation of benzene and fluorobenzene in acetylations with $CH_3CO^+SbCl_6^-$.

TABLE VII

CONCENTRATION VARIATION OF BENZENE AND FLUOROBENZENE IN COMPETITIVE ACETYLATIONS WITH $CH_3CO^+SbCl_6^-$ IN NITROMETHANE SOLUTION AT 25°

| Fluorobenzene: | benzene | Obsd. rel. rate | $k_F:k_B$ |
|---|---|---|---|
| 4 | 1 | 1.84 | 0.46 |
| 2 | 1 | 0.92 | .46 |
| 1 | 1 | .44 | .44 |
| 1 | 2 | .21 | .42 |
| 1 | 4 | .11 | .44 |

The acetylation of halobenzenes with methyloxocarbonium salts shows high positional selectivity, giving the *p*-isomers nearly exclusively. The absence of *m*-isomers is in accord with the results from other electrophilic substitutions in the halobenzenes[10] where the amount of *m*-substitution was also negligible. The absence of *o*-isomers can best be explained by the inductive effect of the halogen substituents and the bulky nature of the attacking reagent.

Fluorobenzene showed in our experiments only modestly decreased reactivity, as compared with benzene, whereas chloro-, bromo-, and iodobenzene showed substantially decreased reactivities and thus high substrate selectivity.

In the acetylation of halobenzenes, the relatively high reactivity of fluorobenzene can be explained by conjugative stabilization of the $\sigma$-complex in the *p*-position. Owing to the opposing negative inductive and positive conjugative effects of the halogens, the fluorobenzene molecule shows a relatively high electron density in the region of the *p*-position (the inductive effect diminishes with the distance, whereas the conjugative effect stays unchanged). It should be mentioned that according to our observation with HF + $SbF_5$ protonation, fluorobenzene is protonated nearly exclusively in the *p*-position. Chloro- and bromobenzene show an increasingly diminishing ability to compensate, even in the *p*-position, for the inductive electron-withdrawing effect of the halogen. At the same time the $-I > +T$ effect of the halogens causes an over-all decrease of electron density.

**Kinetic Isotope Effect.**—In order to determine whether there is a kinetic isotope effect in the acetylation of deuterated aromatics, as compared with the protium compounds, the previously described competitive method[3] was used.

Competitive acetylation of benzene and benzene-$d_6$ was carried out with $CH_3CO^+SbF_6^-$ and $CH_3CO^+SbCl_6^-$ in nitromethane solution at 25°. The reaction mixtures were analyzed by mass spectroscopy to determine the acetophenone:acetophenone-$d_5$ ratio. The data show that some, but not significant, hydrogen–deuterium exchange takes place in the aromatic ring or the methyl group of the acetophenones. The comparison of the relative amounts of acetophenone and acetophenone-$d_5$ formed in the competitive acetylation gave the kinetic isotope effect

| | $CH_3CO^+SbCl_6^-$ | $CH_3CO^+SbF_6^-$ |
|---|---|---|
| $k_H:k_D$ = | 2.15 | 2.22 |

The same kinetic isotope effect was also obtained (with good agreement of results) from the competitive acetylation of toluene–benzene as compared with toluene–benzene-$d_6$ (Table VIII). In this case the relative amounts of acetophenone and methylacetophenone could be determined by gas–liquid chromatography.

TABLE VIII

KINETIC ISOTOPE EFFECT IN ACETYLATION OF BENZENE-$d_6$, TOLUENE-$d_5$, AND MESITYLENE-$d_3$

$CH_3CO^+SbCl_6^-$

| | | | |
|---|---|---|---|
| $k_{toluene}:k_{benzene}$ | = 121 | Benzene $k_H:k_D$ | = 2.27 |
| $k_{toluene}:k_{benzene\text{-}d_6}$ | = 275 | | |

$CH_3CO^+SbF_6^-$

| | | | |
|---|---|---|---|
| $k_{toluene}:k_{benzene}$ | = 125 | Benzene $k_H:k_D$ | = 2.25 |
| $k_{toluene}:k_{benzene\text{-}d_6}$ | = 281 | Toluene $k_H:k_D$ | = 3.25 |
| $k_{toluene\text{-}d_5}:k_{benzene}$ | = 38.6 | | |
| $k_{mesitylene}:k_{benzene}$ | = 11 | Mesitylene $k_H:k_D$ | = 1.90 |
| $k_{mesitylene\text{-}d_3}:k_{benzene}$ | = 58 | | |

The observed kinetic isotope effect is greater for ring-deuterated toluene than benzene. This observation was substantiated by competitive acetylation of toluene-$d_8$ and benzene-$d_6$ with $CH_3CO^+SbF_6$.

$$k_{toluene\text{-}d_8}:k_{benzene\text{-}d_6} = 81$$

$$k_{D\ toluene}:k_{D\ benzene} = 1.54$$

$$k_{toluene}:k_{benzene} = 125$$

Comparison of this value with the ratio of the isotope effects observed in previous experiments gives good agreement.

$$\text{toluene } k_H:k_D = 3.25$$

$$\text{benzene } k_H:k_D = 2.25 \quad T/B = 1.44$$

The larger isotope effect in the case of toluene is probably a consequence of the increased conjugative stabilization of the $\sigma$-complex type transition state by the *p*-methyl group.

In the case of the acetylation of mesitylene the steric hindrance by a pair of flanking *o*-methyl groups may interfere with the conjugative stabilization of the benzenonium ion. Therefore the effect may be a combination of electronic and steric effects.

The primary kinetic isotope effects indicate that the proton elimination in the acetylation of benzene, toluene, and mesitylene is at least partially rate determining. The data obtained indicate that the isotope effect

(10) G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Am. Chem. Soc.*, **83**, 4581 (1961); **84**, 1695 (1962).

depends not only on the isotope used but also on the structure of the aromatic substrate. The Friedel–Crafts acetylation shows significant differences from the previously investigated alkylations, halogenations, and nitrations, all involving only small secondary isotope effects. The proton elimination being kinetically significant in Friedel–Crafts acetylation could at least partially account for the observed high selectivities and therefore merits further consideration.

The high $k_T:k_B$ rates in Friedel–Crafts acetylations seem to indicate that in this case both the substrate and positional selectivity is determined in the same step, namely, formation of a $\sigma$-complex type transition state, as suggested by Pfeiffer and Wizinger[11] and particularly by the fundamental work of Brown and his co-workers.

If the transition state in the rate-determining step is indeed of $\sigma$-complex nature, then it is to be expected that the proton elimination step should be at least partially rate determining and subsequently a primary kinetic isotope effect should be observed. The data have shown that this is indeed the case when comparing the rates of acetylation of benzene and benzene-$d_6$.

If we continue this argument we should also conclude that isotopic substitution of the methyl group in toluene should affect the conjugative stabilization of the $\sigma$-complexes (the conjugative effect of $CD_3$ being smaller than that of $CH_3$) and thus a secondary kinetic isotope effect should also be observable. To prove this suggestion, we extended our investigations to the acetylation of $CD_3C_6D_5$, $CD_3C_6H_5$, and $CH_3C_6D_5$ and compared their reactivities with that of toluene in competitive acetylations with benzene. The data are summarized in Table IX.

TABLE IX

SECONDARY KINETIC ISOTOPE EFFECT IN ACETYLATION OF TOLUENE AND RING-DEUTERATED TOLUENE WITH $CH_3CO^+SbF_6^-$ IN NITROMETHANE SOLUTION AT 25° AS A CONSEQUENCE OF DEUTERATION OF THE METHYL GROUP

| | | |
|---|---|---|
| $k_{toluene}:k_{benzene}$ | = 125 | $k_{\alpha H}:k_{\alpha D}$ = 1.06 |
| $k_{toluene\text{-}\alpha,\alpha,\alpha\text{-}d_3}:k_{benzene}$ | = 118 | |
| $k_{toluene\text{-}d_5}:k_{benzene}$ | = 38.6 | $k_{\alpha H}:k_{\alpha D}$ = 1.04 |
| $k_{toluene\text{-}d_8}:k_{benzene}$ | = 37 | |

As may be seen from the data of Table IX, deuteration of the methyl group causes indeed a small secondary isotope effect (not more than 6%). Thus it was possible to demonstrate that an electrophilic aromatic substitution involving a $\sigma$-complex type rate-determining transition state shows both primary and secondary kinetic isotope effects.

## Conclusions

The close similarity of the results of the acetylations under varying conditions, *e.g.*, with the use of prepared acetylium salts with varying anions or the use of acetyl halides or acetic anhydride with a variety of Lewis acid catalysts, can be explained only if we suggest a common active acetylating agent in all these systems. Whereas in the discussion of the Friedel–Crafts acetylations it has previously repeatedly been suggested that the common acylating agent must be the acylium (oxocarbonium) ion, we believe that our results do not support this suggestion. This opinion concurs with that of Brown, Marino, and Stock,[9] who stated that their kinetic evidence does not distinguish between possible mechanisms involving the oxonium structure, separated acylium ions, or acylium ion pairs. There is no evidence pointing to the existence of free oxocarbonium ions in any of our investigated acylation systems (although it is not possible to exclude a small, subspectroscopic concentration of the ion present in an equilibrium). It seems to be that the acetylating system in the investigated solvents (nitromethane, nitrobenzene, sulfur dioxide) contains only highly solvated and associated ion pairs (or clusters of ion pairs) in equilibrium with the donor–acceptor complexes. The exceedingly small amounts of *o*-isomers formed in the acetylation of toluene, ethylbenzene, and xylenes clearly indicate a substantially bulkier acetylating agent than that represented by the $CH_3CO^+$ ion. The observed very substantial steric hindrance practically eliminates in our view the free methyloxocarbonium ion as the effective acetylating agent. Whether the ion pair $CH_3CO^+SbX_6^-$, in a substantially solvated form (its solubility in polar solvents obviously is due to a high degree of solvation), or the solvated donor–acceptor complex is the effective acetylating agent becomes then fairly immaterial. Both could effect the same high selectivity substitutions and both involve substantial steric hindrance.

The argument of exchange of radiochlorine in $AlCl_3$ in acetylation of aromatics by acetyl chloride as put forward by Fairbrother[12] is not convincing. As Oulevey and Susz have recently pointed out,[13] both the ion and the donor–acceptor complex can account equally for the exchange results. Conductivity measurements also are not decisive as the donor–acceptor complex could easily account for substantial conductivity in polar solvent systems, similar to the solvated ion pair. Difficulty in keeping any Friedel–Crafts system absolutely anhydrous further adds to the difficulty in deciding what really is the conductive species in any of the systems.

In conclusion we should like to stress the following points: (a) In our opinion no generalization of the nature of all Friedel–Crafts acylations is possible from the behavior of certain specific investigated systems. Each system must be evaluated on its own and correlations, if any, should be considered only with proper restriction.

(b) There is sufficient evidence now to show that oxocarbonium (acylium) ions are present in the investigated acetylation system as solvated ion pairs and not as separated, free ions. The weaker electrophilic nature of oxocarbonium ions as compared with alkylcarbonium ions (Brown[14] gave the sequence based on their reactivity as $CH_3CH_2^+ > (CH_3)_2CH^+ > (CH_3)_3C^+ > RCO^+$) is at least partly a consequence of the fact that in the oxocarbonium ions the positive charge is only partially localized on the carbonyl carbon, being more located on the oxygen, in accordance with a triple bonded structure.

(c) The effective acetylating agent can be either the ion-pair itself or equally well the polarized donor–acceptor complex. Ring acetylation therefore can be considered as a nucleophilic displacement of the acetyl halide–Lewis acid complex by the aromatics. This mechanism is in accordance with the observed kinetics

(11) P. Pfeiffer and R. Wizinger, *Ann.*, **461**, 132 (1928).

(12) F. Fairbrother, *J. Chem. Soc.*, 503 (1937).

(13) G. Oulevey and B. P. Susz, *Helv. Chim. Acta*, **44**, 1425 (1961).

(14) H. C. Brown, *et al.*, *Ind. Eng. Chem.*, **45**, 1462 (1953).

of Brown,[8,9] showing first-order dependence in acetylating agent, catalyst, and substrate.

This mechanism in our opinion predominates over an ionic mechanism involving direct electrophilic attack of the free $CH_3CO^+$ ion, even if the latter cannot be entirely excluded, at least as participating in an equilibrium. The substantial steric hindrance shown in acetylations *ortho* to alkyl groups is in accordance with the suggested mechanism. Thus it is possible that both mechanisms work concurrently, but the displacement mechanism is predominant as long as the reactions are not carried out in solvents of very high dielectric constant. Thus our experimental data have allowed us to reach conclusions similar to those suggested by Tedder[15] which were based, however, on no experimental support concerning acetylium salts.

(d) As the proton elimination step in the investigated acetylations was found to be at least partially rate determining (as shown by the observed primary kinetic isotope effect of the acetylation of deuterated benzene, toluene, and mesitylene), the high selectivity acetylations could, to a certain degree, be a consequence of the rate of proton elimination.

(e) We feel it worthwhile to mention correlations between the structure and, to a certain degree, reactivity of $CH_3CO^+$ and $NO^+$ ion salts. The availability of stable nitrosonium salts, *e.g.*, $NO^+BF_4^-$, allows us to investigate the electrophilic nitrosation of aromatics under conditions comparable to those employed for acetylation. Nitrosonium salts show similarities to acylium salts in that they also involve a linear triple bonded structure with the charge only partially localized on nitrogen and to a larger degree on the oxygen atom. A difference between the acetylation and nitrosation reactions is that the primarily formed nitrosoaromatic compounds are generally decomposed immediately by excess $NO^+$, if not stabilized by strong conjugation, because the polar nitroso group is attacked preferentially by excess nitrosonium salt.[16] Electrophilic nitrosation of 2,6-dibromophenol and 2,6-dibromophenol-4*d* have revealed a significant primary kinetic hydrogen isotope effect[17] ($k_H:k_D = 3.6$) in good agreement with the isotope effect observed in acetylation. It should be made clear that in our views the methyloxocarbonium ion structurally and in its reactivity resembles the nitrosonium ($NO^+$) ion but not the nitronium $(NO_2)^+$ ion. In the latter the charge is localized on the nitrogen atom, thus producing a very powerful electrophile with respect to aromatic nitration, whereas, as suggested above, $CH_3CO^+$ and $NO^+$ are considered only as weak electrophiles in acetylation and nitrosation reactions, respectively.

(f) Finally, as to the nature of the transition states in the interaction with the aromatic substrates, we suggest that $\pi$-complex formation with the weakly electrophilic reagent is reversible, followed by a higher energy level transition state of $\sigma$-complex nature, which determines both substrate and positional selectivity. Thus the mechanism of acetylation with prepared methyloxocarbonium salts shows substantial difference from that of nitration with nitronium salts or alkylations with strongly electrophilic alkylating agents.

(15) J. M. Tedder, *Chem. Ind.* (London), 630 (1954).

(16) These investigations will be reported in more detail in a forthcoming publication.

(17) K. M. Ibne-Rase, *J. Am. Chem. Soc.*, **84**, 4962 (1962).

## Experimental

The benzene, alkylbenzenes, halobenzenes, acetyl halides, nitromethane, and antimony pentahalides used were of comparable purity to those used in previous investigations of the series.

Benzene-$d_6$ was purchased from Ciba Ltd., Basel, Switzerland; toluene-$d_8$, toluene-$d_5$, and toluene-$\alpha,\alpha,\alpha$-$d_3$ from Merck Sharp and Dohme Ltd., Montreal, Can.

Mesitylene-$d_3$ was prepared by ring deuteration of mesitylene with $D_2O{\cdot}BF_3$. The purity of all deuterated compounds, based on gas–liquid chromatographic and nuclear magnetic proton and deuteron resonance investigations (showing the D content and H impurities), was better than 98%.

**Preparation of Methyloxocarbonium Hexachloro- and Hexafluoroantimonate.**—Acetyl halide (fluoride or chloride, 0.2 mole) was dissolved in 100 g. of Freon 113 (1,1,2-trifluorotrichloroethane) and placed in a two-necked reaction flask equipped with a dropping funnel and drying tube. The solution was cooled to approximately 0° and 0.2 mole of $SbCl_5$ or $SbF_5$ dissolved in 100 g. of Freon 113 was added within about 20 min., while the temperature of the magnetically stirred reaction mixture was kept around 0° with a cooling bath. The oxocarbonium salts precipitated and were filtered, washed twice with 25 ml. of Freon 113, transferred to a round-bottom flask, and pumped dry. All operations must be carried out with care to exclude atmospheric moisture, preferentially in a drybox.

**Competitive Acylations with Methyloxocarbonium Hexahaloantimonates in Nitromethane Solution.**—Benzene (toluene), 0.25 mole, and 0.25 mole of alkylbenzene were dissolved in 50 g. of nitromethane and 0.05 mole of methyloxocarbonium hexahaloantimonate in 30 g. of nitromethane was added to the vigorously stirred reaction mixture while the reaction temperature was kept at 25° by a constant temperature bath. After the addition was completed the reaction mixture was stirred for a further 10 min., then washed twice with 150 ml. of water, dried over $Na_2SO_4$, and analyzed by gas–liquid chromatography.

**Competitive Acylations with $CH_3CO^+SbCl_6^-$ in Nitrobenzene Solution.**—Benzene (toluene), 0.25 mole, and 0.25 mole of alkylbenzene were dissolved in 50 g. of nitrobenzene and a solution of 0.05 mole of $CH_3CO^+SbCl_6^-$ in 60 g. of nitrobenzene was added to the vigorously stirred aromatic solution, while the reaction temperature was kept at 25° by a constant temperature bath. The reaction mixture was stirred for an additional 10 min., then washed twice with 150 ml. of water, dried over $Na_2SO_4$, and analyzed by gas–liquid chromatography.

**Competitive $AlCl_3$-Catalyzed Acetylations of Benzene and Halobenzenes with Acetyl Chloride in Nitromethane solution.**—Benzene (0.25 mole), 0.25 mole of halobenzene, and 0.05 mole of $AlCl_3$ were dissolved in 50 g. of nitromethane and 0.05 mole of acetyl chloride in 30 g. of nitromethane was added dropwise to the well-stirred reaction mixture. After the addition of acetyl chloride, the reaction mixture was stirred for another 15 min. It was then washed twice with 150 ml. of water, dried over $Na_2SO_4$, and analyzed by gas–liquid chromatography.

Relative rates for chloro- and bromobenzene were also determined from competition of chloro- and bromobenzene with fluorobenzene and that of chlorobenzene with bromobenzene.

**Competitive Acetylation of Benzene and Halobenzenes with $CH_3CO^+SbF_6^-$ and $CH_3CO^+SbCl_6^-$ in Nitromethane Solution.**—Benzene (0.25 mole) and 0.25 mole of halobenzene were dissolved in 50 g. of nitromethane and 0.05 mole of $CH_3CO^+SbCl_6^-$ or $CH_3CO^+SbF_6^-$ in 30 g. of nitromethane was added to the vigorously stirred aromatic solution, while the temperature was kept at 25° by a constant temperature bath. After the addition was completed the reaction mixture was stirred for 10 min., then washed twice with 150 ml. of water, dried over $Na_2SO_4$, and analyzed by gas-liquid chromatography. Relative rates for chloro- and bromobenzene were also obtained from competitive acetylation of chlorobenzene and bromobenzene with fluorobenzene, as well as chlorobenzene with bromobenzene.

**Competitive Acetylation of Benzene and Halobenzenes with $CH_3CO^+SbCl_6^-$ in Nitrobenzene Solution.**—Benzene (0.25 mole) and 0.25 mole of halobenzene were dissolved in 50 g. of nitrobenzene and 0.05 mole of $CH_3CO^+SbCl_6^-$ in 60 g. of nitrobenzene was added to the well-stirred aromatic solution while the reaction temperature was kept as 25°. After the addition was completed the reaction mixture was stirred for 10 min., then washed twice with 150 ml. of water, dried over $Na_2SO_4$, and analyzed by gas–liquid chromatography.

Relative rates for chloro- and bromobenzene were also obtained from competition of chloro- and bromobenzene with fluorobenzene and that of chlorobenzene with bromobenzene.

**Determination of Isotope Effect.**—(a) Benzene-$d_6$ (0.025 mole) and toluene (0.025 mole) were dissolved in 5 g. of nitromethane and acetylated with 0.01 mole of $CH_3CO^+SbX_6^-$ as previously described. The products were analyzed by gas–liquid chromatography. (b) Benzene-$d_6$ (0.025 mole) and benzene (0.025 mole) were dissolved in 5 g. of nitromethane and acetylated with 0.01 mole of $CH_3CO^+SbX_6^-$ as previously described. The products were analyzed by mass spectroscopy. (c) Benzene (0.025 mole) and toluene-$d_8$ (0.025 mole) were dissolved in 5 g. of nitromethane and acetylated with 0.01 mole of $CH_3CO^+SbF_6^-$ as previously. The products were analyzed by gas–liquid chromatography. (d) Benzene-$d_6$ (0.025 mole) and toluene-$d_8$ (0.025 mole) were dissolved in 5 g. of nitromethane and acetylated with 0.01 mole of $CH_3CO^+SbF_6^-$ as previously. The products were analyzed by gas–liquid chromatography. (e) Benzene (0.025 mole) and toluene-$\alpha,\alpha,\alpha$-$d_3$ (0.025 mole) were dissolved in 5 g. of nitromethane and acetylated with 0.01 mole of $CH_3CO^+SbF_6^-$ as described in (a). The products were analyzed by gas–liquid chromatography. (f) Benzene (0.025 mole) and toluene-$d_5$, (0.025 mole) were acetylated as in (e). (g) Benzene (0.025 mole) and mesitylene-$d_3$, (0.025 mole) were acetylated as in (e).

**Analytical Procedure.**—Gas–liquid chromatography was carried out on a Perkin–Elmer Model 154-C vapor fractometer, using a thermistor detector, equipped with a Perkin–Elmer Model 194 electronic printing integrator. A 4-m. × 0.25 in. stainless steel column packed with polypropylene glycol (UCON LB 550-X) supported on diatomaceous earth was used. The column temperature was 180° for all of the determinations; 25 ml. of hydrogen per minute was used for carrier gas.

Relative response was determined by making up known solutions of acetophenone, alkylacetophenones, and haloacetophenones in excess benzene in the ratios approximating those occurring in the reaction mixtures and determining the response per mole relative to acetophenone as analyzed by gas–liquid chromatography.

Characteristic retention times of acetophenone, alkylacetophenones, and haloacetophenones are given in Table X.

TABLE X

RETENTION TIME (MINUTES)

| | | | |
|---|---|---|---|
| Acetophenone | 13 | 3,4-Dimethylacetophenone | 36.8 |
| *o*-Methylacetophenone | 16.4 | 2,4,6-Trimethylacetophenone | 30.4 |
| *m*-Methylacetophenone | 20.0 | *p*-Fluoroacetophenone | 12 |
| *p*-Methylacetophenone | 21.6 | *p*-Chloroacetophenone | 29 |
| 2,5-Dimethylacetophenone | 23.6 | *p*-Bromoacetophenone | 34 |
| 2,4-Dimethylacetophenone | 25.6 | | |

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# Tautomeric Equilibria. VII. Substituent Effects in Dimethylaminoazobenzenes[1]

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The effect of substitution on the tautomeric equilibrium in substituted dimethylaminoazobenzenes has been investigated. The tautomeric equilibrium constants for seven 4′-substituted-4-dimethylaminoazobenzenes have been obtained and have been found to follow the Hammett equation. The spectroscopic behavior of the first conjugate acid of dimethylaminoazobenzene and the comparability of $H_0$ and $H_+$ acidity scales were also investigated.

The structures of the first conjugate acids of 4-dimethylaminoazobenzenes have been under much discussion. A number of workers have reached widely varying conclusions on this problem.[2]

More recently it has become clear that there is a tautomeric equilibrium between ammonium (I) and azonium (II) forms.[3]

With the exception of some semiquantitative work by the method of Sawicki,[3] the only careful attempt at determination of tautomeric equilibrium constants has been performed in this laboratory,[3i,j] and only on the parent compound. We have now re-examined and improved this work, and extended it to a series of substituted derivatives.

## Experimental

**Dimethylaminoazobenzenes (4-DAB).**—4′-Substituted-4-DAB were prepared by diazotization of the appropriate *p*-substituted aniline and coupling of the resulting diazonium salt with dimethylaniline in an acetate buffer.[4] The products were recrystallized from ethanol to a constant melting point, in all cases equal to or greater than values reported in the literature (*cf.* Table I). Elemental analysis[5] on these compounds checked very closely with theoretical values.

**Trimethylammonioazobenzene Chlorides. N,N,N-Trimethyl-*p*-phenylazoanilinium Chloride (4-TAB).**—The 4′-substituted dimethylaminoazobenzene (3 g.) was dissolved in *ca.* 30 ml. of methyl iodide and heated under reflux for 2 to 4 days. The resulting precipitate of trimethylammonioazobenzene iodide was collected, washed with anhydrous ether, and dried. The precipitate was then dissolved in 1:1 ethanol–water and passed through a 10-g. column of Dowex 2-X8 ion-exchange resin. The solvent was then removed under aspirator vacuum and the residue dissolved in absolute ethanol and precipitated by addition of anhydrous ether. The dissolving in ethanol then reprecipitating with ether steps were repeated a number of times. The product was then dissolved in 95% ethanol and passed once more through a 10-g. column of the same ion exchange resin. After removal of solvent, the reprecipitation was repeated once more. Finally the product was collected and dried *in vacuo*. The yields were generally in the range of 60%. The purity of the compounds was checked by elemental analysis (*cf.* Table I).

(1) Support of this work by a research grant from the American Cancer Society is gratefully acknowledged.

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(3) (a) G. M. Badger, R. G. Buttery, and G. E. Lewis, *J. Chem. Soc.*, 1888 (1954); (b) E. Sawicki and F. E. Ray, *J. Org. Chem.*, **19**, 1686 (1954); (c) E. Sawicki, *ibid.*, **21**, 605 (1956); (d) *ibid.*, **22**, 365, 621, 743 (1957); (e) G. Cilento, *Cancer Res.*, **20**, 120 (1960); (f) A. Zenhäusern and H. Zollinger, *Helv. Chim. Acta*, **45**, 1882, 1890 (1962); (g) F. Gerson and E. Heilbronner, *ibid.*, **45**, 42 (1962); (h) I. Granacher, H. Suhr, A. Zenhäusern, and H. Zollinger, *ibid.*, **44**, 313 (1961); (i) H. H. Jaffé and S. J. Yeh, *J. Org. Chem.*, **22**, 1281 (1957); (j) S. J. Yeh and H. H. Jaffé, *J. Am. Chem. Soc.*, **81**, 3283 (1959); (k) G. E. Lewis, *Tetrahedron*, **10**, 129 (1960).

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(5) Elemental analyses were performed by A. Bernhardt, Mülheim (Ruhr), Germany.