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# SYMPOSIUM ON AROMATIC ELECTROPHILIC SUBSTITUTION AT VANDERBILT UNIVERSITY, AUG. 27, 1964, IN HONOR OF SIR CHRISTOPHER K. INGOLD

The year, 1964, has been a most propitious one for the Department of Chemistry at Vanderbilt University. It marked the move of the faculty in chemistry to a new and more efficient building to carry out its research and teaching. Relative to the subject of aromatic substitution, the year also marked a curious combination of events which were related to each other and to the Department. Exactly one hundred years ago Kekulé was formulating his rules for determining orientation in the benzene ring. Empirical rules they were, but they provided the beginning of the growth of theory which would lead to understanding. Exactly one hundred years later, in 1964, the Department was fortunate in obtaining Sir Christopher Ingold as a visiting professor through the kind auspices of the National Science Foundation. Of his many accomplishments through the years, one of the most outstanding has been his delineation of the role of group influences in determining orientation in aromatic compounds. The role is complex, involving a dichotomy of influence including induction, resonance, and changes of these effects in the transition state. Of equal importance has been his visualization of the transition state, named appropriately the sigma complex. These two accomplishments stand as the backbone of aromatic substitution theory. During the nineteen fifties, his theories slowly diffused through the scientific world. And beginning approximately in the late nineteen fifties, publications based on his theories began to appear in greater numbers and soon mushroomed to a large total. The result was the fleshing out of the backbone laid down by Professor Ingold. There was good reason for the acceleration of publications. New tools were at hand to test more rigorously the series of events that led to aromatic substitution-gas chromatography, nuclear magnetic resonance, isotopic labeling among the most important of these tools.

To repeat, the year was most propitious: one hundred years had passed since the thoughts of Kekulé had been recorded; Professor Ingold was at Vanderbilt University; innumerable contributions to theory had been made since Professor Ingold's initial teachings. It was almost inevitable that these events would culminate in a symposium in honor of Professor Ingold. Within the next few pages of this journal are samplings of the talks of the symposium given at Vanderbilt University. They are only samplings as the more topical subjects necessarily were published in more specialized journals. But those of the summary type are to be found in this issue. It is regrettable that the comments of Professor Ingold on each paper cannot be included in this issue, but it can be remarked that they were of the nature that characterizes Professor Ingold: gracious, thought-provoking and stimulating.

Appreciation should be expressed to two persons who guided the course of the symposium, Professor Ingold and Professor C. C. Price (University of Pennsylvania), the latter acting as the Moderator of the discussions.

# KINETIC ISOTOPE EFFECTS AND THEIR ROLE IN THE STUDY OF THE MECHANISM OF ELECTROPHILIC AROMATIC SUBSTITUTIONS

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The "hydrogen isotope effects" are one of the most important of the tools which physical-organic chemists employ in the elucidation of the mechanisms of chemical reactions. The theory of these effects is well advanced, but still offers many unsolved problems.

After the discovery of heavy hydrogen by Urey and coworkers [1],** Cremer and Polanyi [2] and Eyring and Sherman [3] predicted that hydrogen- and deuterium-containing compounds should react at different rates. This difference in the reaction rates of compounds in which deuterium (or tritium) has been substituted for hydrogen is known as the hydrogen isotope effect. It is generally found that bonds to deuterium or tritium have a lower reactivity as compared to the correspond-

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**Numbers in brackets refer to Literature Cited.

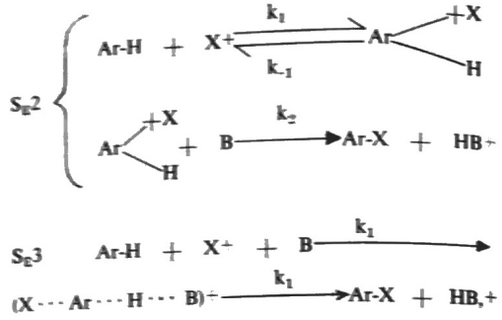
ing bonds to hydrogen. The major contribution to this observation is the difference in free energy of the bonds which arises from the difference in their zero-point energies in the order $E_T$, lower than $E_D$, lower than $E_H$. Since the deuterium or tritium compound has a lower zero-point energy, it will be more stable than the hydrogen analog. The potential energy curves of hydrogen, deuterium and tritium compounds are essentially the same. If one assumes that the bond undergoing reaction is relatively weak in the transition state compared to the one in the reactant, the isotope effect of the zero-point energy becomes apparent. In general, the difference ($\Delta E_o$) in the dissociation of a bonded hydrogen atom and the corresponding bonded deuterium atom is on the order of 1.2 - 1.5 Kcal/mole. Isotope effects are temperature dependent. Maximum values for $k_H/k_D$ range from 8.3 (at 0°) to 6.9 (at 25°) to 4.7 (at 100°) to 2.1 (at 500°) [4].

In general, when a bond to hydrogen or deuterium is broken in the rate-controlling step of a reaction, the rate constant, $k_H$, for the reaction of the hydrogen compound exceeds the constant, $k_D$, for the same reaction of the corresponding deuterium compound.

The question of kinetic hydrogen isotope effects in electrophilic aromatic substitutions has been well reviewed by a number of investigators in the field [5-9]. Therefore it is not intended to give a comprehensive review of the topic and the reader is referred to the given leading references for general background information. The present discussion will center on the role of kinetic hydrogen isotope effects on the mechanism of electrophilic aromatic substitutions, and the author has taken the liberty to include in the discussion some of his own results and views, without wanting to make the impression that he considers these the most relevant to the topic. It is hoped that subsequent discussion at the symposium will add expression of different views and help in clarification of certain aspects of the topic and to point to new future avenues of research.

Hydrogen kinetic isotope effects have a fundamental importance in the elucidation of the reaction mechanism of electrophilic aromatic substitutions. It was Melander [10] who in 1950 reported the first investigation of kinetic isotope effects in electrophilic aromatic substitutions. He showed that a series of tritiated benzene derivatives were nitrated and brominated at the same rate as the corresponding ordinary protium compounds. This was a most elegant experimental support for the $S_E2$- or two stage mechanism suggested by Lapworth [11] and by Professor Ingold [12] and his collaborators ($k_{-1}$ being negligible). The one-stage $S_E2$ or $S_E3$ mechanism should, of course, give rise to an appreciable isotope effect since the carbon-hydrogen is ruptured in the concerted process.

The same should apply to the second stage of the $S_E2$ mechanism. The first step of the $S_E2$ mechanism, however, could not be expected to give more than some secondary isotope effect, because the carbon-hydrogen




bond is somewhat changed but not ruptured. Provided that a substitution proceed by a two stage mechanism and the first step is rate determining, the overall reaction should show only such a weak isotope effect.

The absence of a significant kinetic hydrogen isotope effect in aromatic substitution is usually taken as an indication that the proton removal is not rate determining [5-9]. This interpretation, however, has been questioned by Hammond [13], Westheimer [14] and Wiberg [15].

As pointed out by Hammond, the absence of an isotope effect shows that the zero point energies associated with the bending and stretching of the C-H bond are not changed significantly in going from the reactants to the transition state. Such an observation is usually transformed into the categorical conclusion that the bond to hydrogen is not being broken in the rate-controlling step of the reaction. This is not necessarily a proper conclusion in all cases. In a highly exothermic reaction, such as the removal of a proton from the benzenonium ion type intermediate, the isotope

effect might be undetectably small merely because only a slight weakening of the C-H bond would bring the intermediate to the transition state on either side.

According to Wiberg's views [15], based on arguments given by Westheimer [14], the isotope effect for the proton removal from the aromatic Ar-H by a base B will be small (about 1.4 for $k_H/k_D$ and about 1.7 for $k_H/k_T$ due to the mass factor) if in the transition state Ar...H... B the force constant of the Ar - H bond is considerably greater than that of the H - B bond (or vice versa). If in an electrophilic aromatic substitution the proton removing step has a low activation energy and involves only a small change in the C-H bond force to reach the transition state and the bond between the base and hydrogen in the transition state is weak, for such a reaction even if the proton removing step were rate determining one might find an isotope effect close to $k_H/k_D = 1.4$ and $k_H/k_T = 1.7$. This condition may prevail particularly in electrophilic aromatic substitutions with strong electrophiles like nitration, halogena-



tion, alkylation, etc. where the proton removing step is highly exothermic. Considering the fact that in previous considerations small isotope effects ($k_H/k_D = < 2$ and $k_H/k_T = < 3$) were considered as indicative of only secondary effects (a secondary hydrogen isotope effect is an alteration in the rate of a reaction caused by substitution of deuterium or tritium for a hydrogen atom which is not detached in the rate-determining step of the reaction), the views expressed by Hammond [13], Westheimer [14] and Wiberg [15] may put the question of kinetic hydrogen isotope effects in a new light. Relatively small kinetic hydrogen isotope effects may, in certain cases, have more importance than was previously thought, and only in favorable cases can a sizable isotope effect be expected, even if the proton elimination step is kinetically important. Thus clearly the need is indicated for additional work clarifying many aspects of the importance of kinetic isotope effects on the mechanism of electrophilic aromatic substitutions.

*Nitration*

Proton elimination in electrophilic aromatic nitration was found by Melander [10] using tritiated compounds and by subsequent investigators [16] using deuterated compounds to be not rate determining as no kinetic isotope effect was observed. The absence of a kinetic isotope effect was quoted frequently against a concerted $S_E2$ or $S_E3$ type mechanism in electrophilic aromatic substitutions because such a reaction, for obvious reasons, should show a large isotope effect due to zero point energy differences of C-H, C-T and C-D bonds in the intermediate.

The question of whether a small kinetic isotope effect should be possible in an electrophilic aromatic nitration has been discussed by Melander [6]. He explained why isotopic substitution can have only negligible influence on the ratio of the addition step and why the proton elimination step should show no or only a very small kinetic isotope effect, the direction of which is also impossible to predict.

In a reaction similar to the one observed by Olah, *et al* [16a] with $NO_2^+$ $BF_4^-$ nitration, the primary addition step should have practically no dependence on isotopic substitution. As the primary addition step of $NO_2^+$ to the aromatic is influenced only by the overall pi-donor ability of the molecule, differences between molecules such as $C_6H_6$ and $C_6D_6$ in pi-electron properties should be practically non-existent.

Whether the proton elimination step gives rise to any kinetic isotope effect in nitrations with $NO_2^+$ $BF_4^-$ was investigated in simple competitive experiments.

Benzene and benzene-$d_6$ as well as toluene and toluene-$d_8$ were competitively nitrated in tetramethylene sulfone solution with $NO_2^+$ $BF_4^-$. In control experiments it was found that under the experimental conditions, $HBF_4$, which is formed as a by-product of the nitrations, does not affect hydrogen-deuterium exchange to any detectable amount (using infrared and mass spectroscopy).

The nitration mixtures were analyzed by mass spectroscopy. A secondary isotope effect of $k_H/k_D = 0.85$ was observed for the toluene-$d_8$ nitration and a similar effect of 0.87 for the benzene-$d_6$ nitration (by comparing the amounts of nitrobenzene and nitrobenzene-$d_5$, as well as nitrotoluene and nitrotoluene-$d_7$ formed in the competitive experiments).

To substantiate the observed small kinetic isotope effects, competitive nitrations of benzene and toluene-$d_8$ as well as of benzene-$d_6$ and toluene were carried out with $NO_2BF_4$ in tetramethylene sulfone solutions. The mononitro products obtained could, in these cases, be analyzed by gas-liquid chromatography.

$k_{toluene}/k_{benzene-d_6} = 1.45 \quad k_H/k_D = 0.89 \pm 0.03$
$k_{toluene-d_8}/k_{benzene} = 2.02 \quad k_H/k_D = 0.85 \pm 0.03$
$k_{toluene}/k_{benzene} = 1.67$

The kinetic isotope effects obtained by the mass spectroscopic and gas-liquid chromatographic method thus show good agreement.

As in the case of the nitronium tetrafluoroborate nitration of benzene-$d_6$ and toluene-$d_8$, also in the case of the nitration of fluorobenzene-4-D, a small secondary reverse isotope effect was observed.

$k(C_6H_5F)/k(C_6H_6) = 0.45 \quad k_H/k_D = 0.88 \pm 0.03$
$k(C_6H_4F\text{-}4\text{-}d)/k(C_6H_6) = 0.51$

As para-substitution in nitration of fluorobenzene takes place to an extent of 91.5%, the observed kinetic isotope effect should be corrected accordingly and is slightly larger ($k_H/k_D = 0.82$).

The previously established kinetic isotope effect for the nitration of $C_6D_6$ was again observed in competitive nitration of $C_6D_6$ with fluorobenzene

$k(C_6H_5F)/k(C_6H_6) = 0.45 \quad k_H/k_D = 0.87 \pm 0.03$
$k(C_6H_5F)/k(C_6D_6) = 0.39$

The small secondary isotope effects are thought to be the balance of three effects in the step leading to the reaction intermediate. In the transition state of this step the initial $sp^2$ carbon-hydrogen bond must have changed to some extent at least in the direction toward $sp^3$. Owing to the low frequency of the out of plane bending mode of aromatic carbon-hydrogen bonds, this change in hybridization should increase the zero-point energy leading to a secondary isotope effect with the heavy molecule reacting faster. Furthermore, deuterium is electropositive relative to protium [17, 18]. Accordingly, the ring carbon atoms in $C_6D_6$ will be charged slightly more negative than those in $C_6H_6$, leading to a small isotope effect with the deuterated compound reacting faster. On the other hand, as pointed out by Streitwieser [18], hyperconjugation of the carbon-hydrogen bond removed from the ring plane with the p-orbitals of the other five carbon atoms will tend to

decrease the zero-point energy. The direction of the latter effect is opposite to that of the two former [18, 19].

When the pi-complex formation is rate determining the contribution of this hyperconjugation effect is smaller, and therefore an over-all inverse isotope effect can result.

The inverse isotope effect observed in nitration indicates that the hybridization and inductive effects outweigh the hyperconjugative effect.

The small inverse isotope effect observed in 1961 in the $NO_2^+$ $BF_4^-$ nitration of deuterated aromatics by Olah and coworkers was later substantiated by similar investigations of Ritchie and Win in 1964 [19]. A similar effect was observed in the benzoyl nitrate nitration of thiophene-2-t by Oestman in 1962 [20]. As an inverse primary isotope effect (the heavy compounds reacting faster) is hardly understandable, it is probable that all these observations refer to secondary isotope effects. It is safe to say that the objections raised by Hammond and Wiberg can, at least in the case of nitration, be eliminated and Melander's original finding, upheld, at least to the extent that there is no *primary* kinetic isotope effect. Thus the proton elimination is of no major kinetic importance.

The reported kinetic hydrogen isotope effects in aromatic nitrations are summarized in Table I.

## Friedel-Crafts Alkylation

No previous kinetic hydrogen isotopic effect investigation of aromatic alkylations related to the Friedel-Crafts type was carried out with exception of the work of Bethell and Gold [21] who found no isotopic effect in the diphenylmethylation of anisole with diphenylmethylacetate in acetic acid solution

$$(C_6H_5)_2CH\text{-}OOCCH_3 + C_6H_5OCH_3 \longrightarrow pCH_3OC_6H_4CH(C_6H_5)_2 + CH_3COOH$$

Unpublished work by De Haan was quoted in the dissertation of Goldman [22a] relating the $GaCl_3$ catalyzed methylation of benzene-$d_6$ with methyl chloride at $-36°$ showing no isotope effect.

The observation of kinetic isotope effects in aromatic Friedel-Crafts type alkylation systems is seriously hindered by generally strong hydrogen exchange taking place simultaneously with alkylation due to the acid catalysts employed.

### a) *Benzylation*

The competitive rate determination in substitution of benzene-benzene-$d_6$ mixture was used to determine the kinetic isotope effect in Friedel-Crafts benzylation [22]. Mass spectroscopy revealed a slight hydrogen-deuterium exchange using $AlCl_3 \cdot CH_3NO_2$ as catalyst in benzylations of $C_6D_6$ with benzyl chloride. It was therefore necessary to find a related benzylation system free of hydrogen exchange. Using anhydrous silver tetrafluoroborate as cation-forming agent in the benzylation of benzene-$d_6$ with benzyl chloride in nitromethane solution, no protium-deuterium exchange was found based on mass spectroscopic analysis of the products. Ferric chloride in nitromethane solution also caused only negligible hydrogen exchange.

The benzyl chloride-$AgBF_4$ benzylation in nitromethane solution was used in the determination of the kinetic isotope effect in the competitive benzylation of benzene-benzene-$d_6$. Using mass spectroscopy to analyze the amounts of diphenylmethane and diphenylmethane-$d_5$ formed, a small secondary direct isotope effect was observed: $k_H/k_D = 1.12$.

The kinetic isotope effect was well reproducible when competitive benzylation, under identical conditions, of benzene-toluene and benzene-$d_6$-toluene mixtures were carried out. In this case gas-liquid chromatography could be used to anaylze the products.

$^k$toluene/$^k$benzene $= 3.20$ $\qquad k_H/k_D = 1.13$
$^k$toluene/$^k$benzene-$d_6 = 3.62$

The kinetic isotope effects obtained by the mass spectroscopic and gas-liquid chromatographic method thus show good agreement.

The small secondary, direct isotope effect observed can be explained similarly, as in the case of nitration, by the fact that in the transition state the initial $sp^2$ carbon-hydrogen bond must have been changed in character at least somewhat toward that of $sp^3$ bonding. Owing to the low frequency of the out of plane aromatic carbon-hydrogen vibrations, it could be expected that the transition from $sp^2$ to $sp^3$ should increase the zero point energy and consequently cause a secondary isotope effect with the heavy molecule reacting faster. On the other hand, hyperconjugation of the carbon-hydrogen bond removed from the ring plane with the pi-orbitals of the other five carbon atoms will tend to decrease the zero point energy and the two effects will cancel each other to a certain degree. Streitwieser also demonstrated [18] recently that aromatic deuterium is electropositive relative to protium in the normal state. It is effectively electron donating relative to hydrogen, presumably because of antiharmonicity effects. In the present system, the appearance of a direct secondary isotope effect (with the heavy compound reacting slower to some extent) proves that conjugation is sufficiently strong to overcompensate the increase of zero point energy.

### b) *Isopropylation*

Using the competition between benzene and benzene-$d_6$, the i-$C_3H_7Br$ + $AgClO_4$ alkylation in nitromethane solution was found suitable for the determination of the kinetic isotope effect of Friedel-Crafts isopropylation [23] reaction. Mass spectroscopy has shown only slight hydrogen exchange, as compared with substantial hydrogen exchange when stronger acid catalysts like $AlCl_3 \cdot CH_2NO_3$ were employed.

Mass spectroscopic analysis of the $C_6H_5C_3H_7$: $C_6D_5C_3H_7$ ratios gave a kinetic isotope effect of $k_H/k_D = 1.15 \pm 0.03$. As a check on the reproducibility of the small observed kinetic isotope effect, competitive isopropylation of toluene-benzene and toluene-benzene-$d_6$ was also carried out with i-$C_3H_7Br$ + $AgClO_4$ in nitromethane solution. In this case gas-liquid chromatography could be used to determine the relative ratios which were found to be

$^k$toluene/$^k$benzene $= 2.24$ $\qquad k_H/k_D = 1.17 \pm 0.04$
$^k$toluene/$^k$benzene-$d_6 = 1.91$

The kinetic isotope effects determined from direct competition of $C_6H_6$-$C_6D_6$ and from competition of $C_6H_5CH_3$-$C_6H_6$ and $C_6H_5CH_3$-$C_6D_6$ gave good agreement.

The observation of only a small secondary isotope effect during the Friedel-Crafts isopropylation of deuterated benzene is in accordance with the observation that the rate-determining step involves a transition state closer in nature to an oriented pi- than a sigma-complex.



Table 1

Kinetic hydrogen isotope effects in nitrations.

| Substrate | Reagent | Solvent | Temp. °C | $k_H/k_D$ | $k_H/k_T$ | Ref. |
|---|---|---|---|---|---|---|
| Benzene-t | | $HNO_3/H_2SO_4$ | | | $< 1.19$ | a |
| -d | | $HNO_3/D_2SO_4$ | 45-60 | 1.02±0.04 | | b |
| -$d_6$ | $NO_2^+BF_4^-$ | tetramethylene sulfone | 25 | 0.89±0.03 | | c |
| Toluene-t | | $HNO_3/H_2SO_4$ | | | $< 1.18$ | a |
| -α-t, -2-t and 4-t | | | 0 | | 1.002±0.03 | d |
| -t | benzoyl nitrate | acetonitrile | 0 | | 1.2±0.2 | e |
| -$d_8$ | $NO_2^+BF_4^-$ | tetramethylene sulfone | 25 | 0.85±0.03 | | c |
| -α-$d_3$, α-t | | $HNO_3$ (80% vol.) | 25 | 1.002±0.002 | 1.003±0.003 | f |
| Fluorobenzene -4-d | $NO_2^+BF_4^-$ | tetramethylene sulfone | 25 | 0.82±0.03 | | g |
| Chlorobenzene -4-d | $NO_2^+BF_4^-$ | | 25 | 0.94±0.03 | | h |
| Bromobenzene-t | | $HNO_3/H_2SO_4$ | | | $< 1.28$ | a |
| Anisole-4-t | $N_2O_5$ | $CH_3CN$, $CCl_4$ $HNO_3/CH_3COOH$ | 0 | | 1.0±0.1 | e |
| | benzoyl nitrate | acetonitrile | 0 | | 1.0±0.1 | e |
| Nitrobenzene-t | | $HNO_3/H_2SO_4$ | | | $< 1.35$ | a |
| -$d_5$ | | $HNO_3/H_2SO_4$ | 25 | 1.08±0.1 | | b |
| p-Nitrobromobenzene-t | | $HNO_3/H_2SO_4$ | | | $< 1.23$ | a |
| 1,3,5-Tri-t-butylbenzene-t | | $HNO_3$/AcOH/$Ac_2O$ | 25 | | 1.04±0.06 | i |
| Naphthalene-α-t | | $HNO_3/H_2SO_4$ | | | $< 1.30$ | a |
| Thiophene-2-t | benzoyl nitrate | acetonitrile | 2 | | 0.88 | j |

(a) L. Melander, **Arkiv Kemi 2**,211 (1950) (b) T. G. Bonner, F. Bowyer and G. Williams, **J. Chem. Soc.** 2650 (1953) (c) G. A. Olah, S. J. Kuhn and S. H. Flood, **J. Am. Chem. Soc.** 83,4571 (1961) (d) J. F. Eastham, J. L. Bloomer and F. M. Hudson, **Tetrahedron, 18**,653 (1962) (e) K. Halverson and L. Melander, **Arkiv Kemi 11**,77 (1957) (f) C. G. Swain, T. E. C. Knee and A. J. Kresge, **J. Am. Chem. Soc. 79**,505 (1957) (g) G. A. Olah, S. J. Kuhn and S. H. Flood, **J. Am. Chem. Soc. 83**,4581 (1961) (h) C. D. Ritchie and H. Win, **J. Org. Chem. 29**, 3093 (1964) (i) P. C. Myhre, **Acta Chem. Scand. 41**,219 (1960) (j) B. Oestman, **Arkiv Kemi 19**,499 (1962).

c) *tert-Butylation*

The kinetic isotope effect in the t-butylation of benzene-$d_6$ was determined by the previously used competitive method, using t-$C_4H_9Br$ + $AgClO_4$ as an alkylating agent in nitromethane solution at 25° [24]. Direct competition of benzene and benzene-$d_6$ (analyzed by mass spectroscopy) and competitive butylation of toluene-benzene and toluene-benzene-$d_6$ (analyzed by gas-liquid chromatography) were used. Both methods gave a small secondary kinetic isotope effect.

$^k$benzene/$^k$benzene-$d_6$ = 1.16 $k_H/k_D$ = 1.16 ± 0.03
$^k$toluene/$^k$benzene = 15.3 $k_H/k_D$ = 1.21 ± 0.06
$^k$toluene/$^k$benzene-$d_6$ = 18.5

The t-$C_4H_9Br$ + $AgClO_4$ alkylation system in nitromethane caused only slight hydrogen-deuterium exchange according to mass spectroscopic analysis. Therefore the method could be used for the determination of the kinetic isotope effect. Corrections were applied for di-t-butylated products. The effects causing a small secondary isotope effect were similar to those observed in benzylation and isopropylation. Reported kinetic hydrogen isotope effects in Friedel-Crafts type alkylations are summarized in Table 2.

Table 2

Kinetic hydrogen isotope effects in Friedel-Crafts alkylations.

| Substrate | Alkylating Agent | Solvent | Temp. °C | $k_H/k_D$ | Ref. |
|---|---|---|---|---|---|
| Benzene-$d_6$ | $C_6H_5CH_2Cl$ + $AgBF_4$ | nitromethane | 25 | 1.13±0.03 | a |
| | i-$C_3H_7Br$ + $AgClO_4$ | nitromethane | 25 | 1.15±0.032 | b |
| | t-$C_4H_9Br$ + $AgClO_4$ | nitromethane | 25 | 1.16±0.03 | c |
| | $CH_3Cl$, $GaCl_3$ | | -36 | 1 | d |
| Anisole-4-d | $(C_6H_5)_2CHOH$ | acetic acid | 25 | 0.99±0.02 | e |

(a) G. A. Olah, S. J. Kuhn and S. H. Flood, **J. Am. Chem. Soc. 84,** 1688 (1962) (b) G. A. Olah, S. H. Flood, S. J. Kuhn, M. E. Moffatt, and N. A. Overchuk, **J. Am. Chem. 86,**1046 (1964) (c) G. A. Olah, S. H. Flood, and M. E. Moffatt, **J. Am. Chem. Soc., 86,** 1060 (1964) (d) F. B. DeHaan, unpublished data quoted by G. K. Goldman, Ph.D. Thesis, Purdue University 1961 (e) D. Bethel and V. Gold, **J. Chem. Soc.,** 1905 (1958).

HALOGENATION

a) *Bromination*

Evidence for the absence of kinetic hydrogen isotope effect in bromination was obtained by Melander [10], who used iodine as a catalyst. de la Mare, Dunn and Harvey [25] measured the rates of bromination of benzene-$d_6$ and ordinary benzene with a solution of hypobromous and perchloric acids. Under these conditions the brominating agent is believed to be $Br^+$ or $BrOH_2^+$. The rates were determined in independent runs and found to be equal within a few per cent.

No isotope effects have been observed in the bromination by molecular bromine of phenol, of anisole, and of toluene and pentamethylbenzene, the latter two in the presence of anhydrous zinc chloride. Small effects were found in the bromination by bromine of 3-bromodurene in nitromethane ($k_H/k_D$ = 1.4), and of biphenyl in aqueous acetic acid ($k_H/k_D$ = 1.15). Larger effects were noted in the bromination of 2-napthol-6, 8-disulfonic-1-d-acid (G-salt) by bromine by Zollinger [26] where the isotope effect increased with the ratio of concentration of reactants ($k_H/k_D$ = 1.48 - 2.34), and by hypobromous acid ($k_H/k_D$ = 2.08). A larger effect was also noted in the *ortho*-, but not the *para*-, bromination of dimethylaniline by bromine ($k_Hk_D$ = 2.6). The bromination of m-anisolesulfonate ion has an isotope effect when the brominating agent is bromine ($k_H/k_D$ = 2.6), but not when it is "Br+," presumably $H_2OBr^+$, or hypobromous acid. Finally, a large tritium isotope effect was observed in the bromination of 1, 3, 5-tri-t-butylbenzene with bromine and perchloric acid in dioxane-acetic acid solution ($k_H/k_T$ about 10), and this was attributed to steric hindrance in the intermediate. However, almost no deuterium isotope effect was noted in the bromination of benzene with bromine and silver perchlorate in nitromethane solution [26a]. Anhydrous $AgClO_4$ + $Br_2$ in nitromethane provides a bromination system which causes only slight hydrogen exchange. At 25° a very small secondary isotope effect, $k_H/k_D$ = 1.08 ± 0.03, was observed which was only slightly larger than the error of determination. Competitive bromination of benzene and benzene-$d_6$ with $Br_2$ + $FeCl_3$ in nitromethane could not be used, since mass-spectroscopic investigations showed extensive hydrogen-deuterium exchange.

Reported kinetic hydrogen isotope effects in aromatic brominations are summarized in Table 3.

b) *Chlorination*

The chlorination of benzene with hypochlorous acid and perchloric acid, and of 3-bromodurene with chlorine show only small secondary kinetic hydrogen isotope effects.

Competitive chlorination of benzene and benzene-$d_6$ with $Cl_2$ + $FeCl_3$ in nitromethane solution could not be used, because mass-spectroscopic investigations have shown extensively hydrogen-deuterium exchange. Anhydrous $AgClO_4$ and $Cl_2$ in nitromethane produced only slight hydrogen exchange and could therefore be used for the determination of the kinetic isotope effect.



Table 3

Kinetic hydrogen isotope effects in brominations.

| Substrate | Reagent | Solvent | Temp.°C | $k_H/k_D$ | $k_H/k_T$ | Ref. |
|---|---|---|---|---|---|---|
| Benzene-t | $Br_2$+$I_2$,$FeBr_3$, $AlCl_3$ | benzene | 25 | | 1.64 | a |
| -$d_6$ | HOBr,$HClO_4$ | 50% dioxane | 25 | 1 | | b |
| -$d_6$ | $Br_2$+$AgClO_4$ | nitromethane | 25 | 1.08±0.03 | | c |
| Toluene-$\alpha$-$d_3$,-$\alpha$-t | $Br_2$ | 85% AcOH | 25 | < 1.03 | < 1.04 | d |
| -$d_5$ | $Br_2$+$ZnCl_2$ | AcOH | 25 | 0.95±0.1 | | o |
| 1,3,5-Tri-t-butylbenzene-t | $Br_2$ | AcOH/$Ac_2O$<br>AcOH/dioxane | 25<br>25 | | 0.96-1.02<br>10 | e<br>e |
| Pentamethylbenzene-d | $Br_2$+$ZnCl_2$ | AcOH | 25 | 0.92±0.1 | | o |
| Bromobenzene-4-t | $Br_2$+$I_2$,$FeBr_3$, $AlCl_3$ | | 25 | | 1.64 | a |
| 3-Bromodurene-6-d | $Br_2$ | nitromethane | 30 | 1.4 | | f |
| Phenol-2,4,6-$d_3$ | $Br_2$ | aq.HBr | 20 | 1 | | g |
| Anisole-d | $Br_2$ | AcOH | 25 | 1.05 | | h |
| N,N-Dimethylaniline-$d_3$ | $Br_2$ | $H_2SO_4$,6.4M | 25 | 1.1-1.9 | | i |
| -2,6-$d_2$ | $Br_2$ | $H_2SO_4$,6.4M | 25 | 2.6 | | j |
| -4-d | $Br_2$ | $H_2SO_4$,6.4M | 25 | 1 | | j |
| Anisole-3-sulfonic acid (d) | HOBr | | | 1 | | k |
| | $Br_2$ | | | 2.6 | | k |
| | $Br^+$ | | | 1 | | k |
| -4-sulfonic 2,6-$d_2$ acid | $Br_2$ | aq. buffers | 0 | 1.0-1.31 | | l |
| 2-Naphthol-6,8-disulfonic-1-d acid | $Br_2$ | aq. buffers | 20 | 1.41-2.38 | | m |
| | HOBr | | 20 | 1 | | m |
| Biphenyl-4,4′-$d_2$ | $Br_2$ | 50% AcOH | 25<br>35 | 1.15<br>1.14 | | n |

(a) L. Melander, **Arkiv Kemi 2,**211 (1950) (b) P.B.D. de la Mare, T.M. Dunn and J. T. Harvey, **J. Chem. Soc.,** 923 (1957) (c) G. A. Olah, S. J. Kuhn, S. H. Flood and B. A. Hardie, **J. Am. Chem. Soc. 86,**1039 (1964) (d) C. G. Swain, T.E.C. Knee and A. J. Kresge, **J. Am. Chem. Soc. 79,** 505 (1957) (e) P. C. Myhre, **Acta Chem. Scand. 14,**219 (1960) (f) E. Baciocchi, G. Illuminati and G. Sleiter, **Tetrahdr. Lettrs.** No. 23, 30 (1960) (g) E. A. Shilov, unpublished data quoted by H. Zollinger (7) (h) E. Berlinger, **Chem. and Ind.** (London) 177 (1960), **J. Am. Chem. Soc. 82,**5435 (1960) (i) S. F. Mason and P. G. Farell, **Nature 183,**250 (1959) (j) P. G. Farell and S. F. Mason, **Nature 197,**590 (1963) (k) F. M. Vainshtein and E. A. Shilov, Proc., Acad. Sc. USSR, **Chem. 133,**821 (1960) (l) A. N. Bourns, unpublished results, quoted by H. Zollinger (7) (m) M. Christen and H. Zollinger, **Helv. 45,**2066 (1962) (n) E. Berlinger and K. E. Schueller, **Chem. and Ind.** (London) 1444 (1960) (o) R. R. Josephson, R. M. Keefer and L. J. Andrews, **J. Am. Chem. Soc., 83,** 3562 (1961).

At 25° a small secondary, reverse isotope effect, $k_H/k_D$ = 0.87 ± 0.05, was observed [27].

c) *Iodination*

An isotope effect in iodination was observed by

Table 4

Kinetic hydrogen isotope effects in chlorination.

| Substrate | Chlorinating Agent | Solvent | Temp. °C | $k_H/k_D$ | Ref. |
|---|---|---|---|---|---|
| Benzene-$d_6$ | HOCl,$HClO_4$ | aq. AcOH | 25 | 1 | a |
| Benzene-$d_6$ | $Cl_2$+$AgClO_4$ | $CH_3NO_2$ | 25 | 0.87±0.03 | b |
| 3-Bromodurene-6-d | $Cl_2$ | $CH_3COOH$ | 30 | 0.9±0.1 | c |

(a) P.B.D. de la Mare, I. C. Hilton and S. Varma, **J. Chem. Soc.** 4044 (1960) (b) G. A. Olah, S. J. Kuhn and B. A. Hardie, **J. Am. Chem. Soc. 86,** 1055 (1964) (c) E. Baciocchi, G. Illuminati, and G. Sleiter, **Tetrahdr. Lettrs.** No. 23, 30 (1960).

Grovenstein and Kilby [28], who found $k_H/k_D = 3.97$ at 25°C for the iodination of phenol-2,4,6-$d_3$ and ordinary phenol in separate runs in aqueous medium. It seems therefore that the second reaction step is rate-determining in these iodinations. Effects of similar magnitude were observed in the iodination of aniline, N-methylaniline and N,N-di-methylaniline ($k_H/k_D$ = 3.5, 3.2, and 3.0), of m-aminobenzoate ion ($k_H/k_D$ = 4.8), and of aniline-m-sulfonate ion ($k_H/k_D$ = 2). A smaller effect was noted in the iodination of m-N,N-dimethylaminobenzoate ($k_H/k_D$ = 1.4), but none in the iodination of m- and p-N,N-dimethylaminobenzenesulfonate ions. Appreciable effects were found in the iodination of imidazole ($k_H/k_D$ = 4.4), of phenol-3-sulfonic acid ($k_H/k_D$ = 3.4), and of p-nitrophenol, where the isotope effect depends on the iodide ion concentration ($k_H/k_D$ = 2.3 - 5.4). In all these reactions the bulk iodinating agent was molecular iodine. The iodination of anisole shows an isotope effect both in iodination with iodine ($k_H/k_D$ = 3.2), as well as with iodine monochloride in water ($k_H/k_D$ = 3.8) and in glacial acetic acid ($k_H/k_D$ = 3.9).

As seen, different halogenations show a wide divergence of kinetic hydrogen isotope effects, ranging from small secondary to sizable primary ones. No general pattern can be established, but the more selective reactions show the larger effects.

### Acylation

Jensen observed [29] kinetic hydrogen isotope effects of intermediate magnitude in the Friedel-Crafts benzoylation, and in the acylation of naphthalene. Details of these investigations however are not yet published.

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° [30]. 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.

$$k_H/k_D = \frac{CH_3CO^+SbCl_6^-}{2.15} \quad \frac{CH_3CO^+SbF_6^-}{2.22}$$

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 6). In this case the relative amounts of acetophenone and methylacetophenone could be determined by gas-liquid chromatography.

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

$$^k\text{toluene-}d_8/^k\text{benzene-}d_6 = 81$$
$$^k\text{D toluene}/^k\text{D benzene} = 1.54$$
$$^k\text{toluene}/^k\text{benzene} = 125$$

Comparison of this value with the ratio of the isotope

Table 5

Kinetic hydrogen isotope effects in iodinations.

| Substrate | Reagent | Solvent | Temp. °C | $k_H/k_D$ | $k_H/k_T$ | Ref. |
|---|---|---|---|---|---|---|
| Aniline-2,4,6-$d_3$ | $I_2$ | aqueous buffers | 25-30 | 3.5-4 | | a |
| | | | 25 | 2.4-3.6 | | b |
| N-Methylaniline-2,4,6-$d_3$ | | | 25-30 | 3.2 | | a |
| N,N-Dimethylaniline-2,4,6-$d_3$ | | | 25-30 | 3.2 | | a |
| Metanilate-2,4,6-$d_3$ ion | | | 25-30 | 2 | | a |
| 3-Dimethylaminobenzene 2,4,6-$d_3$ sulfonate ion | | | 25-30 | 1 | | a |
| 1-Dimethylaminobenzene -4-d-3-sulfonate ion | | | 25-30 | 1 | | a |
| 1-Dimethylaminobenzene-2,6-$d_2$-4-sulfonate ion | | | 25-30 | 1 | | a |
| 3-Aminobenzoate-2,4,6-$d_3$ ion | | | 25-30 | 3-4.8 | | a |
| Phenol-2,4,6-$d_3$ | | | 25 | 3.97 | | c |
| Phenol-3-sulfonic acid | | | 30 | 3.44 | | d |
| 4-Nitrophenol-2,6-$d_2$ | | | 50 | 2.3-5.5 | | e |
| Anisole | ICl | aqueous buffers and AcOH | 25 | 3.8-3.9 | | f |
| Imidazole-2-d | $I_2$ | aqueous buffers/KI | 25 | 1.26 | | g |
| -4,5-$d_2$ | | | | 3.7 | | g |
| -2,4,5-$d_3$ | | | | 4.5 | | g |

(a) E. A. Shilov and F. M. Weinstein, **Nature 182**,1300 (1958) (b) E. A. Shilov unpublished data, quoted by Zollinger (7) (c) E. Grovenstein and D. C. Kilby, **J. Am. Chem. Soc. 79**, 2972 (1957) (d) E. A. Shilov unpublished data, quoted by Zollinger (e) E. Grovenstein and N. S. Aprahamian, **J. Am. Chem. Soc. 84**,212 (1962) (f) E. Berlinger, **J. Am. Chem. Soc. 82**, 5435 (1960) (g) E. Berliner and K. Schueller, **Chem. and Ind.** (London) 1444 (1960).



Table 6

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-$d_6$ | = 275 | | |
| | $CH_3CO^+SbF_6^-$ | | |
| $^k$toluene/$^k$benzene | = 125 | Benzene $k_H/k_D$ | = 2.25 |
| $^k$toluene/$^k$benzene-$d_6$ | = 281 | Toluene $k_H/k_D$ | = 3.25 |
| $^k$toluene-$d_5$/$^k$benzene | = 38.6 | | |
| $^k$mesitylene/$^k$benzene | = 11 | Mesitylene $k_H/k_D$ | = 1.90 |
| $^k$mesitylene-$d_3$/$^k$benzene | = 58 | | |

effects observed in previous experiments gives good agreement.

toluene $k_H/k_D = 3.25$
benzene $k_H/k_D = 2.25$ 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 flaking 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 depends not only on the isotope used but also on the structure of the aromatic substrate. The Friedel-Crafts acetylation shows significant differences from alkylations, 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.

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 also should be observable. The acetylation with $CD_3C_6D_5$, $CD_3C_6H_5$, and $CH_3C_6D_5$ was compared with that of toluene in competitive acetylations with benzene. The data are summarized in Table 7.

Table 7

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 | $k_{a_H}/k_{a_D}$ = 1.06 |
| $^k$toluene-$a,a,a$-$d_3$/$^k$benzene | = 118 | |
| $^k$toluene-$d_5$/$^k$benzene | = 38.6 | $k_{a_H}/k_{a_D}$ = 1.04 |
| $^k$toluene-$d_8$/$^k$benzene | = 37 | |

As may be seen from the data of Table 7, deuteration of the methyl group causes indeed a small secondary isotope effect (not more than 6 per cent). Thus it is possible to demonstrate that acylation involving a sigma-complex type rate-determining transition state shows both primary and secondary kinetic isotope effects.

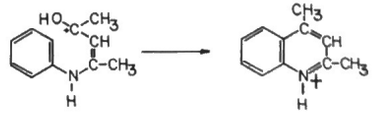
Table 8 summarizes all reported kinetic hydrogen isotope effects in Friedel-Crafts acylations.

### Nitrosation

Carbon-nitrosation should be similar to acetylation because the nitrosonium ion, unlike the nitronium ion, is very selective, and attacks only very highly activated aromatic compounds. An isotope effect of $k_H/k_D$ = 3.6 has been reported recently for nitrosation of 2,3-dibromophenol with nitrous acid [31].

### Friedel-Crafts Cyclizations

A weak isotope effect has been observed by Bonner and Wilkins [32] in the cyclodehydration in aqueous sulfuric acid of 2-anilinopent-2-en-4-one and the same compound trideuterated in the 2, 4, and 6 aromatic positions. The reaction can be considered as cyclization of the conjugate acid.




Separate runs with the two isotopic compounds gave $k_H/k_D$ = 1.43 at 25°. Bonner and Wilkins favor a two-stage mechanism with the first stage being rate-

Table 8
Kinetic hydrogen isotope effects in acylations.

| Substrate | Acylating agent | Solvent | Temp. °C | $k_H/k_D$ | Ref. |
|---|---|---|---|---|---|
| Benzene-$d_6$ | $CH_3CO+SbCl_6^-$ | $CH_3NO_2$ | 25 | 2.27 | a |
| | $CH_3CO+SbF_6^-$ | $CH_3NO_2$ | 25 | 2.25 | a |
| | $C_6H_5COCl,AlCl_3$ | | 25 | 2.4 | b |
| Toluene-$d_3$ | $CH_3CO+SbF_6^-$ | $CH_3NO_2$ | 25 | 3.25 | a |
| -4-d | $C_6H_5COCl,AlCl_3$ | | 25 | 1.6 | b |
| | $C_6H_5COCl,SnCl_4$ | | 39.9 | 1.6 | b |
| | $C_6H_5COCl,AlBr_3$ | $C_6H_5Cl_3$ | 25 | 1.1 | b |
| Mesitylene-$d_3$ | $CH_3CO+SbF_6^-$ | $CH_3NO_2$ | 25 | 1.90 | a |
| Naphthalene-$\alpha$-d | | | | | c |
| Naphthalene-$\beta$-d | | | | | c |

(a) G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, **J. Am. Chem. Soc. 86,** 2203 (1964) (b) F. R. Jensen, Ph.D. Thesis, Purdue University, 1955 (c) F. R. Jensen, 9th. Conference on Reaction Mechanism, Sept. 1962, Brookhaven, New York

Table 9
Kinetic hydrogen isotope effect in nitrosation.

| Substrate | Reagent | Solvent | Temp. °C | $k_H/k_D$ |
|---|---|---|---|---|
| 2,6-Dibromo-phenol-4-d | $NaNO_2$ | aq. $HClO_4$ | 30 | 3.6 |

K. M. Ibne-Rasa, **J. Am. Chem. Soc. 84,** 4963 (1962).

determining. The reaction can be considered as a cyclialkylation.

Acid-catalyzed cyclizations of 2-carboxybiphenyl have been investigated by Denney and Klemchuk [33]. These can be considered as typical Friedel-Crafts cyclizations.

The isotope effect seems to grow stronger with increasing acidity. It seems to be a likely explanation that both steps are partly rate-determining, the second one being of increasing kinetic significance.

### Sulfonation, Sulfonylation

Sulfonation has been found by Melander [10] to proceed with a weak but finite isotope effect, the heavy compound reacting slower. The reaction has been investigated particularly by Berglund-Larsson [34], who sulfonated bromobenzene with oleum in nitrobenzene solution. The experiments were of the competitive type, and small amounts of bromobenzene-4-d or -4-t were used in mixture with ordinary bromobenzene. $k_H/k_D$ was of the order of 1.4, and $k_H/k_T$ of the order of 2, these values being mainly independent of the temperature in the interval 0° to 50°. Brand [35] has reported the value $k_D/k_H = 1.7$ at 25° for the sulfonation of nitrobenzene-$d_5$ and nitrobenzene with oleum.

Cerfontain, et al. found the kinetic isotope effect in the sulfonation of benzene with sulfur trioxide at 25.0° is $(k_H/k_D) = 1.16 \pm 0.06$. It was suggested that this weak effect is a secondary one, due to the step leading to the intermediate. This infers that the proton removing step in the sulfonation with sulfur trioxide is thought not to be rate determining.

The kinetic isotope effect observed in the sulfonylation of benzene with benzene sulfonic acid in the presence of sulfur trioxide at 25.0° is $(k_H/k_D) = 0.86 \pm 0.06$. Consequently the proton removal from the intermediate is in this case no more rate determining than in the case of sulfonation.

In the case of sulfonation the positive secondary

Table 10
Kinetic hydrogen isotope effects in Friedel-Crafts type cyclizations.

| Substrate | Solvent, condensing agent | Temp. °C | $k_H/k_D$ | Ref. |
|---|---|---|---|---|
| 2-(anilino-2′,4′,6′-$d_3$)-pent-2-en-4-one | $H_2SO_4$(89.2-95.5%) | 25 | 1.41-1.51 | a |
| 2-(phenyl-2′-d)-benzoic acid | cc.$H_2SO_4$ | 1 | 1.31 | b |
| | 96.6% $H_2SO_4$ | 1 | 1.13 | |
| | PPA | 95 | 1.31 | |
| | PPA | 25 | 1.46 | |
| | HF | 19 | 3.02 | |
| 2-(phenyl-2′-d)-benzoic acid | benzene, nitrobenzene and $SO_3$, with $SnCl_4$,$ZnCl_2$ and $AlCl_3$ | -10 to -36 | 1.15-4.71 | c |

(a) T. G. Bonner, and J. M. Wilkins, **J. Chem. Soc.** 2358 (1955) (b) D. B. Denney and P. P. Klemchuk, **J. Am. Chem. Soc., 80,** 3285 (1958) (c) D. B. Denney and P. P. Klemchuk, **J. Am. Chem. Soc., 80,** 6014 (1958).



Table 11
Kinetic hydrogen isotope effects in sulfonations.

| Substrate | Reagent | Solvent | Temp. °C | $k_H/k_D$ | $k_H/k_T$ | Ref. |
|---|---|---|---|---|---|---|
| Benzene-t | oleum | | 0-25 | | 1 | a |
| -$d_6$ | sulfur trioxide | | 25 | 1.14±0.06 | | b |
| Bromobenzene-4-t(d) | oleum | | 0-25 | | 2.0±0.5 | a |
| | oleum | nitrobenzene | 0 | 1.50±0.13 | 2.1±0.3 | c |
| | | | 25 | 1.43±0.13 | 2.0±0.3 | |
| | | | 50 | 1.37±0.13 | 2.0±0.3 | |
| Nitrobenzene-$d_5$ | oleum | 14-35% | 25 | 1.7±0.1 | | d |
| 1,4-$BrC_6H_4N(CH_3)_3^+$ | oleum | 35-42% | 25 | 1.9-2.1 | | e |
| 1,4-$CH_3C_6H_4N(CH_3)_3^+$ | oleum | 11-22% | 0,25 | 1.7-1.8 | | e |

(a) L. Melander, **Arkiv Kemi 2,** 211 (1950) (b) H. Cerfontain, H. J. Hofman and A. Telder, **Rec. trav. chim. 83,** 493 (1964) (c) U. Berglund-Larsson and L. Melander, **Arkiv Kemi 6,** 219 (1953); U. Berglund-Larsson **Arkiv Kemi 10,** 549 (1957) (d) J.C.D. Brand, W. C. Horning and M. B. Thornley, **J. Chem. Soc.** 1374 (1952) (e) J.C.D. Brand, A.W.P. Jarvie, W. C. Horning, **J. Chem. Soc.** 3844 (1959)

isotope effect indicates that the hyperconjugative effect outweighs the hybridization and the inductive effect. The opposite is encountered in the sulfonylation where a negative secondary isotope effect (the heavy compound reacting faster to some extent) is observed.

### Azo Coupling

As demonstrated by Zollinger [37] in his investigations of the azo coupling reactions, the substitution step of azo couplings in general proceeds without hydrogen isotope effect and without being catalyzed by bases. If, however, the molecule to be substituted is sufficiently sterically hindered, $k_{-1}$ might be sufficiently increased relative to $k_2$ to make the latter rate-determining. This results in catalysis by bases as well as an appreciable isotope effect.

This effect was indeed observed in the coupling between 4-chlorobenzenediazonium ion and 2-naphthol-6, 8-disulfonic-1-d acid.

This is a very good confirmation of the idea of a two-stage reaction in electrophilic aromatic substitution in general. One of the most interesting achievements of Zollinger is that he has shown that the isotope effect might change with changing base concentration. Since neither $k_1$ nor $k_{-1}$ should depend on the isotopic mass of the hydrogen, any measured effect arises from $k_2$.

Binks and Ridd [38] have reported that the couplings of p-nitrobenzenediazonium ion with indole and indole-3-d at 0° proceed with the same velocity within a few percent, as determined in separate runs. This is a coupling subject to very little steric hindrance.

Table 12
Kinetic hydrogen isotope effects in azo couplings.

| Substrate | Reagent | Solvent | Temp. °C | $k_H/k_D$ | $k_H/k_T$ | Ref. |
|---|---|---|---|---|---|---|
| 1-Naphthol-4-sulfonic-2-d acid | o-methoxydiazo-benzene | aqueous buffers | 10 | 0.97 | | a |
| 2-Naphthol-6,8-disulfonic-1-d acid | p-chlorodiazo-benzene | | 10 | 6.55 | | a |
| | do. | | 10 | 5.48 | | b |
| | p-nitrodiazo-benzene | | 10 | 4.78 | | b |
| 1-Naphthol-4-sulfonic-2-d acid | p-chlorodiazo-benzene | | 20 | 1.04 | | c |
| 1-Naphthol-3-sulfonic-2,4-$d_2$ acid | p-chlorodiazo-benzene | | 20 | 3.10 | | c |
| 2-Naphthol-8-sulfonic-1-d acid | p-chlorodiazo-benzene | | 20 | 6.20 | | c |
| 1,3,5-Trimethoxybenzene-2-t | p-chlorodiazo-benzene | 30% t-butanol in aqueous acetate buffer | 20 | | 0.88 | d |
| Imidazole-2,4,5-$d_3$ | p-diazobenzene-sulfonic acid | aqueous buffers | 25 | 1.0 | | e |
| Indole-3-d | p-nitrodiazo-benzene | | 25 | 1.0 | | f |

(a) H. Zollinger, **Helv. 38,** 1597 (1955) (b) H. Zollinger, **Helv. 38,** 1617 (1955) (c) R. Ernst, O. A. Stamm and H. Zollinger, **Helv. 41,** 2274 (1958) (d) E. Helgstrand and B. Lamm, **Arkiv Kemi 20,** 193 (1962) (e) A. Grimison and J. H. Ridd, **Proc. Chem. Soc.** 256 (1958) (f) J. H. Binks and J. H. Ridd, **J. Chem. Soc.** 2398 (1958).

## The Role of Isotope Effects on the Mechanism of Electrophilic Aromatic Substitutions

For a short time after Melander's pioneering kinetic isotope work, there was some tendency to assume that the proton loss in aromatic substitution is always kinetically insignificant. However, it turned out to be premature to generalize from the experience with nitration to any other substitution reaction. It was the work of Zollinger and co-workers on azo-coupling reactions [37] which elucidated some of the factors that may lead to isotope effects, and which showed that with very similar substrates isotope effects could be produced almost at will depending on conditions and base strengths.

Until Zollinger's work, isotope effects were considered rare, but by now a considerable number of reactions have been shown to have kinetic isotope effects. In fact, every individual reaction has to be investigated for an isotope effect if a mechanistic study is to be considered complete, even if a very similar reaction has already been studied in that respect. Generalizations in this area can be very misleading.

It might not be unreasonable to try to relate the occurrence of isotope effects to the position of the transition state along the reaction coordinate and to the general energy profile. The most important factor which determines the occurrence of an isotope effect is the height of the transition state barriers leading from the intermediate to reactants and products. The intermediate, which is assumed to be present in stationary concentrations, must have the possibility to return. The timing of the transition state on the reaction coordinate will influence the isotope effect. The barrier will be high for exothermic reactions with early transition states, and hence the rate for the reverse step will be slow in these reactions, because the relatively stable intermediate will be in a valley of low potential energy. The designations "stable" and "unstable" intermediate, or "low" and "high" potential energy, imply only a relative distinction referring to two different reactions.

We should, in general, expect a reaction between a powerful electrophile and a highly activated substrate, i.e., a highly exothermic reaction, not to be predisposed to isotope effects. These will be the reactive and unselective reagents. Inversely, poorer electrophiles, the non-reactive but selective reagents, should have reactions with late transition states, and these should be disposed toward isotope effects.

As examples of electrophilic aromatic substitutions involving strongly electrophilic reagents and highly reactive substrates, thus exothermic reactions which should have an early transition state, we investigated nitration, alkylation and halogenation of benzene and alkylbenzenes by positive species.

Since the reactions are very fast, a competitive, rather than kinetic method was used. Data of the competitive nitration of benzene and alkylbenzenes with $NO_2^+ BF_4^-$, as well as data of related competitive benzylation and brominations using strong electrophiles, are summarized in Table 13.

The results indicate that these reactions show very little substrate selectivity, and that the rates of substitution of various alkylbenzenes are much alike. The ratio of reactivity of toluene to benzene is usually about 25 when nitration is carried out with nitric acid in an organic solvent, but with the preformed nitronium ion it is around two. In spite of the low substrate selectivity, the isomer distributions show high selectivity (*ortho-para* directing effect). Because the nitronium ion salts and related electrophilic reagents are very reactive and should be very little discriminating, the low substrate selectivity is expected, but it should be accompanied by low orientational selectivity, which should approach the statistical values. To explain the unprecedented anomaly of low substrate and high orientational selectivity, it must be suggested that the rate-determining step is the formation of a pi-complex, and not of a sigma-complex. The low substrate selectivity can then be accounted for if the whole aromatic pi-electron systems, rather than individual positions, compete for the electrophile.

Supporting the above views is the striking similarity of substitution rates to the stability of pi-complexes, their common lack of spread and lack of discrimination -i.e., the same kind of argument that Brown had used for sigma-complexes (Table 14).

The potential energy diagram of a typical aromatic substitution reaction involving a strongly electrophilic substituting agent can be represented as shown in Fig. 1, where $T_1$ represents the transition state corresponding to a pi-complex and $T_2$ corresponds to the transition state of sigma-complex nature. $T_2$ indeed must be composed of separate transition states corresponding to the m-, p-, and o-positions involved, from which that leading to the m-position represents the highest energy barrier. The proton elimination side of the reaction coordinate is substantially symmetrical with that of the reagent attack side, the relative heights of the activated states being determined by the existence or absence of kinetic isotope effects.

Table 13
Relative rates of substitution with strong electrophiles (at 25°).

| Hydrocarbon | $NO_2BF_4$ in sulfolane | | | | $C_6H_5CH_2Cl \cdot AlCl_3 \cdot CH_3NO_2$ in $CH_3NO_2$ | | | | $Br_2 + FeCl_3 \cdot CH_3NO_2$ in $CH_3NO_2$ | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $k_{Ar}/k_B$ | %o- | m- | p- | $k_{Ar}/k_B$ | %o- | m- | p- | $k_{Ar}/k_B$ | %o- | m- | p- |
| Benzene | 1.00 | | | | 1.00 | | | | 1.00 | | | |
| Toluene | 1.67 | 65.4 | 2.8 | 31.8 | 3.20 | 43.5 | 4.5 | 52.0 | 3.60 | 68.7 | 1.8 | 29.5 |
| o-Xylene | 1.75 | | | | 4.25 | | | | 3.90 | | | |
| m-Xylene | 1.65 | | | | 4.64 | | | | 5.60 | | | |
| p-Xylene | 1.96 | | | | 4.35 | | | | 4.30 | | | |
| Mesitylene | 2.71 | | | | 5.20 | | | | 15.9 | | | |



Table 14
Comparison of relative stabilities of complexes of alkylbenzenes with substitution rates. (p-xylene=1)

| Benzene Ring Substituent | Ag | HCl | $Br_2$ | $I_2$ | Picric Acid | $C_2(CN)_4$ | $NO_2BF_4$ | $C_6H_5CH_2Cl$ $AlCl_3 \cdot CH_3NO_2$ | $BR_2$ $FeCl_3 \cdot$ $CH_3NO_2$ | HF $BF_3$ |
|---|---|---|---|---|---|---|---|---|---|---|
| H | 0.98 | 0.61 | 0.46 | 0.48 | 0.70 | 0.26 | 0.51 | 0.23 | 0.23 | |
| $CH_3$ | 1.04 | 0.92 | 0.64 | 0.52 | 0.84 | 0.49 | 0.85 | 0.74 | 0.83 | 0.01 |
| o-$(CH_3)_2$ | 1.26 | 1.13 | 1.01 | 0.87 | 1.03 | 0.91 | 0.89 | 0.98 | 0.91 | 2.0 |
| m-$(CH_3)_2$ | 1.19 | 1.26 | 0.96 | 1.00 | 0.98 | 0.79 | 0.84 | 1.06 | 1.30 | 20.0 |
| p-$(CH_3)_2$ | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 1,3,5-$(CH_3)_3$ | 0.70 | 1.59 | | 2.65 | 1.12 | 2.22 | 1.38 | 1.20 | 3.70 | 2800.0 |

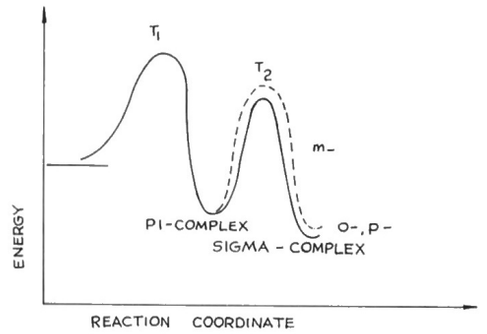



Fig. 1. Energy diagram of a typical aromatic substitution involving a strong electrophile (irreversible pi-complex formation).

As pointed out one should, in general, expect a reaction between a powerful electrophile and a highly activated substrate, i.e., a highly exothermic reaction, not to be predisposed to isotope effects.

Indeed nitration, alkylation, or bromination by positive species having such early transition states usually show, as discussed, no primary isotope effects, only small secondary ones (Table 15).

On the other hand selective substitutions (sharing both high substrate and positional selectivity) like acylations, nitrosations, certain halogenations, azo couplings, etc. have "late" transition states much more like the sigma-complex type intermediates, and such late transition states are more likely to result in an isotope effect.

On the potential energy diagram of reactions of this type, $T_2$ is higher than $T_1$, thus the formation of the pi-complexes becomes reversible and both substrate and positional selectivity are determined by the activation energy needed for formation of the sigma-complex (Fig. 2).

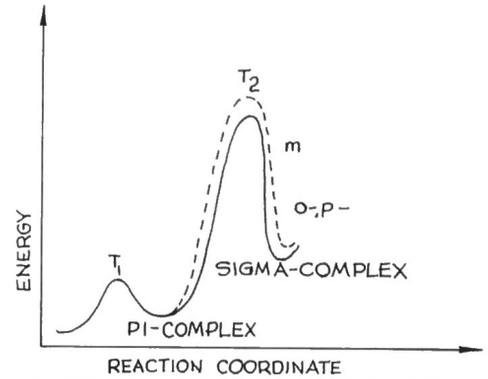



Fig. 2. Energy diagram of a typical aromatic substitution involving a weak electrophile (reversible pi-complex formation).

Table 15
Secondary kinetic isotope effects in substitutions of benzene-$d_6$.

| Substitution | Reagent | Solvent | $k_H/k_D$ |
|---|---|---|---|
| Nitration | $NO_2^+ BF_4^-$ | Tetramethylene Sulfone | 0.87 |
| Benzylation | $C_6H_5CH_2Cl + AgBF_4$ | Nitromethane | 1.13 |
| Bromination | $Br_2 + AgClO_4$ | Nitromethane | 1.08 |

In reactions of this type the intermediate is closer in potential energy to the two transition states on either side of it, and there is an easier passage, requiring less activation energy, from the intermediate in either direction. According to Hammond [13] in such a situation it would require only a small reorganization, such as a very slight loosening of the carbon-electrophile or the carbon-hydrogen bonds, to bring the intermediate to the top of either barrier.

Indeed in acylations, nitrosations, azo couplings etc., as discussed, primary kinetic isotope effects were observed.

It must, however, be clearly understood, as emphasized by Zollinger [7] that the benzenonium (or sigma-complex type) nature of the intermediate is *not* the only criterion for the occurrence of a primary kinetic hydrogen isotope effect. Steric requirements of the intermediate play a very important role. They may cause the reverse reaction of the first step to be favored relative to the proton transfer step ($k_{-1} > k_2$) as demonstrated in the diazo-coupling of 2-naphthol-6,8-disulfonic acid by Zollinger. They also may cause a fast and reversible formation of the intermediate, followed by a slow proton loss. This proton transfer is slow, not because of the existence of an exceptionally strong C-H bond, but because the bulky substituent to be introduced has to move from the tetrahedral into the sterically more strained position in the aromatic plane. This second type of slow proton transfer, established by Zollinger in the bromination of 2-naphthol-6, 8-disulphonic acid, has to be clearly differentiated from the first-mentioned, where the second step is fast, but not as fast as the reverse reaction of the first step. Without this steric factor the bromination of this naphthol derivative would be a very fast reaction.

It would seem at the present time that, under certain conditions, practically all aromatic substitution reactions may proceed with an experimentally noticeable isotope effect.

The significance of "small" effects often encountered and the possible effect of isotopic substitution, not on the rate of the leaving proton but on that of the entering electrophile, and on the change in hybridization of the attacked carbon atom from $sp^2$ toward $sp^3$, must be—besides other factors—always considered before coming to conclusions as to the origin of the effects.

Small isotope effects may not be considered to arise from partial, or incomplete, bond-breaking in the transition state, an interpretation which Westheimer [14] has shown to be inadmissible by the transition state theory. On the other hand primary isotope effects may be expected to be smaller than calculated from the difference of zero-point energies whenever acceptor molecules are involved. This is the case in proton loss in aromatic substitution, where the proton might be expected to be usually less firmly attached to the carbon atom than to a basic acceptor molecule, and it may well acount for the fact that in many substitution reactions the observed isotope effects are fairly small. Small effects therefore may be genuine primary isotope effects, concerned with the breaking of the carbon-hydrogen bond, but which are reduced because of the presence of acceptor molecules.

Small effects may be due also to an entirely different cause. They may reside in the step which leads to the intermediate and may be secondary isotope effects involving differences in $k_1$ on replacing hydrogen by deuterium at the seat of reaction, as has been discussed. In the case of secondary isotope effects, as in the case of primary ones, changes in zero-point energy are the most important factors, and a heavy molecule will react slower than a light one if the frequencies in the transition state are lower than those in the reactant. In the formation of the intermediate in aromatic substitution, the appropriate carbon atom changes its hybridization from $sp^2$ to $sp^3$. Reasoning by analogy from the reverse case, the formation of an $sp^2$-hybridized carbon in a carbonium ion from an $sp^3$-hybridized carbon orbital, only a small increase in stretching frequency may be expected in the transition state, but a considerably larger increase may be expected in out-of-plane bending frequency, which is low in aromatic carbon-hydrogen bonds but much higher in tertiary carbon-hydrogen bonds. This factor alone therefore should lead to an inverse secondary isotope effect with the deuterated compound reacting faster. The increase in p-character of the carbon-hydrogen bond also causes a progressive increase in hyperconjugation of that bond with the p-orbitals of the remaining aromatic carbon atoms, and this effect causes a decrease in rate for the heavy molecule. These two opposing effects may be about equal in magnitude, and the absence of isotope effects in substitution reactions is attributed to a cancellation of the two effects. Both effects would be small, and their relative importance cannot easily be assessed quantitatively. It may happen that a deuterated compound reacts faster, if the hyperconjugation effect is not sufficient to counterbalance the increase in rate caused by the inverse isotope effect. Such inverse isotope effects have been observed. There is also the possibility of another cause for small differences in rate between protonated and deuterated compounds, which is not connected with carbon-hydrogen bond-breaking. As pointed out first by Halevi, this may come from anharmonicity which leads to a slightly shorter bond-distance in C-D than in C-H bonds, and which may be the factor responsible for the many well substantiated observations that C-D bonds behave as if they were more electron-repelling than C-H bonds; that is, they act as if they had a greater electron-releasing inductive effect. This effect may therefore lead to a small increase in rate of the deuterated compound.

In aromatic substitutions where the formation of an early transition state is rate determining (pi-complex type transition state) and therefore $k_1 > k_{-1}$ and $k_2$, no primary kinetic isotope effect is expected, and the so far investigated examples bear out this suggestion.



On the other hand, the absence of primary kinetic hydrogen isotope effects can not rule out entirely the importance of later transition states.

The picture of isotope effects in electrophilic aromatic substitutions is complicated and it is not yet possible to give a completely satisfactory explanation which will answer all questions. It is by no means always clear why in some reactions the proton loss becomes part of the rate-determining step and in others not. Many factors seem to contribute to where exactly the transition state for the rate-controlling step occurs. It does not depend solely on the aromatic substrate, on the substituting agent, steric factors, accepted bases etc., but all these contribute to the general effect. It is, however, obvious that the kinetic hydrogen isotope effects are a powerful tool in the investigation of the mechanism of electrophilic substitutions and further work will help in a better elucidation of the nature of the transition states involved in different type of reactions.

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## NEWS OF TENNESSEE SCIENCE

VICTOR A. NAJJAR, Professor of Microbiology and Chairman of the Department at Vanderbilt University is on leave 1965-1966 as guest investigator at the Rockefeller Institute, working on immunochemistry and enzymology.

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Courtland S. Randall, former vice president of Technical Marketing Associates, Inc., Concord, Massachusetts, has joined the staff of the Oak Ridge Institute of Nuclear Studies (ORINS) as assistant chairman of the ORINS Information and Exhibits Division. Under the Institute's contract with the U. S. Atomic Energy Commission, the Information and Exhibits Division operates the American Museum of Atomic Energy in Oak Ridge and operates the Commission's traveling exhibits program in this country.

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