Cationic intermediates in Friedel–Crafts acylation: structural information from theory and experiment†‡

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Experimentally-determined intramolecular and intermolecular deuterium kinetic isotope effects and computational studies imply three possible kinetic scenarios for the Friedel–Crafts acylation of xylene. The influence of the structural and energetic properties of the π-complexes and σ-complex upon the observed isotope effects is explored.

Mechanisms that invoke π-complexes are very common. Much less common are mechanistic characterisations of these and other cationic intermediate species that serve as important mediators of rate and product determination. While some elegant work[1,2] in this area has begun to clarify these intermediates in terms of their energetic and structural characteristics, their role in even the simplest of reactions remains poorly understood. Studies on electrophilic aromatic substitution were among the first to stimulate discussion of the potential role of π-complexes.[3]

A vast literature is associated with mechanistic explorations of electrophilic aromatic substitution reactions. Classic mechanistic work on electrophilic aromatic substitution reactions by Brown, Olah, and their coworkers has focused primarily upon explaining relationships between reactivity and selectivity with a view toward understanding the transition states responsible for rate and product determination.[4] Brown's selectivity/reactivity relationship studies upon acetylation suggested that reactivity and selectivity are governed by a single step.[5] By contrast, relative reactivity data for Friedel–Crafts benzoylation implied that π-complex formation is at least rate-determining.[6] Together, these findings raised the question of whether a π-complex could determine product distribution in Friedel–Crafts acylation. Crystal structures of η^1-π-complexes between bromine and the *ortho* and *para* positions on toluene made the argument for product-determination at the π-complex seem cogent.[2] Furthermore, excellent linear correlations between the absorbance wavelength of π-complexes of bromine with various aromatic compounds and the bromination rates of the aromatic compounds have been observed.[7] Together, these studies suggested that η^1-π-complex formation might be at once rate- and product-determining in electrophilic aromatic bromination. If the same process were operative in Friedel–Crafts acylation, it might explain the seemingly disparate data presented by the

groups of Brown and Olah. Hammett plots that explored the phenylacylium substituent effects upon rate resulted in a slope of $\rho^+ = 1.858$.[8] While this could be interpreted as evidence for rate-limiting σ-complex formation, it could also be the result of substituent-dependent charge transfer in the π-complex.

Here we approach this problem by performing a suite of inter- and intramolecular ^2H kinetic isotope effect (KIE) measurements upon the Friedel–Crafts acylation of xylene with isobutyryl chloride catalyzed by aluminium chloride. We discuss these results in the context of computed σ-complex and π-complex intermediate structures and estimates of isotope effects derived from these structures.

Intramolecular KIEs have proven useful in accessing information regarding reaction steps that break the symmetry between two groups that differ only in isotopic substitution, even when the symmetry-breaking step follows the rate-determining step.[9] Here we have employed intramolecular ^2H KIEs to probe the step responsible for breaking symmetry between the equivalent methyl groups in *p*-xylene. Intramolecular ^2H KIEs in this system are reflected in the product ratio of $2'$-d$_3$-**1** to $5'$-d$_3$-**1** resulting from the acylation of d$_3$-xylene. Quantitative estimates of the ratio of $2'$-d$_3$-**1** to $5'$-d$_3$-**1** were obtained using quantitative ^2H NMR with 90° pulses separated by delay times of greater than $5 \times T_1$ for the peak of interest with the longest relaxation time. We utilized ^{13}C–^{13}C COSY obtained at natural abundance to assign ^{13}C NMR resonances. We then assigned ^1H NMR resonances (and thereby the corresponding ^2H NMR resonances) using an HMQC experiment. Both of the 2-dimensional NMR experiments used for assignments were performed on a sample utilized in KIE determinations to ensure against potential concentration effects upon chemical shift. We found the $2'$-methyl group to have a ^1H NMR resonance downfield of that for the $5'$-methyl group. The intramolecular ^2H KIE resulting from three determinations is shown in Table 1. The magnitude of the intramolecular ^2H KIE translates into a small but significant preference for deuterium residing at the nascent $5'$-methyl position in the product-determining transition state. This could imply product-determining π-complex formation whereby the methyl groups on the dimethylacylium electrophile come into incidence with the $5'$-methyl position on xylene. Alternatively, the intramolecular ^2H KIE could reflect the influence of both hyperconjugative[10]

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Table 1 Values of intra- and intermolecular ^2H KIEs

Rate constant ratio	Experimental value
$k_{2'\text{-d}_3}/k_{5'\text{-d}_3}$	0.957 ± 0.002
$k_{\text{d}_6\text{-}\mathbf{1}}/k_{\text{d}_{10}\text{-}\mathbf{1}}$	1.010 ± 0.007
$k_{\mathbf{1}}/k_{\text{d}_6\text{-}\mathbf{1}}$	0.946 ± 0.004

and steric[11] effects at the 2′-methyl position such that the substantial normal β-^{2}H KIE due to hyperconjugation that one might anticipate is compensated by the inverse steric ^{2}H KIE. Finally, deprotonation which leads to rearomatization might exhibit the observed intramolecular ^{2}H KIE due to a combination of steric and hyperconjugative influences.

A few previous studies have shown deprotonation to be at least partially rate-limiting in Friedel–Crafts acylations.[12] We explored this possibility by measuring the ^{2}H KIE at the aromatic positions. Four replicates of competition experiments (d$_6$-**1** *vs.* d$_{10}$-**1**) were performed whereby the extent of reaction (F) was measured for each isotopolog. The KIE was computed using eqn (1). The average KIE with associated error is reported in Table 1. While measurements in similar Friedel–Crafts acylations typically yield a ^{2}H KIE of 2 or greater, the value reported here is very near unity. Our measurement seems to suggest that deprotonation is not rate-limiting. As this is the last step in the consensus mechanism, deprotonation can also be excluded as the product-determining step.

$$\text{KIE} = \frac{k_\text{H}}{k_\text{D}} = \frac{\ln(1 - F_\text{H})}{\ln(1 - F_\text{D})} \qquad (1)$$

Having narrowed putative rate-limiting steps down to π-complex or σ-complex formation, we sought to distinguish between the two possibilities. To accomplish this, we performed four measurements of the intermolecular ^{2}H KIEs resulting from substitution at the methyl positions on xylene (*i.e.* d$_6$-**1** *vs.* **1**) using the same method used for the previous intermolecular KIE experiment. We found that $k_1/k_{d_6\text{-}1} = 0.946 \pm 0.004$ (Table 1). This value is close to the value measured for the intramolecular KIE, which may suggest that the rate-limiting and product-determining steps are the same. At first glimpse, this overall inverse ^{2}H KIE would seem to preclude σ-complex formation as the rate-limiting step based on the assumption that electronic (hyperconjugative) effects would outweigh steric effects upon the KIE. Computational work discussed below, however, suggests that a number of scenarios are commensurate with the experimental KIEs reported in Table 1.

To gain insight regarding the nature of the putative σ- and π-complex(es), we attempted to optimize stationary points upon the potential energy surface corresponding to these structures. There are a number of challenges that make the computational estimation of KIEs difficult in this system. First, it is quite likely that saddle points upon the potential energy surface that lead to the σ- and π-complexes are a poor representation of the transition state.[13] This situation occurs largely because the potential energy surface is almost certainly quite flat in the vicinity of the π-complexes considered here. In fact, it is often assumed that the formation of π-complexes is a barrierless process.[14]

Another challenge to optimizing stationary points upon the Friedel–Crafts acylation potential energy surface is that most commonly used density functionals are incapable of accurately reproducing correlation-mediated attractive and repulsive dispersion forces.[15] On the other hand, MP2 theory is capable of reproducing these interactions but is more computationally
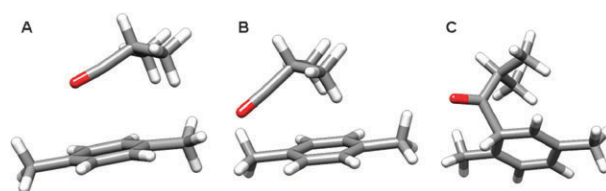

Fig. 1 Optimized [M06-2X/6-31 + G(d,p)] local minima corresponding to the (A) η^6-π-complex, (B) η^1-π-complex, and the (C) σ-complex. Optimizations include a polarizable continuum model for dichloromethane using the IEFPCM method.

expensive and often does not perform as well as most local density functional methods in reproducing vibrational frequencies. As a compromise, we have elected to use the M06-2X functional which has been found to reproduce non-bonding interactions well while not sacrificing fidelity in estimates of vibrational frequencies.[16] We found three unique cationic structures both with and without the presence of a polarizable continuum model for the dichloromethane solvent: an η^6-π-complex, an η^1-π-complex, and a σ-complex.[17] While structures computed in the presence of a polarizable continuum model for dichloromethane solvent (Fig. 1) are similar in kind to gas phase structures, they have quite different structural properties (Fig. 2; Table 2).

In systems where quantum mechanical tunneling is unimportant, it is often assumed that the equilibrium isotope effect (EIE) is an upper bound for the KIE.[18] Here, we compute intra- and intermolecular *EIEs* as an upper bound estimate of the KIEs that one might expect for the fundamental steps leading to the three cationic intermediates (Table 3). The first thing that can be gleaned from these calculations is that gas phase and polarizable continuum structures lead to drastically different predictions. All gas
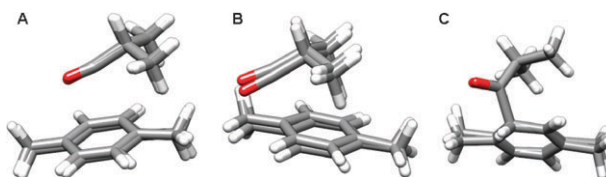

Fig. 2 Overlays of (A) η^6-π-complex, (B) η^1-π-complex, and (C) σ-complex structures computed in the gas phase and utilizing a polarizable continuum solvent model.

Table 2 Structural and energetic properties of cationic intermediates

| Complex | Distances to C($\equiv$O$^+$)/Å | | | | | | $E_\text{rel}{}^a$ |
	1′	2′	3′	4′	5′	6′	
σ^b	1.741	2.521	3.578	4.036	3.715	2.677	3.2
η^1-π^b	2.964	3.210	4.101	4.674	4.539	3.727	1.2
η^6-π^b	3.438	3.513	3.355	3.152	3.129	3.245	0.0
σ^c	1.613	2.528	3.667	4.110	3.723	2.588	5.3
η^1-π^c	3.155	3.407	4.284	4.838	4.679	3.877	0.1
η^6-π^c	3.529	3.590	3.494	3.372	3.355	3.407	0.0

^{a} Energy relative to that of the σ-complex in kcal mol^{-1}. ^{b} Structures optimized in the gas phase. ^{c} Structures optimized in the presence of a polarizable continuum; relative energies do not include solute cavitation, solute–solvent dispersion, or solute–solvent repulsion contributions.

Table 3 Equilibrium isotope effects corresponding to the KIEs shown in Table 1 as computed from optimized cationic complexes

	σ^a	η^1-π^a	η^6-π^a	σ^b	η^1-π^b	η^6-π^b
$k_{2'\text{-d}_3}/k_{5'\text{-d}_3}$	1.003	1.035	0.999	0.945	1.023	0.930
$k_1/k_{\text{d}_6\text{-}1}$	0.894	0.944	0.948	0.930	0.950	0.950

^{a} Structures optimized in the gas phase. ^{b} Structures optimized in the presence of a polarizable continuum.

phase structures yield intramolecular EIEs that are either near unity or favor deuterium in the 2′-methyl position, which is contrary to our intramolecular KIE measurements. The computed intramolecular EIE for the η^1-π-complex is also contrary in direction and smaller in magnitude than our measured intramolecular KIE. This leaves fundamental reaction steps resulting in the σ-complex or η^6-π-complex in consideration as product-determining steps.

The intermolecular KIE determined from the competitive reaction of **1** and d$_6$-**1** is 0.946. If one considers that the EIE is an upper bound to the KIE, then σ-complex formation is the most likely candidate as the rate-limiting step. If one assumes a direct progression from the η^1-π-complex to the σ-complex along the reaction pathway, then it is reasonable to expect the transition state that separates these two intermediates to yield a KIE between the computed EIEs corresponding to these structures. Furthermore, if we consider the energetic properties of the η^1-π-complex to the σ-complexes (Table 2), the higher relative energy of the σ-complex implies that the transition state leading to this complex is rate-limiting. The relative energies in Table 2 do not take vibrational entropy into consideration; however, it is reasonable to expect entropy terms to be larger for the π-complexes, resulting in an even lower free energy for these structures. These considerations, taken in the context of the intermolecular competitive (d$_6$-**1**/d$_{10}$-**1**) KIE, which eliminates deprotonation as the rate-limiting step, further implicate σ-complex formation as being product-determining. It is satisfying, then, that the intramolecular EIE approximation (0.945) for the σ-complex is in excess of but quite close to the measured intramolecular KIE (0.957). This result is surprising in view of what might intuitively be expected. Scheme 1 illustrates one resonance
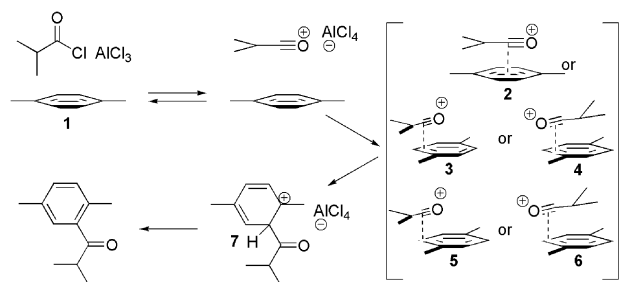
Scheme 1 Consensus mechanism for the Friedel–Crafts acylation of xylene including putative representations of the π-complex.

structure of the σ-complex (**7**). One would expect the β-^{2}H KIE resulting from hyperconjugation to dominate the intermolecular KIE if σ-complex formation were rate-limiting. However, it appears that steric interactions that develop at both the nascent 2′- and 5′-methyl positions override this effect, yielding an overall inverse ^{2}H KIE.

In summary, the results presented here represent a cogent mechanistic argument for rate- and product-limiting σ-complex formation in the Friedel–Crafts acylation of xylene. Computed structures of cationic intermediates yield insight into the energetics that control reactivity and selectivity in the Friedel–Crafts acylation. Finally, the substantial role of steric interactions in determining the direction and magnitude of the KIEs measured here has been highlighted and are in accordance with steric ^{2}H KIEs measured in other systems.[19] This work has implications upon future reaction development as inroads to asymmetric Friedel–Crafts reactions are made.[20]

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