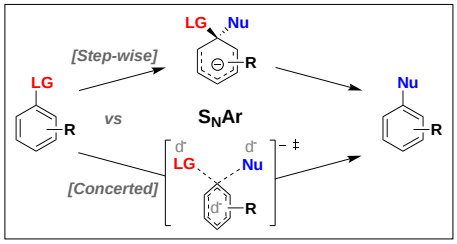
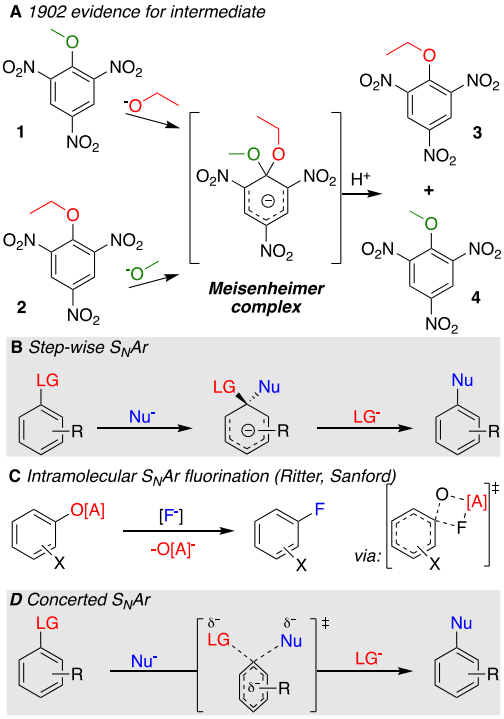
Meisenheimer Complexes in S_NAr reactions: Intermediates or Transition States?

Abstract:
Meisenheimer's Missing!: Anionic σ-complexes, best known as Meisenheimer complexes, have long been assumed to be intermediates in S_NAr reactions. New evidence from Jacobsen and co-workers now suggests that these intermediates may only be formed in select cases and that a concerted pathway is more common. These claims are supported by $^{12}C/^{13}C$ kinetic isotopes effects, measured using a new method based on ^{19}F NMR, and DFT calculations.



In 1902, Jakob Meisenheimer (University of Munich) reported evidence for the structure of a very intense violet coloured compound that is produced when mixing trinitrobenzene with an alcohol in the presence of alkali,[1] Scheme 1A. When reacting either the methoxy-nitroaromatic **1** with ethoxide, or the ethoxy-nitroaromatic **2** with methoxide, the same ratio of products, **3** and **4**, was recorded, thus suggesting reaction through a common intermediate. Despite unambiguous evidence not appearing until the birth of mainstream NMR analysis in the 1960s,[2] these anionic intermediates are still most commonly known as *Meisenheimer complexes*.



Scheme 1: Anionic σ-complexes as Meisenheimer complexes (**A**) and intermediates in S_NAr reactions (**B**). Concerted intramolecular S_NAr fluorination (**C**) and concerted intermolecular S_NAr (**D**).

It has since become widely accepted that Meisenheimer complexes are common intermediates in nucleophilic aromatic substitution (S_NAr) reactions, Scheme 1B. An intense colour is frequently observed in such reactions and many stabilised adducts, containing electron withdrawing groups (e.g., nitro) and poor leaving groups (e.g., fluoride), have been isolated and characterised.[3] Arenes carrying electron-rich substituents tend not to react under typical S_NAr conditions, as an anionic Meisenheimer intermediate cannot be stabilised. On this evidence, for reactions that do proceed but contain less stabilised anionic intermediates or better leaving groups, a step-wise mechanism has also generally been assumed to exist.

In recent years, a number of reports have appeared in the literature that describe S_NAr reactions that do, in fact, proceed successfully with substrates containing electron-rich substitution, which is in direct contrast to the widely accepted mechanism, Scheme 1B. Most recently, Clayden has reported an intramolecular *ipso*-addition of enolates into aniline moieties with a full range of electronic characteristics.[4] Hammett studies (σ^-) for these 'unactivated' S_NAr reactions revealed a ρ-value of 4.5, which is half the value previously reported (8.6)[5] for a typical S_NAr reaction with anion-stabilising substitution. Yet more surprising is a ρ-value of 1.8 recorded by Ritter in an intramolecular S_NAr fluorination reaction, Scheme 1C.[6] This low value demonstrates that the rate limiting step is relatively insensitive to the electronic effects of the substituents, which is inconsistent with the existence of an intermediate Meisenheimer complex. Sanford has also reported a related phenol fluorination reaction that displays similar features.[7] While an alternative S_N1-like substitution mechanism is unique to the decomposition of diazonium cations,[3] and an elimination to an aryne intermediate has long been discounted through the lack of regio-isomeric mixtures,[8] Ritter and Sanford both postulated a concerted, single-step, mechanism, Scheme 1D. In each case, their mechanistic proposals were supported by DFT calculations that found no evidence for the existence of an intermediate. Presumably, these concerted intramolecular substitutions are aided by the proximal location of nucleophile and electrophile and milder entropy of activation, much like a number of the related Newman-Kwart, Smiles and Chapman rearrangements. Several other computational studies have previously revealed Meisenheimer complexes are not always readily accessed energetically,[9,10] and that a concerted pathway with a single barrier can better account for nucleophilic attack, disruption of aromaticity, and loss of the leaving group. However, until now, convincing experimental data for a single step pathway has not been reported.

Recently, Eric Jacobsen and his team from Harvard University have reported in *Nature Chemistry* a remarkably convincing study that is destined to redefine how S_NAr is taught to undergraduate students.[11] Using experiments to verify their calculations, the authors predict that most S_NAr reactions of interest, i.e., *intermolecular* substitutions of substrates that are more typically applied to pharmaceutical syntheses, will actually proceed *via* a concerted pathway: 99/120 test-set reactions (83%) were calculated to be concerted. Moreover, a step-wise pathway should only operate with substrates that contain the highest-level of anionic resonance stabilisation and a poor leaving group, *i.e.*, with nitro and fluoride, respectively.

The key concept exploited to differentiate between concerted and step-wise mechanisms relies on the comparison of kinetic isotope effects (KIEs) for different S_NAr reactions. Substitution of an atom with a heavier isotopologue will naturally undergo a slower rate of bond-breaking (or bond-forming) because of a higher activation energy. The KIE is the ratio of these rates, and crucially, provides information on the bonding in the transition state

(TS). Larger KIEs are observed for concerted pathways with a more symmetrical TS and weaker bonds to both the incoming nucleophile and electrophile. Step-wise mechanisms alter a single bond at a time and the TS is closer to either the reactant or product so the activation energy difference between isotopologues is smaller, thereby leading to lower KIEs. $^{12}C/^{13}C$ KIEs should be the most informative kinetic probe for S_NAr reactions, and can be measured by a natural abundance ^{13}C NMR method introduced by Singleton,[12] which avoids tedious and expensive syntheses of isotopically enriched substrates.

In a development of the Singleton method, Jacobsen and co-workers realised that when a C-F bond is made or broken, highly sensitive ^{19}F NMR can be employed. Using a pulse sequence that suppresses the parent ^{12}C-F singlet in the ^{19}F NMR, integrating the ^{13}C-F satellite gives a quantitative assessment of ^{13}C isotope enrichment or depletion in the reactant or product, respectively. The technique is more sensitive because ^{19}F has a larger gyromagnetic ratio and shorter T1 relaxation times than ^{13}C nuclei, which translates to a 185-fold reduction in acquisition time and a much lower commitment of material to the experiment.

The method was verified by comparing KIEs measured for a simple S_N2 reaction against other methods, and then applied to three different S_NAr reactions that were chosen based on intuitive predictions of a step-wise (**A**), concerted (**B**) and borderline (**C**) reaction mechanisms, Figure 1. Interestingly, the KIEs for reactions **A** and **B**, were both measured to be 1.035(3). However, this coincidence is meaningless, as it is important to compare the magnitude of the measured KIE to the maximum KIE for each specific reaction. The measured KIE for reaction **A** was 47% of the maximum KIE calculated by DFT, which is low and reflects a step-wise mechanism, while the KIE for reaction **B** was 87% of the maximum value, which should originate from a more symmetrical TS and concerted pathway. Calculations of the potential energy surface concurred with experiment as an intermediate was clearly revealed in reaction **A**, while no such evidence was found for reaction **B**. In addition, quasi-classical dynamics modelled 200 trajectories initialized from TS **B** that were almost all productive and proceeded to product. The bonding in TS **B** is described as essentially a delocalised but non-aromatic anion, generated by two concurrent but asynchronous processes, and was aptly named a "*Meisenheimer transition state*".

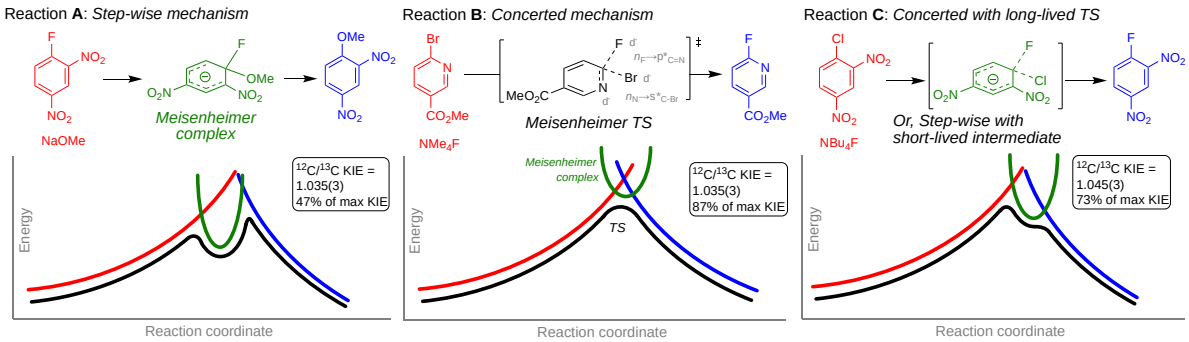


Figure 1: Simplified Marcus analysis for three S_NAr reactions that proceed by a step-wise, concerted and in-between mechanisms.

The anionic Meisenheimer complex in reaction **C** is stabilised but has a better leaving group (Cl^- vs F^-), and the measured KIE relative to the maximum theoretical KIE was indeed found to be of intermediate value to reactions **A** and **B**. The quasi-classical dynamics trajectories initialised from TS **C** detected a clustering of points in a shallow region in which a hidden intermediate lingered for multiple vibrations before proceeding toward product.

Reaction **C** can therefore be described as either being concerted with a long-lived TS, or stepwise with a short lived intermediate.

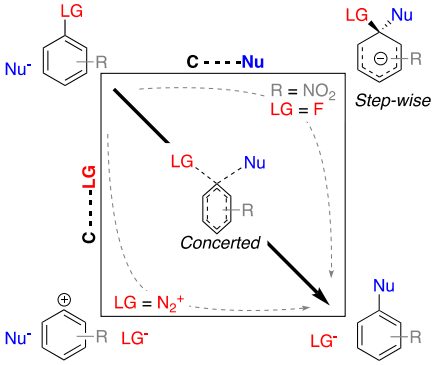


Figure 2: More O'Ferrall-Jencks plot for S_NAr reactions

The description of reaction **C** emphasises an important conclusion: the concerted and step-wise mechanisms sit at the ends of a continuum, which, with the S_N1 mechanism, can be clearly depicted in a More O'Ferrall-Jencks plot, Figure 2. For any S_NAr reaction, the position along this continuum solely depends on the relative energy of the Meisenheimer complex relative to the intersection of potential energy surfaces of the reagents and products (red and blue lines, respectively, Figure 1). Where the anionic intermediate is stabilised but adjacent to a good leaving group, such as Cl^-, the Meisenheimer complex may intersect the reaction coordinate as a shallow minimum. The evidence now suggests that only S_NAr reactions of arenes containing nitro-groups and fluoride leaving groups will proceed through a detectable Meisenheimer complex. For everything else, a more concerted pathway should operate. With this new insight and methodology, no doubt more examples of concerted S_NAr reactions will be revealed. So, Meisenheimer is not missing: just marginal or momentary…

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