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Activation of the S_N2 Reaction by Adjacent π Systems: The Critical Role of Electrostatic Interactions and of Dissociative Character

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Supporting Information Placeholder

ABSTRACT: The activation of the S_N2 reaction by π systems is well documented in textbooks. It has been shown previously that this is not primarily due to classical (hyper)conjugative effects. Instead, π -conjugated substituents enhance favorable substrate–nucleophile electrostatic interactions, with electron-withdrawing groups on the sp² system leading to even stronger activation. Herein we report computational and experimental results which show that this activation by sp²EWG-substitution only occurs in fact in a fairly limited number of cases, when the nucleophile involves strong electrostatic interactions (usually strongly basic negatively charged nucleophiles). In other cases, where bond breaking is more advanced than bond making at the TS, electrophile–nucleophile electrostatic interactions are less important. In such cases, (hyper)conjugative electronic effects determine the reactivity, and EWG-substitution leads to decreased reactivity. The basicity of the nucleophile as well as solvent effects can help to determine which of these two regimes occurs for a given electrophile.

It is well documented that allylic and benzylic derivatives react faster than corresponding alkyl derivatives in S_N2 reactions, and that the activation is greater with electron deficient π systems.^{1,2} In the classical textbook explanation, this is because the π -symmetric p orbital at the central α -carbon becomes more populated in the TS due to donation from the nucleophile, and delocalization into the π system results in stabilization of the TS.³ Brauman,⁴ Allen and Galabov,⁵ and many others⁶ have however showed that conjugative and hyperconjugative effects are limited and should not be considered as the main origin of “allylic” and “benzylic” effects in S_N2 reaction. According to Allen and Galabov⁵ the critical effect of the (substituted) π system is instead to make substrate–nucleophile electrostatic interactions more favorable in the TS (Figure 1). This effect can be probed by calculating the electrostatic potential at the C α and C β nuclei at the transition state (TS) structure. The additional activating effect of electron-withdrawing substituents^{1a,5,6b} is then attributed to an increased positive charge at C α , and the associated strengthened electrostatic interactions with the approaching nucleophile.

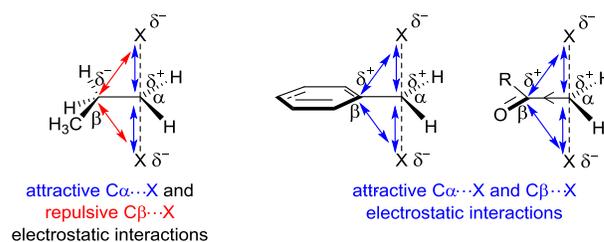


Figure 1. Allen and Galabov⁵ rationale for activation of S_N2 reaction by π systems.

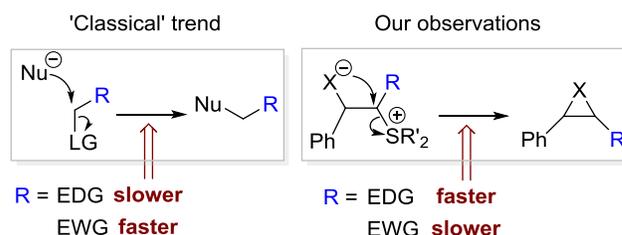


Figure 2. Substituent effects in intermolecular S_N2 reaction and cyclization to epoxides or aziridines (X = O or NSO₂Ph).

We were thus surprised when, in the context of the development of sulfur ylide-mediated epoxidation and aziridination reactions, we observed *decreased* reactivity in the intramolecular nucleophilic displacement step with conjugated EWGs (e.g. R = CONMe₂, CO₂Me or electron-poor aryls), whereas electron-rich aryls were found to activate this step (Figure 2).⁷⁻⁹

This unexpected difference in substituent effects between intramolecular (3-exo-tet) and intermolecular S_N2 reactions prompted us to investigate the factors governing substituent effects in the elimination step of the ylide-mediated epoxidation and aziridination reactions. We report herein computational and experimental data which show that the **conventional** EWG-acceleration effect only occurs when electrostatic interactions play a dominant role. Where such interactions are less important due to the nature of nucleophile or to stereoelectronic factors, (hyper)conjugative

electronic effects can determine the order of reactivity. In such cases, EWGs then deactivate the substrate.

We have used density functional theory (DFT) to compute activation barrier heights and to analyze the factors that affect them.¹⁰The analysis relies in part, as in previous work,⁵on the calculated electrostatic potential V_{TS} at the position of $C\alpha$ and $C\beta$ nuclei within the system, at the structure of the TS. We also use a calculated property of the nucleophile that relates to the extent it will stabilize the TS through electrostatics, which we call the “unrelaxed proton affinity”, PA_X . This is calculated as the difference in energy between the bare nucleophile, and the nucleophile to which a proton has been added at the position of $C\alpha$ or $C\beta$ in the TS structure. This is in fact very similar to the electrostatic potential created by the electron density of the nucleophile at the position of $C\alpha$ and $C\beta$ (V_X , reported in SI) though PA_X includes electronic relaxation effects. The V_{TS} electrostatic potential property can be calculated on the whole system, including the nucleophile, and so can be treated identically for inter- and intramolecular cases. However, PA_X needs to be calculated for the nucleophile only. For the intramolecular case, we therefore used a truncated system, based on the $-CH_2-X$ nucleophilic part, which was capped with a hydrogen atom; the structure of the resulting CH_3 group was optimized while holding the rest of the system at the TS structure (see SI for details).

We considered first the set of reactions in Table 1, with an initial focus on the typically used DMSO solvent. The trend in DFT free energy barriers for elimination to epoxides (eq. 2) matched the experimental trends.¹⁰Para substitution of the aromatic ring by an EDG led to a decrease in barrier, while EWGs increased it, as shown in the penultimate column of Table 1. In contrast, for the analogous intermolecular reactions with methoxide (eq. 1), DFT predicted that EWGs lowered the barrier, in agreement with the conventional observation of acceleration by these substituents (see second column in Table 1).

Table 1. Substituent effects in intermolecular and intramolecular (3-exo-tet) S_N2 reactions.^a

R	Intermolecular (eq. 1)		Intramolecular (eq. 2)	
	X = O	NSO ₂ Me	O	NSO ₂ Me
Me	29.6	37.9	11.3	16.8
<i>p</i> -MeOPh	28.4	25.6	5.5	6.8
<i>p</i> -MePh	27.3	26.5	6.8	7.2
Ph	26.9	27.0	7.8	7.8
<i>p</i> -CNPh	26.1	28.1	9.0	9.3
<i>p</i> -NO ₂ Ph	25.8	28.6	8.3	11.8
CO ₂ Me	24.2	31.6	11.4	13.3

^a Free energy barriers in kcal/mol.

Our calculations suggest that the reason for the inverted substituent effect in cyclization to epoxides is stereoelectronic. The TS for formation of the three-membered ring has a very different structure to the intermolecular TS, which makes electrostatic interactions less important. Indeed, strain reduces by 5 kcal/mol the stabilizing electrostatic interactions of the nucleophilic oxygen atom with $C\alpha$ and $C\beta$ in the TS, as measured by PA_X (Table 2 and Figure 3). Another difference is the more dissociative character of the S_N2 TS in the intramolecular case, as shown by the greater

increase in positive charge ΔQ_{CHR} for the alkyl group part of the substrate at the TS in this latter case (see Table 2). There is greater bond breaking than bond making in the TS. Because of this, standard conjugation and hyperconjugation interactions between $C\alpha$ and the substituent play a dominant role in governing reactivity in the intramolecular case. Accordingly, groups capable of stabilizing positive charge (conjugated EDG substituents) lead to relative stabilization of TSs and hence an activation of the reaction, with EWGs having the opposite effect.¹¹

Table 2. Electronic and structural parameters for intermolecular and intramolecular (3-exo-trig) S_N2 reactions (R = Ph)^a

X =	Intermolecular		Intramolecular	
	O	NSO ₂ Me	O	NSO ₂ Me
ΔG^\ddagger	26.9	27.0	7.8	7.8
$V_{TS}(C\alpha)$	-405.973	-404.792	-405.540	-404.033
$V_{TS}(C\beta)$	-404.661	-403.589	-404.762	-403.094
$PA_X(C\alpha)$	256.2	221.9	251.2	217.9
$PA_X(C\beta)$	235.6	205.9	231.1	197.9
ΔQ_{CHR}	0.075	0.206	0.252	0.315

^a Free energy barrier in kcal/mol. $V_{TS}(C\alpha)$ and $V_{TS}(C\beta)$ are the electrostatic potential (Volt) at, respectively, $C\alpha$ and $C\beta$ in the S_N2 TS. $PA_X(C\alpha)$ and $PA_X(C\beta)$ are the unrelaxed proton affinity (kcal/mol) of X at the position of $C\alpha$ and $C\beta$, in the S_N2 TS, respectively. ΔQ_{CHR} = NBO charge of $C\alpha H_X R$ at TS – NBO charge of $C\alpha H_X R$ in reactant.

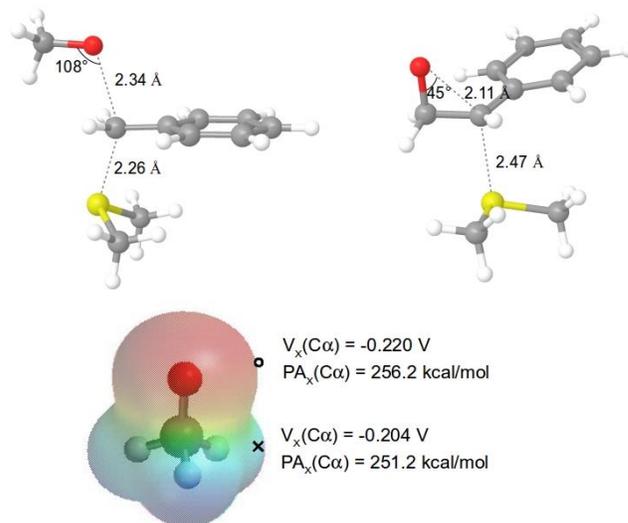


Figure 3. Transition state structure for inter-(left) and intra-(right)molecular S_N2 reactions (X = O ; R = Ph) and electrostatic potential surface of methoxide anion (o and x show the relative positioning of $C\alpha$ in the S_N2 transition state for inter- and intramolecular case, respectively).

With the sulfonamide nucleophile (X = NSO₂Me), EWG substituents are predicted to decrease reactivity in both the inter- and

intra-molecular cases (see Table 1). This could be explained by lesser electrostatic stabilization of the TS by the nucleophile (with its delocalized charge), associated with a more dissociative mechanism, as shown by the PA_X metric in Table 2. The subsequent greater increase in positive charge ΔQ_{CHR} for the alkyl group part of the substrate at the TS means that substituents capable of stabilizing positive charge (conjugated EDG substituents) lead to relative stabilization of TSs and hence an activation of the reaction, as in the intramolecular epoxide formation.

We have extended this study to a much broader set of nucleophiles (Table 3) and found that, contrary to the received textbook wisdom, EWG deceleration of S_N2 reactions is in fact quite common. Here, only the intrinsic S_N2 barrier¹² for self-exchange was computed, and this was found to increase with EWG substitution for many nucleophiles. Specifically, those nucleophiles with a lower PA_X (all of the neutral nucleophiles and some (red) anionic ones) showed an EWG-decelerated trend, whereas only nucleophiles involving strong electrostatic interactions, i.e. with high PA_X , showed EWG acceleration.¹³ It should be noted that most of the EWG-decelerated cases involve a fairly dissociative character for the S_N2 TS (see ΔQ_{CHR} in Table 3), though the borderline cases with $X = SMe, NMe_3$ and $N(Me)SO_2Me$ deviate from this rule. This increase in positive charge ΔQ_{CHR} of the substrate at the TS explains the activation of the reaction by EDGs, by stabilization of the positive charge in the TSs, and its deceleration by conjugated EWGs.

Table 3. Influence of substitution on the free energy barrier in identity S_N2 reaction of benzylic derivatives.^a

	R =	<i>p</i> -MeOPh	Ph	<i>p</i> -NO ₂ Ph	$PA_X(C\alpha)^b$	$\Delta Q_{CHR}^{2R^b}$
Anionic S_N2:						
		$X^- + RCH_2X \rightarrow RCH_2X + X^-$				
X=	NMe ₂	53.2	52.3	48.6	296.5	-0.111
	OMe	57.6	47.2	44.8	273.0	-0.057
	F	33.5	33.0	31.1	251.5	-0.025
	PMe ₂	55.4	50.8	42.5	311.0	0.021
	SMe	38.4	37.9	37.5	275.9	0.120
	Cl	19.1	21.6	23.3	233.6	0.184
	Br	30.5	33.0	33.2	236.1	0.169
	I	14.2	14.3	17.1	242.7	0.234
	N(Me)SO ₂ Me	47.8	48.2	48.6	229.6	0.125
Neutral S_N2:						
		$X + RCH_2X^+ \rightarrow RCH_2X + X$				
X=	NMe ₃	31.0	31.4	31.8	126.8	0.058
	OMe ₂	16.8	18.5	21.2	78.4	0.224
	PMe ₃	52.2	52.2	53.5	146.4	0.246
	SMe ₂	25.4	26.3	26.9	112.8	0.290

^a Free energy barrier in kcal/mol. Nucleophiles giving rise to EWG-accelerated trend are in green and those involving the EWG-decelerated trend are in red. One has to note that for some of these reactions the S_N1 mechanism is probably more favored (see SI).^b For R = Ph

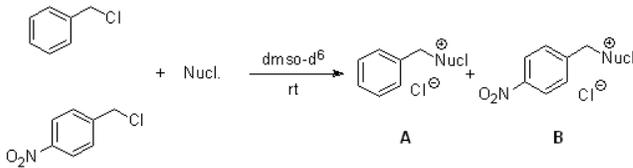
We have shown that the importance of electrostatic interactions in the TS for a given nucleophile depends strongly on PA_X . For intermolecular cases, this property is quite well correlated to the basicity of the nucleophile. Accordingly, it is possible to predict whether a conjugated EWG or EDG substituent at $C\alpha$ will accelerate or decelerate reaction purely based on the pK_a of the nucleophile's conjugate acid. Strongly basic nucleophiles such as dialkylamides, (thio)alkoxides or fluoride lead to EWG-accelerated

S_N2 reactions, whereas for weakly basic nucleophiles such as chloride, bromide, iodide, or neutral nucleophiles, there is an EWG-decelerated trend.

It is important to note that solvation effects are expected to influence the magnitude of stabilization by electrostatic interactions as well as the associative/dissociative character of the TS. The limit between EWG-decelerated and -accelerated nucleophiles may thus well vary with the nature of the solvent.¹⁴ Chloride nucleophile, for instance, was computed to follow the EWG-decelerated trend in DMSO (see Table 3) whereas, in the gas phase, the opposite trend was predicted (see SI).¹⁵ Reactions of neutral nucleophiles were found to be decelerated by sp^2 EWG-substitution even in the gas phase (see SI).

Our observations are important for a series of reactions, one example being formation of onium salts. Contrary to expectation based on the classic model, we have found that alkylation of tertiary amines or sulfides with electron-poor benzylic derivatives are slower with non- or EDG-substituted analogues as revealed by competition experiments (Table 4). However, the results fit with the new model proposed. In the case of the anionic nucleophile, MeSNa, acceleration due to the EWG was predicted and observed.

Table 4. Competition experiments^a



Nucl.	Conv. (%)	A/B	
		Comput.	Exp.
Et ₃ N	28	84/16	69/31
	21	>99/1	70/30
MeSNa	29	36/64	23/77

^aConversion of the more reactive chloride derivatives and A/B ratio were determined by ¹H NMR.

In summary, we have shown that the conventional received wisdom whereby EWGs at $C\alpha$ accelerate S_N2 reactions is actually only applicable in a limited number of circumstances: those that involve highly basic nucleophiles which can lead to strong electrostatic stabilization of the TS. In such cases, incipient bond-making effects dominate over bond breaking ones. In the case of neutral or delocalized anionic nucleophiles or where strained rings are created, electrophile-nucleophile electrostatic interactions are less important and bond-breaking is more advanced at the TS than bond-making. Hence EWGs decelerate S_N2 reactions, in line with the expected (hyper)conjugative electronic effects at what is a partially positively charged carbon center in the TS.

ASSOCIATED CONTENT

Supporting Information

Details of computational methods. Cartesian coordinates and energies for all structures. Additional data on onium salt formation reactions as well as on identity reactions. Relative energy of S_N1 intermediates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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- (8) As an example, computed energy barrier for cyclization to epoxide is ~4 and 6–9 kcal/mol for R = Ph and CONMe₂, respectively. See ref 7a.
- (9) Similar observations have also been done with ammonium ylides, see: (a) Pichler, M.; Novacek, J.; Robiette, R.; Poscher, V.; Himmlsbach, M.; Monkowius, U.; Müller, N.; Waser, M. *Org. Biomol. Chem.* **2015**, *13*, 2092–2099. (b) Robiette, R.; Conza, M.; Aggarwal, V. K. *Org. Biomol. Chem.* **2006**, *4*, 621–623.
- (10) Computations have been carried out at the B3LYP-D3/aug-cc-pVQZ//B3LYP/6-31+G(d,p) level of theory, including a continuum description of DMSO solvent for both the geometry optimization and the single point energy calculation using the Jaguar 6.5 and 8.5 program package (Jaguar, version 6.5, Schrodinger, LLC, New York, NY, **2005** and Jaguar, version 8.5, Schrodinger, Inc., New York, NY, **2014**). See SI for full computational details and data.
- (11) The increase in conjugative effects with electron-donating character of the sp²substituent can be observed by the variation of C α -C β bond length according to substitution (see SI).
- (12) It was shown that substituent effects in benzylic S_N2 reactions are the result of variations in the intrinsic barrier. See, for instance, ref. 1a, 4a and 5. This is also supported by our calculations showing the total absence of correlation between the trend of substituent effects on the free energy barrier and the reaction free energy (see SI).
- (13) Variations in substituent effects trends in S_N2 reactions according to the strengths of the nucleophile have already been reported and discussed using a correlation diagram model of S_N2, see (a) Shaik, S. S. *J. Am. Chem. Soc.* **1983**, *105*, 4360–4367. (b) Shaik, S. S. *Prog. Phys. Org. Chem.* **1985**, *15*, 197–337, and references therein.
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- (15) The EWG-accelerated trend for chloride nucleophile in the gas phase was also predicted by Streitwieser (see ref. 1a) and Uggerud (see ref. 6b).

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