JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

# Activation of the $S_N2$ Reaction by Adjacent $\pi$ Systems: The Critical Role of Electrostatic Interactions and of Dissociative Character

Raphaël Robiette,*[,†] Tran Trieu-Van,[†] Varinder K. Aggarwal,*[,‡] and Jeremy N. Harvey*[,‡,§]

[†]Institute of Condensed Matter and Nanosciences, Université Catholique de Louvain, Place Louis Pasteur 1 box L4.01.02, B-1348 Louvain-la-Neuve, Belgium

[‡]School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, United Kingdom

[§]Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, B-3001 Heverlee, Belgium

Supporting Information

**ABSTRACT:** The activation of the $S_N2$ reaction by $\pi$ systems is well documented in textbooks. It has been shown previously that this is not primarily due to classical (hyper)conjugative effects. Instead, $\pi$-conjugated substituents enhance favorable substrate−nucleophile electrostatic interactions, with electron-withdrawing groups (EWG) on the $sp^2$ system leading to even stronger activation. Herein we report computational and experimental results which show that this activation by $sp^2$ EWG-substitution only occurs 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 transition state, 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 $\pi$ systems.[1,2] In the classical textbook explanation, this is because the $\pi$-symmetric p orbital at the central $\alpha$-carbon becomes more populated in the transition state (TS) due to donation from the nucleophile, and delocalization into the $\pi$ system results in stabilization of the TS.[3] Brauman,[4] Allen, and Galabov,[5] and many others,[6] 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 Galabov,[5] the critical effect of the (substituted) $\pi$ 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$\alpha$ and C$\beta$ nuclei at the TS structure. The additional activating effect of electron-withdrawing substituents[1a,5,6b] is then attributed to an increased positive charge at C$\alpha$ and the associated strengthened electrostatic interactions with the approaching nucleophile.

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 electron-withdrawing groups (EWGs) (e.g., R = $CONMe_2$, $CO_2Me$ or electron-poor aryls), whereas electron-rich aryls were found to activate this step (Figure 2).[7−9]

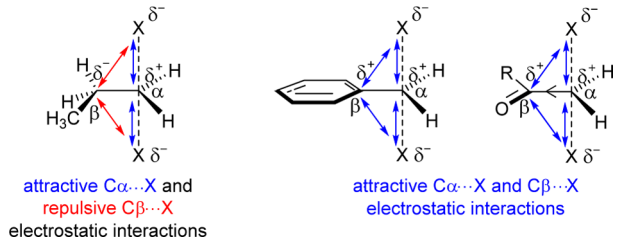



**Figure 1.** Allen and Galabov[5] rationale for activation of $S_N2$ reaction by $\pi$ systems.

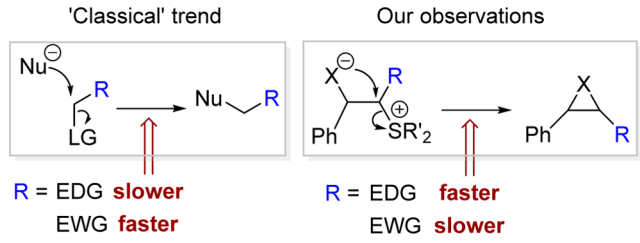



**Figure 2.** Substituent effects in intermolecular $S_N2$ reaction and cyclization to epoxides or aziridines (X = O or $NSO_2Ph$).

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.

**Received:** October 31, 2015
**Published:** January 3, 2016



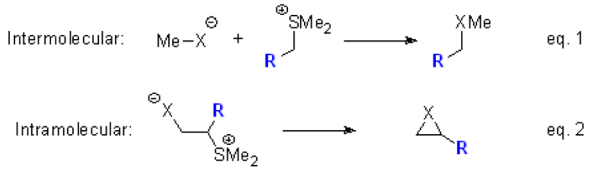


DOI: 10.1021/jacs.5b11402
J. Am. Chem. Soc. 2016, 138, 734−737

We have used density functional theory (DFT) to compute activation barrier heights and to analyze the factors that affect them.[10] The analysis relies in part, as in previous work,[5] on 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

**Table 1. Substituent Effects in Intermolecular and Intramolecular (3-*exo*-tet) $S_N2$ Reactions**[a]



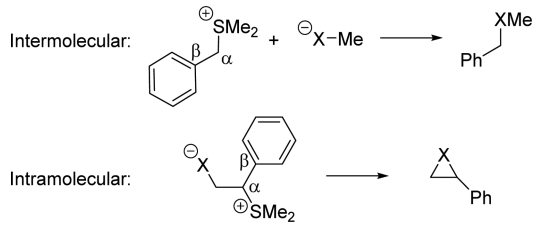

| | intermolecular (eq 1) | | intramolecular (eq 2) | |
|---|---|---|---|---|
| R | X = O | $NSO_2Me$ | O | $NSO_2Me$ |
| Me | 29.6 | 37.9 | 11.3 | 16.8 |
| *p*-MeOPh | 28.4 | 25.6 | 5.5 | 6.8 |
| *p*-MePh | 27.3 | 26.5 | 6.8 | 7.2 |
| Ph | 26.9 | 27.0 | 7.8 | 7.8 |
| *p*-CNPh | 26.1 | 28.1 | 9.0 | 9.3 |
| *p*-$NO_2$Ph | 25.8 | 28.6 | 8.3 | 11.8 |
| $CO_2Me$ | 24.2 | 31.6 | 11.4 | 13.3 |

[a]Free energy barriers in kcal/mol.

DFT free energy barriers for elimination to epoxides (eq 2) matched the experimental trends.[10] Para 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, Table 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).

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

**Table 2. Electronic and Structural Parameters for Intermolecular and Intramolecular (3-*exo*-trig) $S_N2$ Reactions (R = Ph)**[a]




| | intermolecular | | intramolecular | |
|---|---|---|---|---|
| X = | O | $NSO_2Me$ | O | $NSO_2Me$ |
| $\Delta G^{\ddagger}$ | 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 |
| $\Delta Q_{CHR}$ | 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. $\Delta Q_{CHR}$ = NBO charge of C$\alpha H_x$R at TS − NBO charge of C$\alpha H_x$R in reactant.

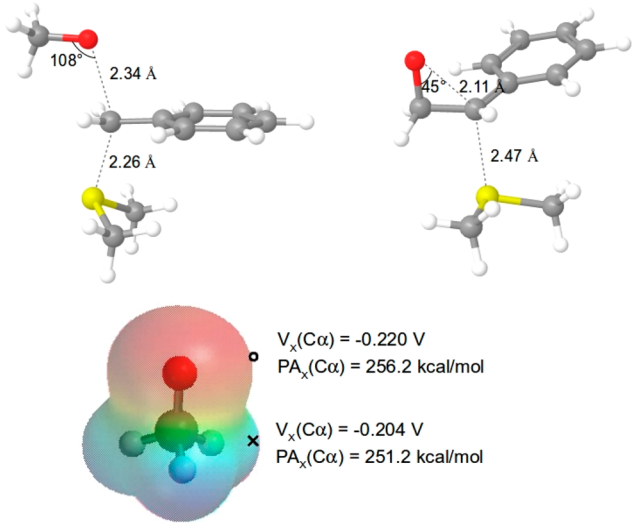



**Figure 3.** TS structure for inter(left) and intra(right)molecular $S_N2$ reactions (X = O ; R = Ph) and electrostatic potential surface of methoxide anion (o and x show the relative positioning of C$\alpha$ in the $S_N2$ transition state for inter- and intramolecular case, respectively).

dissociative character of the $S_N2$ TS in the intramolecular case, as shown by the greater increase in positive charge $\Delta Q_{CHR}$ 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]

With the sulfonamide nucleophile (X = $NSO_2Me$), EWG substituents are predicted to decrease reactivity in both the inter- and intramolecular cases (see Table 1). This could be explained



DOI: 10.1021/jacs.5b11402
J. Am. Chem. Soc. 2016, 138, 734−737

Table 3. Influence of Substitution on the Free Energy Barrier in Identity $S_N2$ Reaction of Benzylic Derivatives[a]

| | R = | *p*-MeOPh | Ph | *p*-$NO_2$Ph | PAx(Cα)[b] | $\Delta Q_{CH2R}$[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 |
| | $N(Me)SO_2Me$ | 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 |

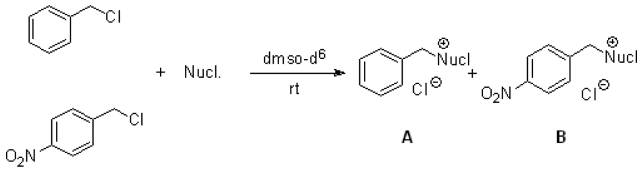
[a]Free energy barrier in kcal/mol. Nucleophiles giving rise to EWG-accelerated trend are in green and those involving the EWG-decelerated trend are in red. One has to note that for some of these reactions the $S_N1$ mechanism is probably more favored (see SI). [b]For R = Ph

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 $\Delta Q_{CHR}$ 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 $S_N2$ barrier[12] 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 $\Delta Q_{CHR}$ 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 $\Delta Q_{CHR}$ 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.

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 Cα will accelerate or decelerate reaction purely

Table 4. Competition Experiments[a]




| Nucl. | Conv. (%) | A/B Comput. | A/B Exp. |
|---|---|---|---|
| $Et_3N$ | 28 | 84/16 | 69/31 |
|  | 21 | >99/1 | 70/30 |
| MeSNa | 29 | 36/64 | 23/77 |

[a]Conversion of the more reactive chloride derivatives and A/B ratio were determined by $^1H$ NMR.

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.

In summary, we have shown that the conventional received wisdom whereby EWGs at Cα 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11402.

Details of computational methods. Cartesian coordinates and energies for all structures. Additional data on onium



DOI: 10.1021/jacs.5b11402
J. Am. Chem. Soc. 2016, 138, 734−737

salt formation reactions as well as on identity reactions. Relative energy of $S_N1$ intermediates (PDF)

## AUTHOR INFORMATION


### Corresponding Authors

*raphael.robiette@uclouvain.be
*v.aggarwal@bristol.ac.uk
*jeremy.harvey@chem.kuleuven.be


### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

Computational resources have been provided by the Université catholique de Louvain (CISM/UCL) and the Consortium des Équipements de Calcul Intensif en Fédération Wallonie Bruxelles (CÉCI) funded by the Fond de la Recherche Scientifique de Belgique (F.R.S.-FNRS) under convention 2.5020.11. R.R. is a Senior Researcher of the F.R.S.-FNRS.

## REFERENCES


(1) See for instance: (a) Streitwieser, A.; Jayasree, E. G.; Leung, S. S.-H.; Choy, G. S.-C. *J. Org. Chem.* **2005**, *70*, 8486. (b) Lee, K. S.; Adhikary, K. K.; Lee, H. W.; Lee, B.-S.; Lee, I. *Org. Biomol. Chem.* **2003**, *1*, 1989. (c) Kim, W. K.; Ryu, W. S.; Han, I.-S.; Kim, C. K.; Lee, I. *J. Phys. Org. Chem.* **1998**, *11*, 115. (d) Kost, D.; Aviram, K. *J. Am. Chem. Soc.* **1986**, *108*, 2006. (e) Bordwell, F. G.; Brannen, W. T., Jr *J. Am. Chem. Soc.* **1964**, *86*, 4645. (f) Streitwieser, A. *Chem. Rev.* **1956**, *56*, 571. (g) DeWolfe, R. H.; Young, W. G. *Chem. Rev.* **1956**, *56*, 753.

(2) Note that the influence of EDG is more controversial: Some kinetic studies indicate an activation of the reaction by EDG, whereas others suggest the opposite trend see: Streitwieser, A. *Solvolytic Displacement Reactions*; McGraw-Hill Book Co.: New York, 1962. This may be due to the $S_N2/S_N1$ borderline, which depends highly on experimental conditions.

(3) (a) Carey, F. C.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanism*; 5th ed.; Springer-Verlag, Inc.: New York, 2007. (b) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: Oxford, 2012. (c) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2007. (d) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1954.

(4) (a) Wladkowski, B. D.; Wilbur, J. L.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 2471. (b) Wladkowski, B. D.; Lim, K. F.; Allen, W. D.; Brauman, J. I. *J. Am. Chem. Soc.* **1992**, *114*, 9136.

(5) (a) Wu, C.-H.; Galabov, B.; Wu, J. I.-C.; Ilieva, S.; Schleyer, P. v. R.; Allen, W. D. *J. Am. Chem. Soc.* **2014**, *136*, 3118. (b) Galabov, B.; Ilieva, S.; Koleva, G.; Allen, W. D.; Schaefer, H. F., III; Schleyer, P. v. R. *WIREs Comput. Mol. Sci.* **2013**, *3*, 37. (c) Galabov, B.; Nikolova, V.; Wilke, J. J.; Schaefer, H. F., III; Allen, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 9887.

(6) (a) Erden, I.; Gronert, S.; Keeffe, J. R.; Ma, J.; Ocal, N.; Gärtner, C.; Soukup, L. L. *J. Org. Chem.* **2014**, *79*, 6410. (b) Ochran, R. A.; Uggerud, E. *Int. J. Mass Spectrom.* **2007**, *265*, 169. (c) Streitwieser, A.; Jayasree, E. G.; Leung, S. S. H.; Choy, G. S. C. *J. Org. Chem.* **2005**, *70*, 8486. (d) Lee, I.; Kim, C. K.; Lee, B.-S. *J. Phys. Org. Chem.* **1995**, *8*, 473.

(7) (a) Aggarwal, V. K.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105. (b) Robiette, R. *J. Org. Chem.* **2006**, *71*, 2726.

(8) As an example, computed energy barrier for cyclization to epoxide is ∼4 and 6−9 kcal/mol for R = Ph and $CONMe_2$, respectively; see ref 7a.

(9) Similar observations have also been made with ammonium ylides, see: (a) Pichler, M.; Novacek, J.; Robiette, R.; Poscher, V.; Himmelsbach, M.; Monkowius, U.; Mûller, N.; Waser, M. *Org. Biomol. Chem.* **2015**, *13*, 2092. (b) Robiette, R.; Conza, M.; Aggarwal, V. K. *Org. Biomol. Chem.* **2006**, *4*, 621.

(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 *Jaguar*, versions 6.5 and 8.5; Schrodinger, Inc.: New York, 2005 and 2014, respectively. See SI for full computational details and data.

(11) The increase in conjugative effects with electron-donating character of the $sp^2$ substituent can be observed by the variation of C$\alpha$-C$\beta$ 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, refs 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*, 4359. (b) Shaik, S. S. *Prog. Phys. Org. Chem.* **1985**, *15*, 197 and references therein.

(14) For a previous computational study predicting this influence of solvation on the substituent effects trend, see: (a) Ruff, F.; Farkas, Ö.; Kucsman, Á. *Eur. J. Org. Chem.* **2006**, *2006*, 5570. (b) Ruff, F.; Farkas, Ö. *J. Phys. Org. Chem.* **2008**, *21*, 53.

(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).




DOI: 10.1021/jacs.5b11402
*J. Am. Chem. Soc.* 2016, 138, 734−737