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Nucleofugality in Oxygen and Nitrogen Derived Pseudohalides in Menshutkin Reactions: The Importance of the Intrinsic Barrier*

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Abstract: In order to study the nucleofugality of polyatomic anionic leaving groups derived from oxygen and nitrogen, a contingent of 19 methylating agents consisting of amines or alcohols activated with carbonyl or sulfonyl substituents has been examined via ab initio calculations. We have calculated gas phase activation energies for alkylation of ammonia, and methyl cation affinities. We find that polyatomic anionic leaving groups derived from nitrogen will have higher activation energies for Menshutkin (S_N2) alkylation even when they have similar methyl cation affinities. This inherent deficit in the nucleofugality of nitrogen-derived leaving groups appears to be a result of the way bond cleavage is synchronized with bond formation to the incoming ammonia nucleophile. The nitrogen leaving groups showed greater dissociation from the methyl fragment than oxygen leaving groups relative to the length of the forming carbon-nitrogen bond. Additionally the second sulfonyl group present in a sulfonimide appears to be less effective at activating nitrogen due to a preference for tetrahedral geometries at

* We dedicate this work to the memory of Gregory L. Baker, who was a mentor, colleague and friend.

the departing nitrogen in the transition states involving leaving sulfonamide groups. Optimal delocalization of electron density is therefore frustrated due to the geometry of the leaving group.

Introduction

Nucleofugality, or leaving group ability, is a fundamental concept of organic chemistry, and plays a key role in a broad array of chemical reactions. Despite its centrality to reactions such as E1, E2, S_N1 and S_N2, that feature a leaving group (nucleofuge) departure in the rate limiting step, nucleofugality was sparsely studied until fairly recently.[1] The last decade, however, has seen several attempts to develop an absolute scale of nucleofugality.[2,3,4,5] These began with the work of Ayers et al. who attempted to use a truncated Taylor series to model the electronic energy of a leaving group as a function of increasing charge. In that expression the first order term is μ, the electronic chemical potential (which can be expressed as [I+A]/2) and the second order term is η, or chemical hardness (expressed as 2[I-A]).[2] Using this construction they argued that electrophilicity ω, could be defined as

$$\omega = \frac{\mu^2}{2\eta} = \frac{(I+A)^2}{8(I-A)} \quad (1)$$

Where *I* is the ionization potential and *A* is electron affinity; thus this formulation approximates continuous derivatives of energy with respect to charge based on quantities that represent a change in energy with the gain or loss of a full electron.[3] Electrophilicity in this sense is described as "the energy [of] stabilization resulting from the presence of a perfect

electron donor".[2] In an attempt to correct for partial charge already present in a leaving group prior to leaving, they derived a related quantity $\Delta E_{\text{nucleofuge}}$ which is defined such that

$$\Delta E_{\text{nucleofuge}} = \frac{(\mu+\eta)^2}{2\eta} = \frac{(I-3A)^2}{8(I-A)} \quad (2)$$

Because $\Delta E_{\text{nucleofuge}}$ is derived solely from the ionization potential and electron affinity, this quantity is relatively easy to calculate, and several groups have followed up by conducting DFT studies wherein attempts were made to apply or refine this scale.[3,4] Most notably, Geerlings et al. modified the theory to include solvent effects, and applied the resulting formalism to an extended set of leaving groups.[3]

Mayr et al., have taken a different approach, utilizing an empirical scale parameterized with rate constants for the solvolysis of benzhydryl derivatives.[5] The benzhydryl group has the advantage of being tunable via addition of electron donating and withdrawing groups on the aryl rings, such that leaving groups whose solvolysis rate constant is too fast or slow for study on one scaffold can be measured on another.[5] The group focused on sulfonate, carboxylate and halide leaving groups in this analysis, and claims to have found a scale that is useful for rates spanning 12 orders of magnitude.[5]

Another notable contribution to the field has been made by Contreras et al. who have used DFT to calculate group electrophilicity (eq. 1) and electrofugality, and are actively working on the derivation a set of related –philicity and –fugality concepts and their relationships as quantities.[4,6,7,8,9,10] This set of works includes among other things an attempt to apply a nucleofugality index to α-eliminations,[9] and an attempt to extend the concept to homolytic abstraction reactions by deriving a related index, "homofugality".[8]

A rarity in the recent literature on nucleofugality is the amine-derived anionic leaving group.[2-5] While sulfonates and carboxylic acid esters are relatively common, carboxamides, azides, nitrites and thiocyanates are relatively uncommon inclusions,[11,12] and sulfonamides, carboximides and sulfonimides have to the best of our knowledge been absent from any study of nucleofugality to date.

Attempts to activate amines for substitution and elimination by addition of activating carbonyl or sulfonyl groups do exist in the literature, however, and date back to the 1960s. Based on its low pK_a of 1.6,[13] initial work explored derivatives of saccharine.[14] Unfortunately these were found to undergo preferential attack at the carbonyl carbon; however, the authors discovered that bis(sulfonyl)imides (e.g. ditosylamines) could undergo substitution and elimination.[14] The most common activation in this vein appears to be through the addition of dual triflyl groups to form bis(trifluoromethanesulfonyl)imide derivatives.[15,16,17] This strategy for activation is becoming more common in part because the bis(trifluoromethanesulfonyl)imide (TFSI) anion is an attractive component in certain types of ionic liquids.[18] Metal salts and ionic liquids derived from TFSI have attracted a great deal of attention from scientists researching transport materials for lithium ion batteries. TFSI is generally considered to be a poorly associating ion; it is also thought to plasticize polymeric lithium ion conductors, leading to a lower glass transition temperature in the polymer, and hence better conductivity than other anions of similar lithium ion affinities.[18,19]

Despite this trend, the activation of nitrogen as a nucleofuge remains a rare strategy. While various researchers have pointed out the viability of alkyl TFSI derivatives for the synthesis of ionic liquids,[16,17] TFSI containing liquids are more commonly accessed by the general synthetic method used for ionic liquids:[20] an onium halide salt is first formed by reaction

of an alkyl halide with an amine; it is then subjected to ion exchange metathesis by treatment with silver TFSI.[20]

We elected to study the nucleofugality of polyatomic anionic oxygen and nitrogen derived leaving groups by modeling the Menshutkin reaction, in which ammonia displaces a leaving group via an S_N2 mechanism. The S_N2 reaction is itself much better studied than nucleofugality as a general concept; theoretical studies exist for both ionic and Menshutkin-type S_N2 reactions, including solvent effects,[21,22] S_N2 reactions at neutral nitrogen,[23,24] comparisons of front side vs. back side S_N2,[25,26] studies employing valence bond methods,[27] analyses of Marcus theory using S_N2 as a model,[28] and analyses of the influences of periodicity on the anionic S_N2 reaction.[52,53] Additionally, the formation of quaternary amine mesylates via the Menshutkin reaction has been modeled using DFT methods.[29] Although we are unaware of any recent reviews of theoretical work on the S_N2 reaction, a contribution from Laerdahl and Uggerud provides a good perspective on the state of the field as of twelve years ago, including discussion on experimental mechanistic work, and reaction dynamics.[30] Surprisingly there seem to be no studies that systematically analyze and compare the reactivities of nitrogen and oxygen derived polyatomic anionic leaving groups as a class.

Reservations have previously been expressed about using S_N2 reactions as a probe of nucleofugality.[1] In particular Stirling argues in his 1978 account that S_N2 and E2 reactions are tainted by the involvement of a nucleophile or base in the rate limiting step of the reaction.[1] While it is true that the nucleophile is an integral part of an S_N2 reaction, the present work controls for this issue by using the same nucleophile throughout the study. Moreover, studies of bimolecular reactions are necessary to understand the role of nucleofugality in mechanisms that feature electronic reorganization concurrent with leaving group departure.

Computational Methods

All calculations were performed using GAMESS versions 12 R3 (2009) and 1 R1 (2012).[31] Calculations were run on a personal laptop, the MSU chemistry department hydra cluster, or the MSU High Performance Computing Cluster (HPCC) depending on the demands of the job.

Activation energies were calculated by finding minima for association complexes of ammonia and each respective alkylating agent shown in scheme 1, then by locating transition states for the S_N2 reaction. $\Delta E^{\ddagger}$ was considered to be the difference in these two energies. $\Delta E_{complex}$ is the difference in energy between the association complex and the sum of ammonia and the alkylating agent being studied. Association complexes and transition state structures were first located at the HF/3-21G level of theory, and in cases where the conformational space allowed multiple minima or transition state structures, the lowest energy of these were selected. Additional geometric optimizations were run at HF/6-31G(d), and MP2(full)/6-31G(d). In all cases vibrational analyses were run at HF/6-31G(d) on the HF/6-31G(d) geometries in order to confirm that minima and transition states had zero and one imaginary vibrations respectively. All calculations were initially run with C_1 symmetry. After optimization, structures were found which converged to C_1, C_s, C_2, C_{2v} and C_{3v} symmetries. Structures which appeared to converge out of C_1 symmetry were rerun at MP2(full)/6-31G(d) using the new point group. Coordinates for stationary points and their corresponding Abelian point groups are listed for all structures in the supporting information.

In order to get relatively accurate energies economically, we chose to simplify the G3(MP2) method of Pople et al.[32] The G3(MP2, CCSD(T)), or G3(MP2, CCSD) as it is also

known, is the variant of G3(MP2) implemented in GAMESS.[33] The difference between the two is that QCISD(T) calculations are not available in GAMESS, and therefore have been replaced by CCSD(T) calculations as shown in equation 3.

$$E_0[\text{G3(MP2, CCSD(T))}] = E[\text{CCSD(T)/6-31G(d)//MP2(full)/6-31G(d)}] + E[\text{MP2(FC)/G3large//MP2(full)/6-31G(d)}] - E[\text{MP2(FC)/6-31G(d)//MP2(full)/6-31G(d)}] + \text{ZPE} + \text{HLC} \quad (3)$$

Here HLC is a higher level correction and ZPE is the zero point energy at the HF/6-31G(d) level of theory scaled by an empirical factor of 0.8929.[32,33] We modified this method by omitting the CCSD(T)/6-31G(d) calculation and the higher level correction. For brevity we will refer to this as an "MP2/G3large" calculation; it is defined below in equation 4.

$$E_0[\text{MP2/G3large}] = E[\text{MP2(FC)/G3large//MP2(full)/6-31G(d)}] + \text{ZPE} \quad (4)$$

The quantities described as "ΔE" in this paper are ΔE_0[MP2/G3large] energies unless otherwise indicated. $\Delta H^{\ddagger}$ was also calculated for all activation energies by applying thermal corrections from the HF/6-31G(d) vibrational analyses which were calculated at 298K.

MP2/G3large calculations of activation energies showed good agreement with the G3(MP2, CCSD(T)) values in sulfonates (Supporting information). A second set of calculations at the CCSD(T)/6-31+G(2d,p)//MP2(full)/6-31G(d) level suggested that MP2/G3large might systematically overestimate barriers, unfortunately this higher level of theory was not a feasible basis for the study overall. MP2/G3large calculations had mean average deviations (MAD) from experimental methyl cation affinity data similar to G3 and W1 calculations performed by Zipse et al. (Table 2).[34] It is often considered important to include diffuse functions in quantum chemical descriptions of ions and structures with partial bonding. This concern has been studied

in the case of S_N2 reactions with ionic nucleophiles.[35] Boyd et al. found that S_N2 transition states had different geometries when calculations were done with and without diffuse functions, but that the differences in energy between these geometries were negligible in single point calculations including diffuse functions.[35] Taken together these data lead us to conclude that the MP2/G3large calculation is adequate for our analysis in this paper.

All graphical representations of wavefunctions or geometries shown in this paper were generated using MacMolplot V 7.4.3.[36]

Results and Discussion

Energies Associated with Nucleofugality, and their Trends

Gas phase activation energies ($\Delta E^{\ddagger}$ and $\Delta H^{\ddagger}_{298K}$) were calculated at the MP2/G3large level of theory for all alkylating agents found in Scheme 1. These energies are defined in Scheme 2. The alkylating agents studied consisted of 20 methylating agents, including a contingent of sulfonamides, sulfonimides, sulfonates, carboxylate esters, carboxamides, and one carboximide. Additionally, two of the alkylating agents studied were five membered rings which would be opened by the attack of nitrogen; these were 1,3-propanesultone, and N-triflyl-1,3-propanesultam (TPS). The methyl halides[†] were run as convenient reference points because of their familiarity,

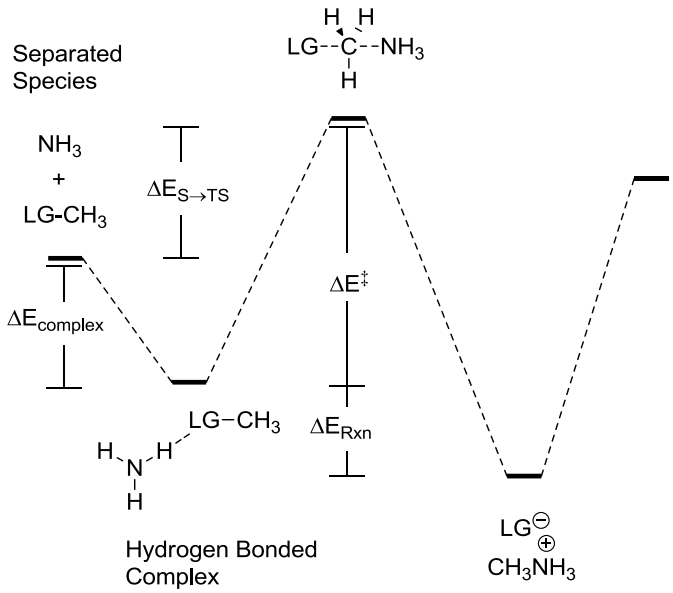
[†] The transition state of methyl fluoride was found to converge to a distorted C_s saddle point at HF/6-31G(d) and MP2(full)/6-31G(d) which featured a strong bend in the N-C-F angle of 164°. At MP2(full)/6-31+G(d) a linear C_{3v} stationary point was found which was ~0.5 kcal/mol lower in energy than the bent structure at this level of theory (data not shown). Less pronounced bends were found in the nitrogen leaving groups, as expected based on their strong internal dipoles. Linear saddle points could not be located for the nitrogen leaving groups when we checked. The $\Delta E^{\ddagger}$ values for methyl fluoride also varied significantly between levels of theory. Our results for this structure should be interpreted with caution as it appears to represent a pathological case.

but methyl iodide was omitted due to our computational method due to a need to account for relativistic effects, which are not present in our calculations, and the fact that the G3large basis set is not available for iodine.

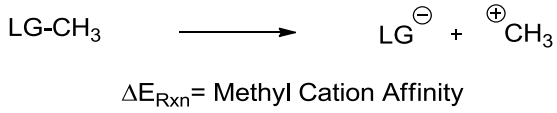
The results of these calculations are displayed in order of $\Delta E^{\ddagger}$ magnitude in figure 1. It was found that most methylating agents had comparable $\Delta E_{complex}$ energies, which were on the order of 4 – 6 kcal/mol. Carboxamides proved to be an outlier, as they contained a hydrogen bond from the ammonia lone pair to the amide proton, instead of an ammonia proton to oxygen bond. However, the $\Delta E_{complex}$ should not be relevant to analyses of nucleofugality, and therefore was subtracted out of the activation energy, so that the "activation energy" presented, $\Delta E_{S\rightarrow TS}$, represents the energy difference between the separated species and the transition state of interest. Geometrical parameters of interest from the transition states were tabulated, and can be found in table 1.

Methyl cation affinity is defined as the sum of the energies of a leaving group anion and a methyl cation, less the energy of the parent methylating agent (scheme 2).[34] Methyl cation affinities appear in table 2, along with a set of experimental and calculated values which appear in the work of Zipse et al. for comparison.[34]

A)



B)



ΔE_{Rxn}= Methyl Cation Affinity

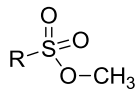
Scheme 2 – Relevant energies are derived from electronic structures calculated along the reaction coordinate of an S_N2 reaction (A) The difference in energy between a methylating agent in its bound state, and the sum of the separated ions after heterolytic cleavage is defined as the methyl cation affinity (MCA) (B)

Because the energy of a methyl cation is invariant between methylating species, the methyl cation affinity should depend straightforwardly on the energy of the leaving group anion relative to its methylated counterpart. Methyl cation affinity should therefore give the contribution to ΔE_{rxn} arising directly from anion stability, where methylating agents with lower methyl cation affinities arise from more stable anions. This quantity should also give a trend analogous to $\Delta E_{nucleofuge}$, of Ayers et al. as it shows the change in energy resulting from the

leaving event, and can be thought of as the activation energy for the corresponding gas phase S_N1 reaction.

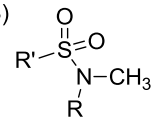
The $\Delta E_{S\rightarrow TS}$ values for nitrogen and oxygen derived leaving groups follow an intuitive pattern. Sulfonates have the lowest average $\Delta E_{S\rightarrow TS}$ (25.8 kcal/mol), followed by sulfonimides (30.3 kcal/mol) followed by esters (38.7 kcal/mol), followed by sulfonamides (50.3 kcal/mol) followed by amides (58.4 kcal/mol). Nothing in this series challenges conventional thinking, but a few interesting observations can be made. The first of these is simply that while excellent leaving groups can be obtained by adding sulfonyl groups to alcohols, those obtained from the less electronegative amines are significantly and uniformly less reactive, even though a second sulfonyl group may be added to the amine. On average the difference in $\Delta E^{\ddagger}$ between a sulfonate and its sulfonimide analogue (for instance methyl mesylate and methyl MSI) was 4.5 kcal/mol.

A)



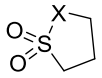
R	Name	[abbreviation]
CH_3	Methylmethyanesulfonate	[Methyl Mesylate]
OCH_3	Dimethylsulfate	-
F	Methylfluorosulfonate	-
CF_3	Methyltrifluoromethanesulfonate	[Methyl Triflate]

B)



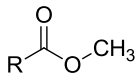
R	R'	Name	[abbreviation]
SO_2CH_3	CH_3,	Methyl bis(methylsulfonylimide)	[MethylMSI]
SO_2F	F,	Methyl bis(fluorosulfonylimide)	[MethylFSI]
SO_2CF_3	CF_3,	Methyl bis(trifluoromethanesulfonylimide)	[MethylTFSI]
H	CH_3	Methylmethanesulfonamide	[MethylMSA]
H	F	Methylfluorosulfonamide	[MethylFSA]
$(CH_3)_2CH$	F	Methylisopropylfluorosulfonamide	[MeIprFSA]

C)



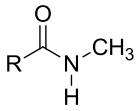
X	Name	[abbreviation]
O	1,3-propanesultone	-
NSO_2CF_3	N-triflyl-1,3-propanesultam	[TPS]

E)



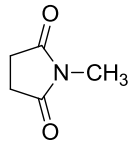
R	Name
CH_3	Methyl Acetate
OCH_3	Dimethylcarbonate
CN	Methylcyanoformate
CF_3	Methyltrifluoroacetate

F)



R	Name
CH_3	Methyl Acetamide
OCH_3	Dimethylurethane
CN	Methylcyanoformamide
CF_3	Methyltrifluoroacetamide

G)



Methylsuccinimide

H)

X-CH_3	
F	Methyl Fluoride
Cl	Methyl Chloride
Br	Methyl Bromide

Scheme 1 – Alkylating agents and the names they are referred to by in this study.

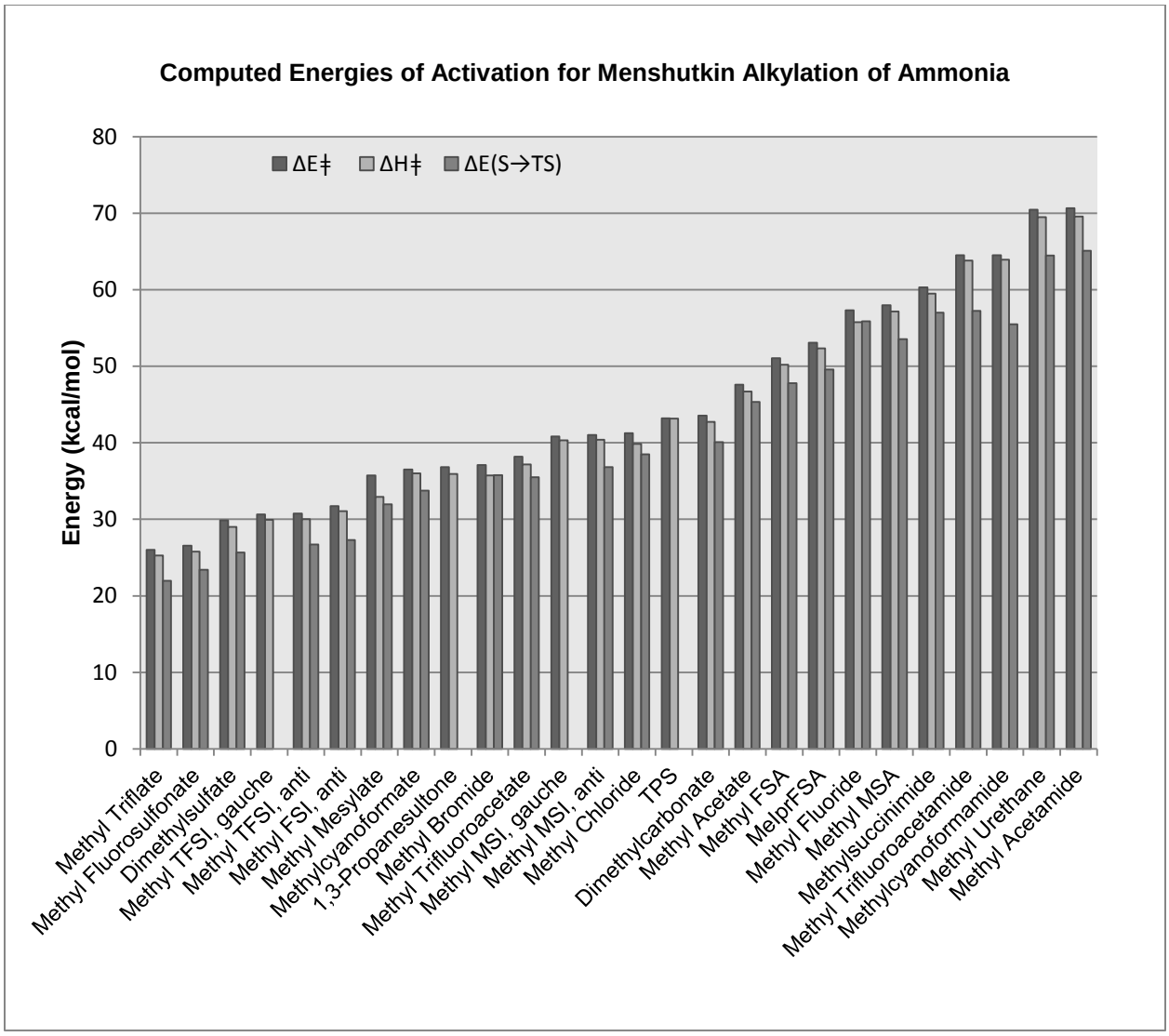


Fig. 1 - Computed Barrier Heights from the MP2/G3large level of theory. Thermal corrections for the ΔH values were computed at 298K. The reader is referred to Scheme 2 for definitions of the energies tabulated.

Table 1 – Calculated $\Delta E_{S\rightarrow TS}$ values and Relevant Transition State Geometries

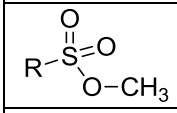
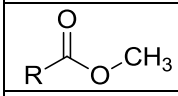
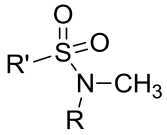
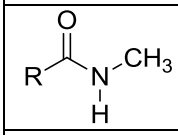
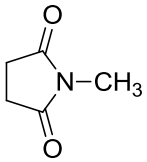
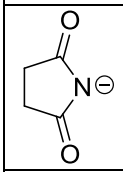
	r_{TS}(N-C) Å	r_{TS}(C-X) Å	r_0(C-X) Å	$\Delta E_{S\rightarrow TS}$ kcal/mol	% C-X elongation
					
R= CH_3	1.907	2.000	1.451	31.9	38
R= OCH_3	1.926	1.963	1.454	25.7	35
R= CF_3	1.962	1.940	1.459	22.0	33
R= F	1.951	1.944	1.457	23.4	33
					
R= CH_3	1.798	2.088	1.439	45.3	45
R= CF_3	1.858	2.028	1.446	35.5	40
R=OCH_3	1.836	2.040	1.440	40.1	42
R=CN	1.873	2.016	1.448	33.8	39
					
R'= CF_3 R= SO_2CF_3	1.960	2.004	1.484	26.7	35
R'= CH_3 R=SO_2CH_3	1.899	2.050	1.475	36.8	39
R'= F R=SO_2F	1.964	1.995	1.480	27.3	35
R'= CH_3 R= H	1.805	2.178	1.459	53.5	49
R'= F R= H	1.840	2.121	1.467	47.8	45
R'= F R= $CH(CH_3)_2$	1.818	2.135	1.471	49.6	45
					
R=CH_3	1.771	2.199	1.448	65.1	52
R=CF_3	1.809	2.154	1.475	57.2	46
R=OCH_3	1.771	2.185	1.448	64.5	51
R=CN	1.816	2.146	1.453	55.5	48
					
Methylsuccinimide	1.779	2.158	1.449	57.0	49

Table 2 – Methyl Cation Affinity in Experiment and Theory. All values are in kcal/mol.

Methyl Cation affinity (Kcal/mol)	MP2/G3large	Experiment[34]	G3[34]	W1[34]
Cl (-)	225.3	228	226.6	227.0
Br (-)	218.0			
CH_3SO_3(-)	209.1			
CH_3OSO_3(-)	201.2			
FSO_3(-)	193.2			
CF_3SO_3(-)	190.5			
CH_3CO_2(-)	238.2			
CF_3CO_2(-)	215.8			
CH_3OCO_2(-)	227.7			
$NCCO_2$(-)	210.1			
$CH_3C(O)NH$(-)	262.4			
$CF_3C(O)NH$(-)	234.8			
$CH_3OC(O)NH$(-)	258.5			
NCC(O)NH(-)	238.1			
$(CH_3SO_2)_2N$(-)	218.2			
$(CF_3SO_2)_2N$(-)	192.8			
$(FSO_2)_2N$(-)	191.6			
CH_3SO_2NH(-)	240.3			
FSO_2NH(-)	227.0			
$CH_3SO_2NCH(CH_3)_2$(-)	230.6			
	243.7			
F(-)	258.1	258.1	258.0	258.8
OH (-)	276.0	277	276.9	276.8
SH (-)	246.3	246.9	246.6	247.8
PH_2 (-)	268.6	266.7	268.0	269.5
NH_3	104.6	105	104.8	105.4
H_2O	65.4	66.7	66.0	66.5
Mean Absolute Deviation	1.13		0.66	0.89

It is well known that alkylating agents can be activated by factors such as ring strain and inductive effects, and our series was designed to assess these effects on the barrier height to alkylation. The most familiar activated sulfonates are activated with fluorine, and this is for good reason; the replacement of a methyl group with a trifluoromethyl lowers the barrier by 10 kcal/mol between methyl mesylate and methyl triflate, and 10 kcal/mol between methyl MSI and methyl TFSI. Perhaps the most interesting illustration of the activating power of fluorine is seen in the amides, where trifluoroacetamide has a barrier 7.9 kcal/mol lower than acetamide, while succinimide with an extra carboxyl group is a roughly equivalent 8.1 kcal/mol lower. Halogens are often considered to be π electron donating, but the differences we find on barrier height between a fluorine and a trifluoromethyl group are modest. Oxygen can also act as an electron withdrawing group by way of the inductive effect so it is unsurprising that we find the barrier for dimethylsulfate 5.9 kcal/mol lower than the barrier for methyl mesylate. The effect of ring strain on alkylation is more difficult to assess in our series, as changing the substitution from methyl to primary alkyl is known to increase the barrier to alkylation for S_N2 reactions. It has been recently proposed that this effect is due to weakening of the electrostatic interactions between the alkyl chain and the incoming nucleophile, although steric repulsion remains a popular explanation among organic chemists.[37] Calculations done at the B3LYP/6-31G(d) level of theory estimate the ring strain in 1,3-propanesultone to be 10 kcal/mol, and 9.0 kcal/mol in TPS (see supporting information for more details). While these species are not used for further analysis, we can conclude that the activation of a 5-membered ring for sulfonates and sulfonimides is not enough to counteract the transition from methyl to primary alkyl.

Conformations in the sulfonates are degenerate with regard to an S-C bond rotation, however N-S bond rotations of sulfonimides are capable of producing *anti*, *gauche* and *syn*

rotamers with bond rotation. Methyl TFSI and methyl MSI were found to have minima in the *anti* and *gauche* geometries, and transition states were found corresponding to these minima. Methyl FSI did not appear to have a *gauche* minimum, but instead converged toward an eclipsed relationship between the two fluorine substituents. This geometry was discarded, and only the *anti* geometry was used for FSI in this study. *Gauche* MSI, and TFSI were found to have $\Delta E^{\ddagger}$ values very close in energy to their corresponding *anti* geometries, but the *anti*-conformers (lowest minima) were found to lie ~2 kcal/mol and ~6 kcal/mol lower in energy in TFSI and MSI respectively.

In order to assess the degree to which the Hammond postulate is obeyed by these Menshutkin reactions we have taken an approach similar to that used by Schlegel et al. for ionic S_N2.[38,39] These authors defined a % bond elongation (%BE) formula for a similar analysis of the geometries of S_N2 transition states.[39] We use this formula in our analysis as it is given in equation 5.

$$\%BE = 100[\, r_{TS}(C\text{-}X) - r_0(C\text{-}X)]/r_0(C\text{-}X) \qquad (5)$$

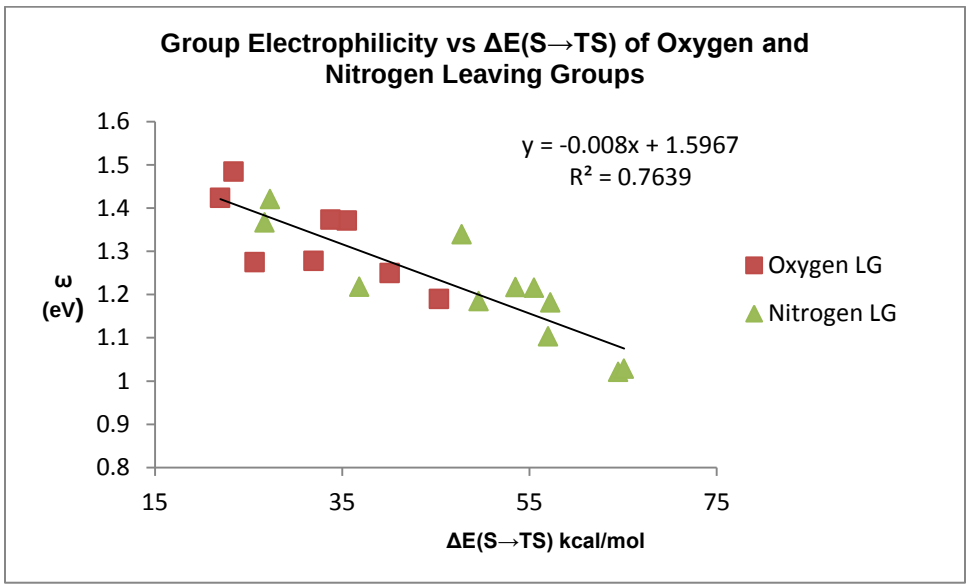
Where %BE is percent bond elongation, $r_{TS}(C\text{-}X)$ is the transition state C-X bond length, and $r_0(C\text{-}X)$ is the C-X bond length in the isolated species.

We found the correlation between %BE of the transition state and the methyl cation affinity to be strong (R^2=0.9646, fig. 3B). Schlegel et al. reported that barriers correlate strongly with transition state geometry in the ionic S_N2 reaction with simple leaving groups derived from a variety of elements including H, N, C and O.[39] The dependence of $\Delta E_{S\rightarrow TS}$ on %BE in our own work is even stronger than the correlation with methyl cation affinity (R^2=0.9813, fig. 3A). With

respect to these dependencies, the full set of nitrogen and oxygen derived leaving groups behave as a single set.

While a faithful comparison to recent work on the nucleofugality indices of Ayers and Geerlings et al. would require an additional set of calculations, we favored decided to emply the approach of Perez et al. and Contreras et al. who employ group electrophilicity, ω (as defined in eq. 1) as an index for rating the nucleofugality of methylating agents.[6-10,40] These authors estimated electronic chemical potential, μ, and chemical hardness, η, from the frontier molecular orbitals of DFT calculations such that $\mu \approx (E_{HOMO}+E_{LUMO})/2$ and $\eta \approx E_{LUMO}-E_{HOMO}$.[40] While energies of virtual orbitals in computations are often problematic, and typically better results are obtained using specialized methods[41] this scheme gives us a means of semi-quantitatively comparing an index to our computational results. To this end we calculated values of ω using our MP2/G3large//MP2(full)/6-31G(d) wavefunctions.

A)



B)

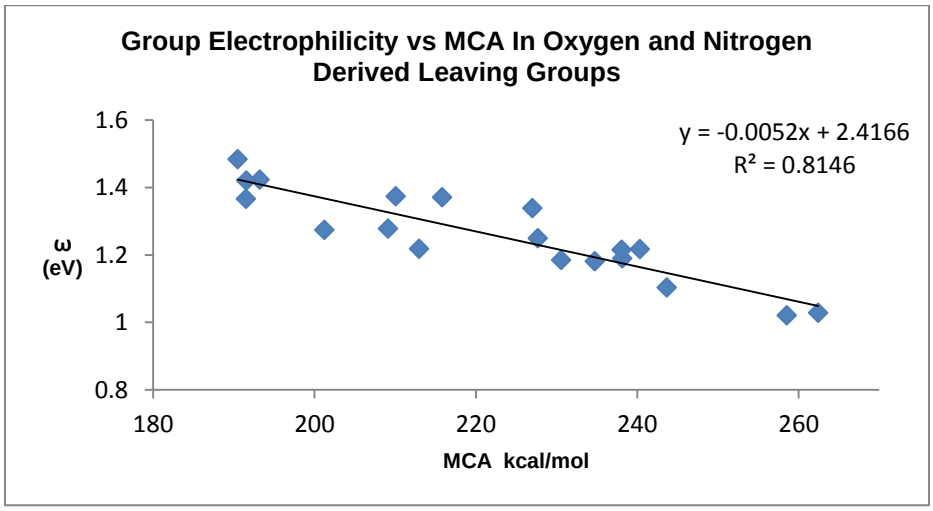


Fig. 2 – A comparison between $\Delta E_{S\rightarrow TS}$ (A) MCA (B) and group electrophilicity, computed by analogy to Perez et al. and Contreras et al. Halogens are omitted from this comparison, however their presence weakens the correlations considerably.

Results for our analysis in the spirit of Perez et al. are shown in figure 2. We found that when the halogens were added to the analysis they were extreme outliers that effectively nullified the correlation. Whether this is due to a deficiency in the calculation or is simply a limitation of group electrophilicity is unknown. We have omitted the halogens, however, in order to clearly show trends that occur within oxygen and nitrogen derived leaving groups.

We find that both MCA and $\Delta E_{S\rightarrow TS}$ correlate with ω, but neither correlation is particularly strong. This may be partly due to faulty energies for LUMOs used in the calculation. It is worth noting, however, that the correlation between ω and MCA is stronger than the correlation with $\Delta E_{S\rightarrow TS}$, which is expected. The relationship between MCA and $\Delta E_{S\rightarrow TS}$ in oxygen and nitrogen derived polyatomic anionic nucleofuges is the crux of this paper, and will be explored at length in the next section.

On the Fitness of MCA to Describe Nucleofugality

Perhaps the most unexpected and important finding presented here is the quantitatively different relationship between the $\Delta E_{S\rightarrow TS}$ and methyl cation affinity between oxygen and nitrogen derived leaving groups. As shown in figure 3, these quantities are strongly correlated within each class of leaving group, but they resolve into distinct groups; with two lines appearing when these energies share the same plot. This discrepancy suggests that there are differences in $\Delta E_{S\rightarrow TS}$ that derive solely from the electronic structure of the transition states, which are not captured simply by the differences in energy between methyl bonded and ionized leaving groups. In order to better understand this, analysis was extended to the transition state geometry.

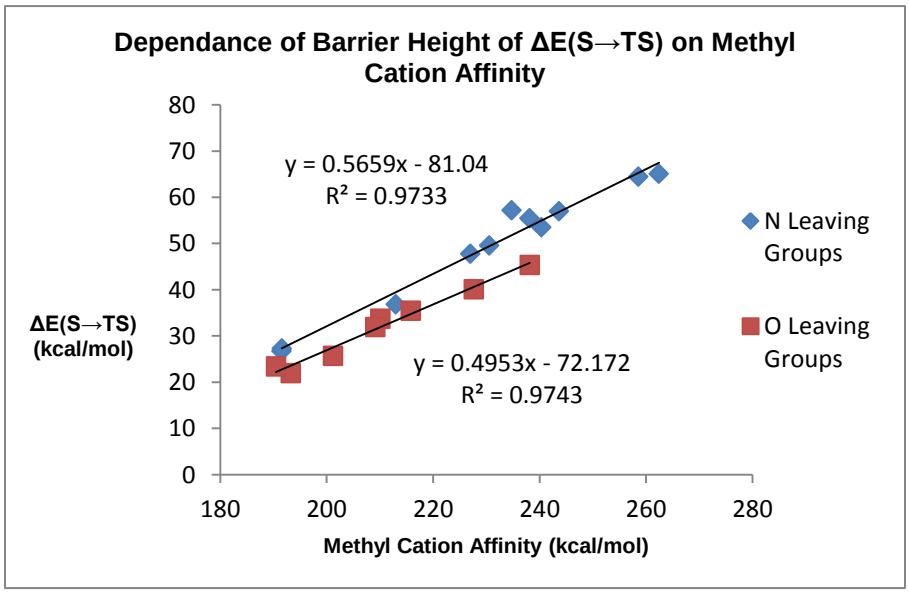
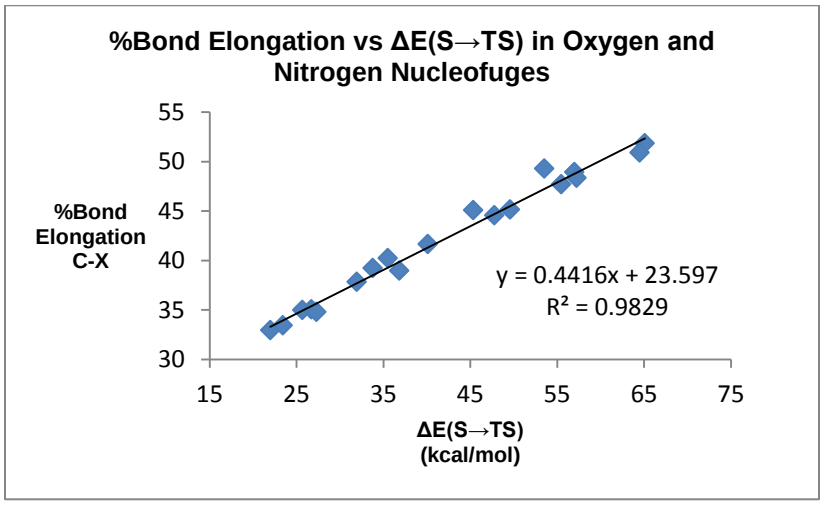


Fig. 3 – Barrier heights are very well predicted by methyl cation affinities within subsets derived from oxygen and nitrogen, but less so in the full set. Nitrogen leaving groups universally have higher barriers at a given value of MCA

A)



B)

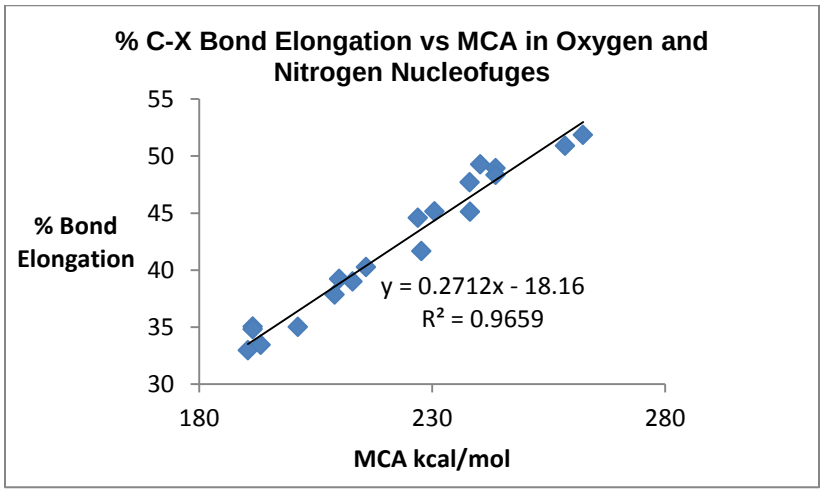


Fig. 4 – $\Delta E_{S\rightarrow TS}$ correlates very strongly to methyl leaving group bond length, as a percentage of its value in the parent methylating agent at its ground state (A) This is also true for the MCA (B) which shows that our simulated reactions obey the Hammond postulate.

While MCA and $\Delta E_{S\rightarrow TS}$ both correlate well with %BE (fig. 4), in the transition states with nitrogen derived leaving groups the elongation of the C-X bond is more pronounced relative

to shortening of the nascent C-N bond than it was in the oxygen derived leaving groups (fig. 6). This effect is especially noticeable when the bond lengths are compared directly (fig. 6A) but it remains significant even when the C-N and C-O bonds are normalized via %BE to the lengths of those found in their parent electrophiles (fig. 6B). With nitrogen derived leaving groups, compared to oxygen, the dissociation process of the S_N2 is ahead of the displacement process.

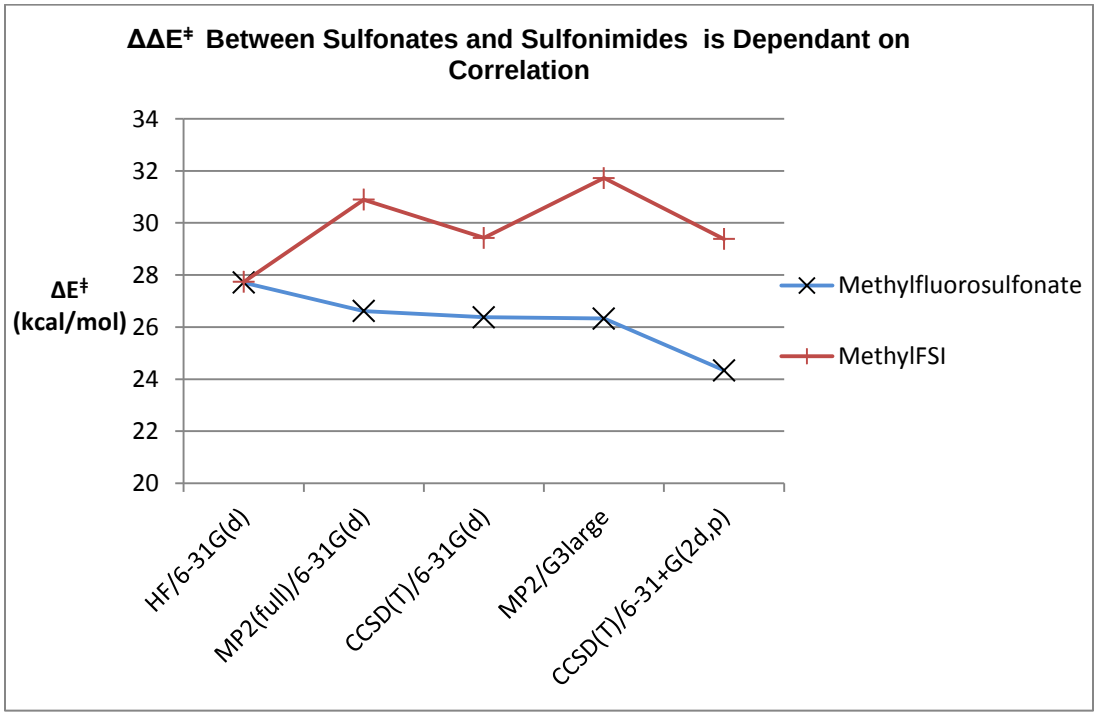
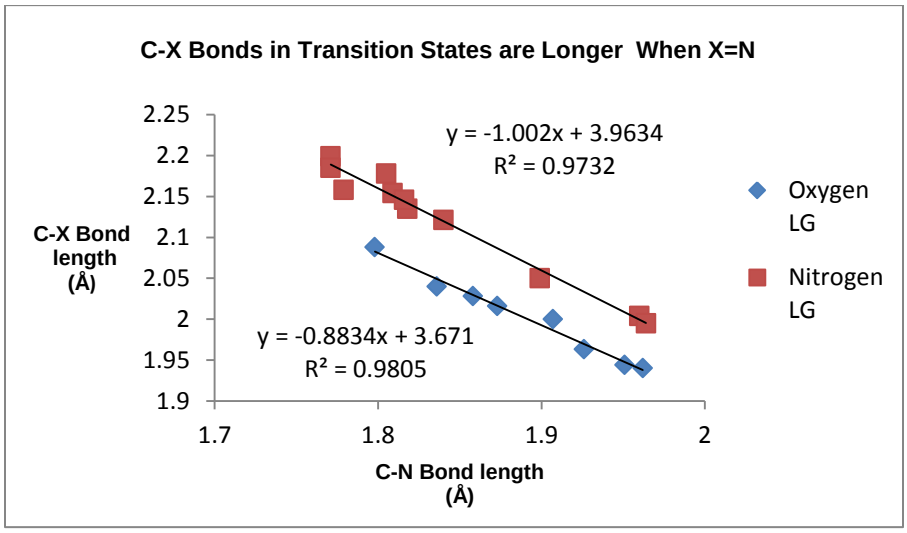


Fig. 5- At HF/6-31G(d) Methyl FSI and Methylfluorosulfonate have the same activation energy. When the wave function is correlated FSI is found to have a higher activation energy by several kcal/mol. Additional MP2 and CCSD(T) calculations at the MP2(full)/6-31G(d) geometry confirm this trend. Of the leaving groups calculated, only the sulfonimides show a higher activation energy at MP2(full)/6-31G(d) than HF/6-31G(d).

According to the principle of nonperfect synchronization proposed by Bernasconi, a reaction containing two or more fundamental processes will have a higher inherent barrier if these processes are poorly synchronized than if they are concurrent.[42,43] This clearly describes the difference between the transition states of nitrogen and oxygen leaving groups seen in this

work; however, why this difference would lead to systematically higher $\Delta E_{S\rightarrow TS}$ is difficult to understand. A strong correlation was not observed between the $\Delta E_{S\rightarrow TS}$ and the order of either of the partial bonds found at the transition state. A classic case of nonperfect synchronization cited by Bernasconi is the late development of resonance stabilization in the deprotonation of carbon acids.[42] An analogy could be drawn between that and the stabilization of the charge on the leaving group. However, we found no indication that the charge is distributed significantly differently between the transition states and the corresponding anions of our methylating agents.

A)



B)

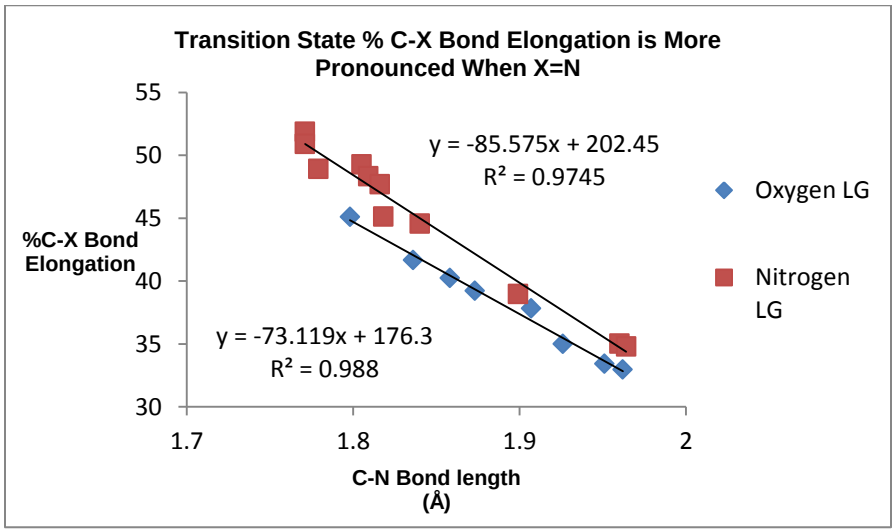


Fig. 6- Nitrogen leaving groups exhibit more extensive C-X bond elongation in their transition states than do oxygen groups. This is very apparent when raw bond lengths are compared (A) But this trend holds up even when %C-X elongation is used to correct for the longer C-N bonds present in the parent alkylating agents (B).

A reasonably strong correlation does exist between the natural charge on the leaving group atom at the transition state, and the $\Delta E_{S\rightarrow TS}$ (supporting information). The effect of the nonperfect synchronization in the nitrogen cases could be explained based on this fact, as the nitrogen groups tended to have stronger charges which were more localized on the nitrogen atom. It seems likely that the gap in barriers is explained generally by the fact that the C-N bond had to move further, ionizing almost completely, with less involvement of the nucleophile. Distortions from linearity were observed in the transition states of the nitrogen derived groups which could be explained by this notion. Whereas oxygen derived groups departed along nearly linear paths, nitrogen derived groups exhibited N-C-X angles which ranged down to ~173° and correlated moderately well with %BE (supporting information). Additionally, carboxamides and imides formed hydrogen bonds between the carbonyl oxygen and the in-plane hydrogen of the

departing methyl fragment. These hydrogen bonds, which appeared to oppose the forward path of the reaction, were not observed in the transition states of esters.

Additional support for rationalizing these results can be found in the work of Shaik et al. who have developed models for understanding kinetic barriers using concepts from valence bond (VB) theory.[44,45] The central theme of their work is the view of a transition state as an avoided crossing between the ground states and high energy vertically excited states.[44] Ionic character may play a role in one or both of these representations.[44] A correlation diagram can be constructed including the reactant and product complexes in which lines are drawn from the high energy VB states to the product ground states (and vice versa) and the center point is defined as the crossing.[44] The activation energy can then be given as $\Delta E^{\ddagger} = \Delta E_c - B$ where ΔE_c is the energy at the crossing, and B is "quantum mechanical resonance energy" which results from mixing between different valence bond representations of the transition state.[44,45] Factors influencing B were studied for S_N2 transition states including $H_3(-)$ and $CH_5(-)$ and in both cases it was found that B was at its highest (i.e. lowest activation energy) when the angle corresponding to the reaction coordinate was 180°, and decreased with as the angle became more accute.[45] Additionally B decreases when the bond lengths of the forming and breaking bond increase.[45] Both effects were attributed to a destabilizing increase in the amount of ionic character present in the transition state.[45] These findings seem consistent with our own observations, and might imply a causal relationship between the relatively loose and bent transition states of nitrogen centered nucleofuges, and their higher barriers.

A separate phenomenon is evident in the difference between sulfonates and sulfonimides. Two of the three sulfonimides (methyl TFSI and methyl FSI) had comparable barriers to their sulfonate analogues at the HF/6-31G(d) level of theory; the $\Delta E^{\ddagger}$ values of

methylfluorosulfonate and methyl FSI differed by only 0.03 kcal/mol. When the geometries were reoptimized using MP2(full)/6-31G(d) we found that the difference had expanded to 4.3 kcal/mol. In order to exclude the possibility of an artifact in the MP2 calculation, the barriers to alkylation in methylfluorosulfonate and methyl FSI were calculated using two coupled cluster calculations,[46,47,48] CCSD(T)/6-31G(d) and CCSD(T)/6-31+G(2d,p) at the MP2(full)/6-31G(d) geometry. These calculations affirmed the difference, with the CCSD(T)/6-31+G(2d,p) showing a $\Delta\Delta E^{\ddagger}$ of 5.1 kcal/mol, whereas the $\Delta\Delta E^{\ddagger}$ for the MP2/G3large (the single point calculation without vibrational correction) was 5.4 kcal/mol. These energies are displayed in figure 5. We also note that while differences were present among the methyl cation affinities of sulfonates and sulfonimides, they were not systematic. The change in activation energy in sulfonimides going from an HF to a correlated wavefunction occurs concurrently with a geometric perturbation. The nitrogen atoms of sulfonimide groups are nearly planar at HF/6-31G(d), whereas they become mildly pyramidal at MP2(full)/6-31G(d). A similar, but more dramatic effect is noticeable in sulfonamides, where FSA and MSA pyramidalize to the point of being nearly tetrahedral at MP2(full)/6-31G(d), and MSA shows some pyramidalization at HF/6-31G(d) (see table 3). When an isopropyl group is introduced onto the sulfonamide in the case of MeiprFSA, the pyramidalization effect is somewhat retarded, but not as much as in the case of Methyl FSI with two sulfonyl groups.

The above observations suggest that orbital interactions between the nitrogen atom and the two sulfonyl groups are preventing a pyramidalization analogous to that which occurs when only one is present. Sulfonyl groups have been well studied, and it is commonly concluded that hyperconjugative $n_N \rightarrow \sigma^*$ interactions with the S-O bond, delocalize electrons in the sulfonyl group.[49,50] Additionally, it has been shown that sulfamidates, which have a negatively charged

sulfonamide bound to a nitrogen cation, have sulfonyl oxygens that form significantly stronger hydrogen bonds than do sulfonamides, or even the usually more basic sulfones and sulfoxides.[51] This suggests an explanation for the drive to pyramidalization as sulfonamide derived species ionize: a pyramidal geometry at nitrogen facilitates better overlap in the n→σ* conjugation, but when two sulfonyl groups are present, ideal interaction with each is not possible. While the size of the sulfonimide wave functions and the relative ambiguity of their frontier orbitals make a full accounting of this phenomenon difficult, a convincing example of this is illustrated in figure 7, in the HOMO-5 and HOMO-6 energy levels of the FSI transition state. In the HF/6-31G(d) structure, HOMO-5 contains a bonding orbital that spans the length of the imide moiety, whereas at MP2(full)/6-31G(d), mixing occurs between HOMO-5 and HOMO-6, destabilizing both orbitals.

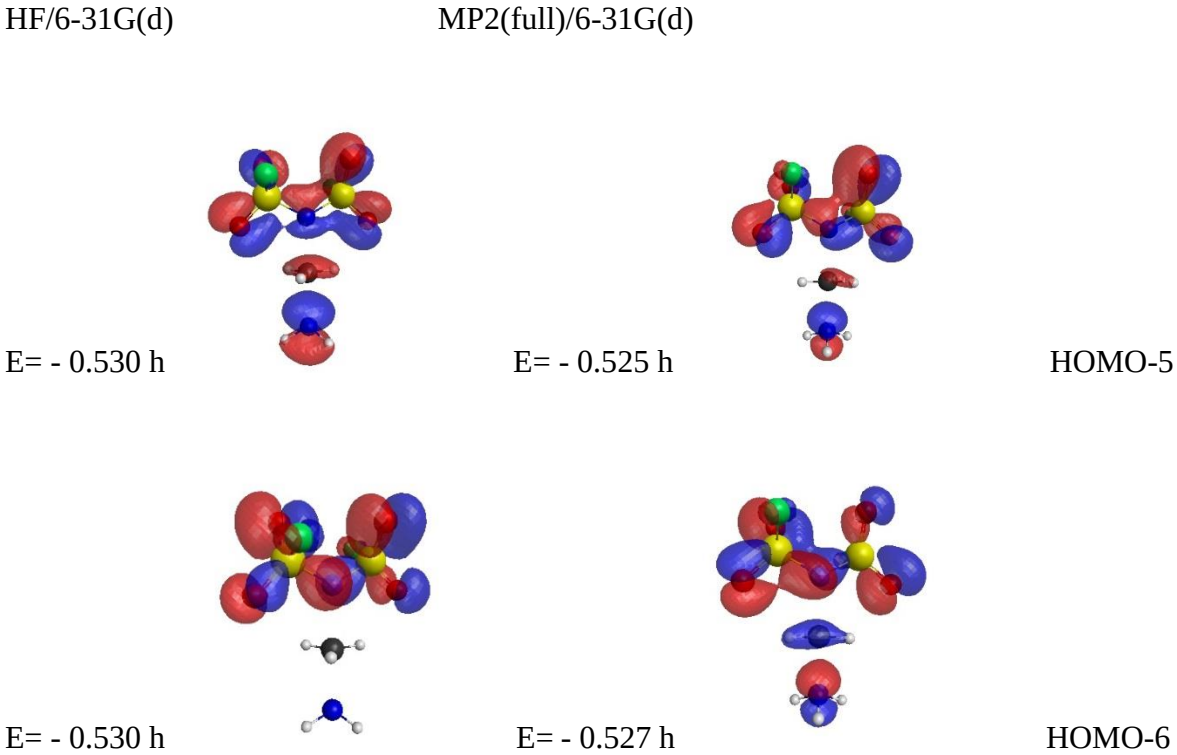


Fig. 7 – Some origins in the gap between the nucleofugality of sulfonimide and sulfonate leaving groups can be linked to differences in the electronic structure. Imide spanning orbitals such as HOMO-5 in FSI (Top Left) have

are stabilizing because they have more bonding character across the imide in the planar HF/6-31G(d) geometry (left) as compared to the MP2(full)/6-31G(d) geometry (Right) where HOMO-5 and HOMO-6 mix. Presumably these bonding interactions are opposed by n → σ* interactions localized to one sulfonyl group or the other.

Table 3 – Transition State Pyramidalization in Sulfonamide Species at HF and MP2 Geometries. All values are in degrees.

	HF/6-31G(d)	MP2(full)/6-31G(d)	
	Dihedral (S-N-R-C)	Dihedral (S-N-R-C)	Angle(S-N-R)
Methyl FSI	178.86	161.00	121.39
Methyl FSA	174.97	126.36	109.31
Methyl MSI	178.83	169.65	121.89
Methyl MSA	132.05	121.27	107.27
MeiprFSA	177.83	134.43	119.9

A literature precedent does exist for the dependence of the intrinsic barrier of S_N2 reactions on the leaving group atom. Hoz et al. used G2 derived calculations to study symmetrical anionic S_N2 reactions and concluded that the intrinsic barrier changes between groups of the periodic table, and stays relatively constant within them, up until the border between metals and non-metals.[52] Nitrogen and oxygen had intrinsic barriers of 29.3 and 19.5 kcal/mol respectively, whereas the halogens clustered near 10 kcal/mol.[52] This inherent difference was then shown to extend to similar S_N2 displacements occurring at nitrogen.[53] This work suggests that these findings may generalize beyond symmetric, charged variants of the S_N2, as we see a similar pattern in Menshutkin reactions of polyatomic nucleofuges, and may suggest that the principle of imperfect synchronization while seemingly applicable is actually not. On the other hand the connection is somewhat tenuous because the symmetric anionic cases of Hoz et al. have only one symmetrically distinct well, and do not separate charge throughout the course of the reaction.

Analysis of our barriers using Marcus theory was considered in order to make our results more directly comparable to those of Hoz, but there are several confounding factors. The most notable of these was characterized by Schaefer et al. who used coupled cluster calculations with complete basis set extrapolation to characterize the barriers of a series of S_N2 displacements.[28] The authors then showed that deviations ranging from 1.3 to over 22 kcal/mol occurred when calculating the central barrier from a standard Marcus equation of the form

$$\Delta E^{\ddagger} = \Delta E_0^{\ddagger} + \frac{\Delta E_{rxn}}{2} + \frac{(\Delta E_{rxn})^2}{\Delta E_0^{\ddagger}} \quad (6)$$

Where $\Delta E^{\ddagger}$ and ΔE_{rxn} are the forward barrier and thermodynamic driving force of the reaction respectively, and are defined similarly to those shown in scheme 2, and $\Delta E_0^{\ddagger}$ is the intrinsic barrier of the reaction.[28] When the equation was revised to omit the contribution of well depth from ΔE_{rxn} and $\Delta E^{\ddagger}$ the errors became significantly less pronounced.

This finding is particularly important for our systems, as our complexes consist of hydrogen bonded complexes of neutral molecules and ion pairs. Our choice of $\Delta E_{(S\rightarrow TS)}$ as a surrogate for activation energy, was in part because the variability of the hydrogen bond strength in complexes obscured correlations with the MCA values, and in any case, the ability of a functional group to hydrogen bond has no real relevance to its ability to function as a leaving group. Additionally our products are ion pairs whose separation is highly endothermic, and this makes using the separated species in place of the complexes for the purpose of Marcus theory analysis problematic.

An interesting direction for future study might be the computation of symmetric S_N2 reactions using some or all of the polyatomic anionic leaving groups used in this study. This

would enable a more rigorous comparison with the findings of Hoz et al. and add a better perspective on their finding that intrinsic barriers track with group identity in the periodic table.

Conclusion

The $\Delta E_{S\rightarrow TS}$ of nitrogen and oxygen derived leaving groups in the Menshutkin reaction correlate well with the thermodynamic stability of the ions, as determined by MCA, but differences exist between the two classes. These differences are rooted in the synchronization of the events inherent in the S_N2 process, as well as geometric limitations on the efficiency of activating groups on nitrogen. This finding is relevant to recent work on indices of nucleofugality, because it shows that complicating factors may exist which are relevant to the dissociation of a nucleofuge, but are not directly related to the stability of the fully dissociated group.

Acknowledgements

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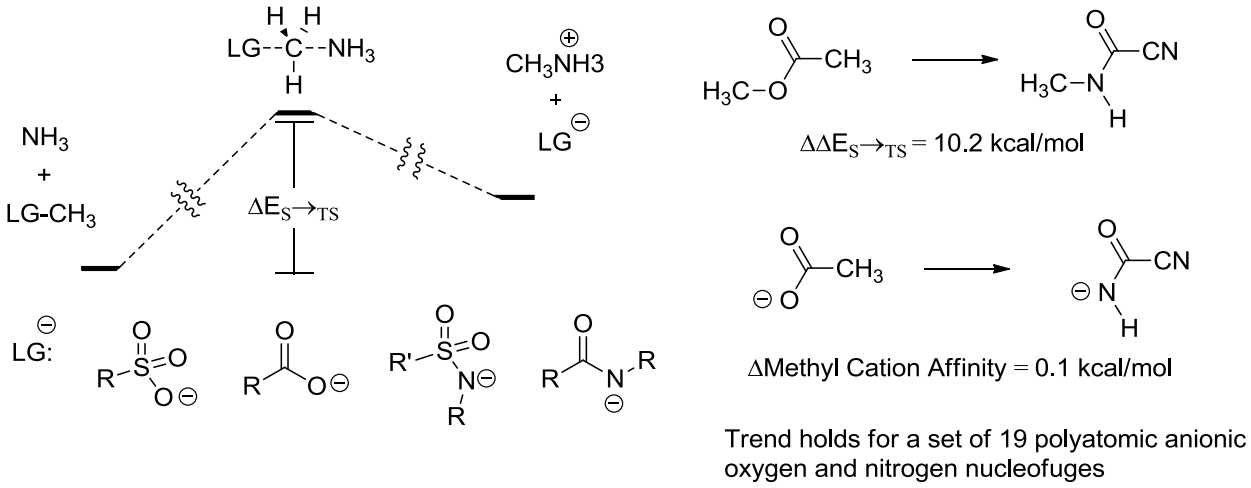
Graphical Abstract



References

[1] C. J. M. Stirling, *Acc. Chem. Res.* 1978, **12**, 198 – 203.

[2] P. W. Ayers, J. S. M. Anderson, J. I. Rodriguez, and Z. Jawed, *Phys. Chem. Chem. Phys.* 2005, **7**, 1918 – 1925.

[3] L. Brockaert, J. Moens, G. Roos, F. De Proft, and P. Geerlings, *J. Phys. Chem. A* 2008, **112**, 12164-12171.

[4] R. Ormazábal-Toledo, P. R. Campodónico and R. Contreras, *Org. Lett.* 2011, **13**, 822 – 824.

[5] B. Denegri, A. Streiter, S. Jurić, A. R. Ofial, O. Kronja, and H. Mayr, *Chem. Euro. J.* 2006, **12**, 1648 - 1656.

[6] R. Ormazábal-Toledo, P. R. Campodónico, A. Aizman and R. Contreras *Chem. Phys. Lett.* 2010, **498**, 221 – 225.

[7] P. R. Campodónico, A. Aizman and R. Contreras *Chem. Phys. Lett.* 2006, **422**, 340 - 344.

[8] D. Guerra, R. Castillo, J. Andrés, P. Fuentealba, A. Aizman, and R. Contreras *Chem. Phys. Lett.* 2006, **424**, 437 – 442.

[9] P. R. Campodónico, J. Andrés, A. Aizman, and R. Contreras *Chem. Phys. Lett.* 2007, **439**, 177 – 182.

[10] P. R. Campodónico, C. Pérez, M. Aliaga, M. Gazitúa, and R. Contreras *Chem. Phys. Lett.* 2007, **447**, 375 – 378.

[11] H. Mayr, M. Breugst, and A. Ofial *Angew. Chem. Int. Ed.* 2011, **50**, 6470 – 6505.

[12] N. Streidl, B. Denegri, O. Kronja, and H. Mayr *Acc. Chem. Res.* 2010, **12**, 1537 – 1549.

[13] R. P. Bell and W. C. E. Higginson, *Pro. Royal Soc.* 1949, **197**, 141-159.

[14] P. J. DeChristopher, J. P. Adamek, J. P. Lyon, J. J. Galante, H. E. Haffner, R. J. Boggio, and R. J. Baumgarten, *J. Am. Chem. Soc.* 1969, **91**, 2384-2385.

[15] J. B. Hendrickson, R. Bergeron, A. Giga, and D. Sternbach, *J. Am. Chem. Soc.* 1973, **95**, 3412-3413.

[16] J. Zhang, G. R. Martin, and D.D. DesMarteau, *Chem. Commun.* 2003, 2334 – 2335.

[17] R. Arvai, F. Toulgoat, B. R. Langlois, J. Sanchez, and M. Médebielle, *Tetrahedron* 2009, **65**, 5361 – 5368.

[18] B. A. Shainyan, and L. L. Tolstikova, *Chem. Rev.* 2013, **113**, 699 – 733.

[19] M. Armand, F. Endres, D. MacFarlane, H. Ohno and B. Scrosati, *Nat. Mater.* 2009, **8**, 621 – 629.

[20] T. Welton, *Chem. Rev.* 1999, **99**, 2071 – 2083.

[21] H. Castejon, and K. B. Wiberg, *J. Am. Chem. Soc.* 1999, **121**, 2139 – 2146.

[22] J. Poater, M. Solá, M. Duran, and X. Fradera, *J. Phys. Chem. A* 2001, **105**, 6249 – 6257.

[23] M. Bühl, and H. F. Schaefer, *J. Am. Chem. Soc.* 1993, **115**, 9143 – 9147.

[24] Y. Xing, X. Xu, Z. Cai, X. Zhao, and J. Cheng, *Chem. Phys.* 2004, **298**, 125 – 134.

[25] P. Bento, and F. M. Bickelhaupt, *J. Org. Chem.* 2008, **73**, 7290 – 7299.

[26] Z. Yang, Y. Ding, and D. Zhao, *J. Phys. Chem. A* 2009, **113**, 5432 – 5445.

[27] P. Su, F. Ying, W. Wu, P. C. Hiberty, and S. Shaik, *Chem. Phys. Chem.* 2007, **8**, 2603 – 2614.

[28] J. M. Gonzales, W. D. Allen, and H. F. Schaefer, *J. Phys. Chem. A* 2005, **109**, 10613 – 10628.

[29] A. Nowacki, B. Dmochowska, E. Jaczkowska, K. Sikora, and A. Wisniewski, *J. Comput. and Theor. Chem.* 2011, **973**, 53 – 61.

[30] J. K. Laerdahl, and E. Uggerud, *Int. J. Mass. Spec.* 2012, **142**, 277 – 314.

[31] W. M. Schmidt, K. K. Baldidge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. A. Su, T. L. Windus, M. Dubuis and J.A. Montgomery *J. Comput. Chem.* 1993, **14**, 1347 – 1363.

[32] L. A. Curtiss, P. C. Radfern, K. Raghavachari, V. Rassolov, and J. A. Pople, *J. Chem. Phys.* 1999, **110**, 4703 – 4709.

[33] L. A. Curtiss, K. Ragavachari, P. C. Redfern, A. G. Baboul, and J. A. Pople, *Chem. Phys. Lett.* 1999, **314**, 101 - 107.

[34] Y. Wei, T. Singer, H. Mayr, G. N. Sastry, and H. Zipse, *J. Comput. Chem.* 2008, **29**, 291 – 297.

[35] Z. Shi, and R. J. Boyd, *J. Am. Chem. Soc.* 1990, **112**, 6789 – 6796.

[36] B. M. Bode, and M. S. Gordon, *J. Mol. Graphics and Modeling* 1998, **16**, 133 – 138.

[37] I. Fernández, G. Frenking, and E. Uggerud, *Chem. Euro. J.* 2009, **15**, 2166 – 2175.

[38] (a) S. Wolfe, D. J. Mitchell, and H. B. Schlegel, *J. Am. Chem. Soc.* 1981, **103**, 7692 – 7694.

(b) S. Wolfe, D. J. Mitchell, and H. B. Schlegel, *J. Am. Chem. Soc.* 1981, **103**, 7694 – 7696.

[39] S. Shaik, H. B. Schlegel, and S. Wolfe, *J. Chem. Soc. Chem. Commun.* 1988, 1322 – 1323.

[40] P. Jaramillo, L.R. Domingo and P. Pérez *Chem. Phys. Lett.* 2006, **420**, 94 – 95.

[41] A. Dreuw and M. Head-Gordon *Chem. Rev.* 2005, **102**, 4009 – 4037.

[42] C. F. Bernasconi, *Acc. Chem. Res.* 1987, **20**, 301-308.

[43] C. F. Bernasconi, *Acc. Chem. Res.* 1992, **25**, 9-16.

[44] S. Shaik, and A. Shurki, *Angew. Chem. Int. Ed.* 1999, **38**, 586 – 625.

[45] S. Shaik, E. Duzy, and A. Bartuv, *J. Phys. Chem.* 1990, **94**, 6574 – 6582.

[46] P. Piecuch, S. A. Kucharski, K. Kowalski, and M. Musial, *Comp. Phys. Commun.* 2002, **149**, 17 – 96.

[47] J. L. Bentz, R. M. Olson, M. S. Gordon, M. W. Schmidt, and R. A. Kendall, *Compute. Phys. Commun.* 2007, **176**, 598 – 600.

[48] R. M. Olson, J. L. Bentz, R. A. Kendall, M. W. Schmidt, M. S. Gordon, *J. Comput. Theoret. Chem.* 2007, **3**, 1312 – 1328.

[49] E. Denehy, J. M. White, and S. J. Williams, *Inorg. Chem.* **2007**, *46*, 8871 – 8886.

[50] P. V. Bharatam, A. A. Gupta, and D. Kaur, *Tetrahedron* 2002, **58**, 1759 – 1764.

[51] A. Chardin, C. Laurence, M. Berthelot, and D. G. Morris, *J. Chem. Soc. Perkin Trans. 2* 1996, 1047 – 1051.

[52] S. Hoz, H. Basch, J. L. Wolk, T. Hoz, and E. Rozental, *J. Am. Chem. Soc.* 1999, **121**, 7724 – 7725.

[53] R. Yi, H. Basch, and S. Hoz, *J. Org. Chem.* 2002, **67**, 5891 – 5895.