Reactivity Studies

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On the Importance of Leaving Group Ability in Reactions of Ammonium, Oxonium, Phosphonium, and Sulfonium Ylides**

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Dedicated to Professor Steven Ley on the occasion of his 60th birthday

Ammonium, phosphonium, and sulfonium ylides are powerful and versatile reagents in organic chemistry, which undergo three important types of reaction: olefination, cyclization to a three-membered ring, and rearrangement.[1] The reactivity and selectivity of the ylides in these reactions depend on the nature of the central heteroatom. The nucleophilicity of the carbon centre of the ylides is one important aspect of their reactivity, which is affected by the degree to which the onium group stabilizes the adjacent negative charge. It has been shown that stabilization increases in the order O < N ≪ P < S.[2] However, this feature alone does not explain all the observed reactivity. We present comparative computational data which suggest that the differences are mainly due to the differing leaving group ability of the respective onium groups. The calculations[3] are carried out using the accurate B3LYP density functional, which is known to describe trends of the kind studied here accurately.[4,5] We also include a continuum solvent model in all calculations as the gas-phase potential energy surfaces are qualitatively inaccurate for some of these very polar species.[5]

In the reaction with organoboranes, sulfonium ylides give homologation products at low temperature[6] while the more nucleophilic ammonium ylides react only at reflux of THF,[7] and phosphonium ylides require temperatures above 130 °C.[8] The energy profile[3] for the reaction of BMe_3 with ylides **1** involves barrierless addition to form ate complex **2**, followed by rate-determining 1,2-migration (Figure 1). The first step is most exothermic for the ammonium and oxonium ylides while the barrier for migration is smallest with the oxonium ylide and largest with the phosphonium derivative. Nucleophilicity of the onium ylides is clearly irrelevant for this process, with the key factor being instead the leaving group ability of the onium group, which decreases in the order O > S > N > P.

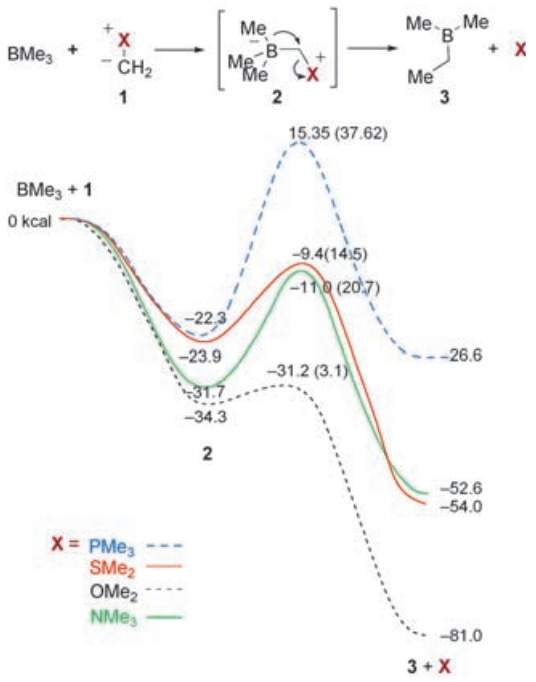

Figure 1. Calculated[3] energy surface (in kcal mol^{-1}) for reaction of BMe_3 with **1**. Values in parentheses are relative to **2**.

For epoxidation, observed reactivity does not correlate with carbon nucleophilicity either. Sulfonium ylides react with aldehydes at temperatures as low as −78 °C,[9] whilst room temperature is required using ammonium ylides.[10] This is consistent with the energy profile[3] for the reaction of the ylides **1** with benzaldehyde, and again, the higher reactivity of the sulfur-based species is due to a lower barrier in the intramolecular substitution step (Figure 2). In this reaction, the initial addition step is barrierless with the more nucleophilic ammonium ylide, and hence more favorable than with the sulfonium ylide, where a small barrier is observed. In the latter case, though, addition is the only demanding (and rate-limiting) step, whereas with nitrogen, betaine formation is followed by slower decomposition over a 15 kcal mol^{-1} barrier. This is consistent with the experimental observation that β-hydroxy ammonium salts are isolated upon work-up of the reaction of ammonium ylides at low temperature.[11] Wittig reaction leading to alkenes is the main pathway with phosphonium ylides. This difference in reaction behavior compared to sulfonium ylides has a number of reasons,[12] such as the fact that oxathietanes are not formed in the sulfur reaction.[5] One important effect is clearly leaving group ability: our calculations show that *trans* betaines can be formed from phosphorus ylides over a low barrier, but nucleophilic displacement of the phosphine involves a very significant barrier. Cyclization to the oxaphosphetane (see Figure S1, Supporting Information), or indeed facile direct formation of the latter, and subsequent phosphine oxide loss, therefore compete very effectively. As with the borane reaction, calculations suggest that the reaction with oxonium ylides would be very favorable, although no examples are

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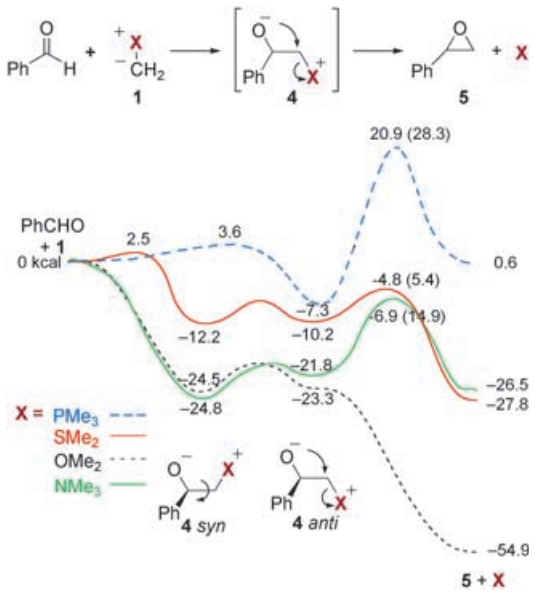
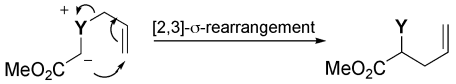


Figure 2. Computed[3] potential energy surface (in kcal mol^{-1}) for styrene oxide formation from **1**. Values in parentheses are relative to **4** *anti*.

reported in the literature. Overall, leaving group ability plays an extremely important role in determining reactivity and the nature of products formed in this set of reactions.

[2,3]-σ-Rearrangement is known for ammonium, oxonium, and sulfonium ylides[1] but only one low-yielding example has been reported for phosphonium ylides.[13] This process can in principle involve radical intermediates (Stevens rearrangement), but experimental evidence suggests a concerted pathway in most cases.[11,14] For the latter, the rate could be expected to depend both on nucleophilicity of the ylide carbon atom (which decreases in the order O > N > P > S) and on the leaving group ability of the corresponding onium (which should decrease as O > S > N > P, as in the other two reactions). Experimentally, the rearrangement is very facile even at low temperature for all but the phosphonium ylides. Our calculations[3] (Table 1) show that the barrier height follows the order O < S < N ≪ P, indicating that leaving group ability is the dominant effect in this case also. The magnitude of the barriers for the O, N, and S ylides confirms that their rearrangement should be rapid, while the high activation energy for phosphonium ylides accounts for the dearth of examples in this latter case. Considering the similarity in nucleophilicity of phosphonium and sulfonium ylides, the very different activation barriers for rearrangement emphasizes the dominant effect of leaving group ability.

Table 1: Computed[3] activation energies ($\Delta E^{\neq}$) and reaction energies (ΔE) of [2,3]-σ-rearrangements (in kcal mol^{-1}).



Y	$\Delta E^{\neq}$	ΔE
NMe_2	12.18	−27.29
OMe	2.94	−60.44
PMe_2	35.13	−4.71
SMe	7.83	−33.45

The consistent order of leaving group ability of the four onium groups in these three reactions is intriguing. Which factors cause ether and thioether groups to be excellent leaving groups, amines to be somewhat less good, and phosphines to be so poor? Nucleophilic substitution is one of the most important reactions in organic chemistry,[15] and extensive efforts have been made to develop a quantitative description of nucleophilicity,[16] and, to a lesser extent, the complementary kinetic property of leaving group ability.[17] It is generally recognized that both intrinsic factors and thermochemistry contribute to the barrier height. The combined impact of these two effects can be treated quantitatively using Marcus theory,[18] which has been applied successfully to group transfer reactions[19] and in particular to S_N2 reactions.[15,20] The intrinsic nucleophilicity of a given species is the same as its intrinsic leaving group ability, and can be measured by the rate or barrier height for the identity S_N2 reaction $X + CH_3X^+ \rightleftarrows X^+CH_3 + X$. The calculated[3] energy barriers for these reactions give a reactivity order similar to that found above, with O > S > N ≫ P (Table 2).[21,22]

Table 2: Intrinsic barrier heights (in kcal mol^{-1})[3] for the identity reaction $X + CH_3X^+ \rightleftarrows X^+CH_3 + X$; forward and reverse barrier heights and exothermicity for the reaction $H_2O + CH_3X^+ \rightleftarrows H_2O^+CH_3 + X$.

X =	OMe_2	SMe_2	NMe_3	PMe_3
		$X + CH_3X^+ \rightleftarrows X^+CH_3 + X$		
$\Delta E^{\neq}$	15.5	22.5	26.3	40.1
		$H_2O + CH_3X^+ \rightleftarrows H_2O^+CH_3 + X$		
$\Delta E^{\neq}$ forward	13.2	25.6	38.9	50.7
$\Delta E^{\neq}$ backward	10.6	9.4	2.1	4.8
ΔE	2.6	16.3	36.8	45.9

These intrinsic reaction barriers have been discussed for other nucleophiles previously, and depend on the strength of the C–X bond but also on the balance between bond-making and bond-breaking at the exchange transition state.[23] All other factors being equal, then, ether oxygens are (intrinsically) the best nucleophiles (and leaving groups), followed by sulfides and amines, with phosphines being poor for both types of reaction.

However, all factors are not equal: the thermodynamics of substitution vary considerably due to differences in the carbon–element bond strength, which decreases in the order P > N > S > O.[24] In trying to understand the trend in leaving group ability in reactions with a common nucleophile—the topic of the present study—these differences in bond energies need to be taken into account as well as the intrinsic reactivity, as the resulting changes in thermodynamics have an indirect impact on barrier heights. Assuming a constant intrinsic reaction barrier, leaving group ability would increase with decreasing bond energy, in the order P < N < S < O. In fact, the intrinsic barriers are not identical (Table 2), and indeed follow the same order of increased reactivity going from P to O, so that the two factors combine synergistically to yield an overall hierarchy of leaving group ability P < N < S < O.[25]

This is shown for three different nucleophiles: an alkyl group in Figure 1, an alkoxide anion in Figure 2, and water in Table 2. To take another better known example, this trend explains the stability of alkyl phosphonium and ammonium salts in the presence of halide counterions, and the instability of the corresponding sulfonium salts.[26] A nucleophilic halide counterion can displace a good leaving group (sulfide), but not a poor one (amine, phosphine). It also accounts for why nature, with ready access to compounds containing N, O, S and P, has chosen a sulfonium salt (*S*-adenosyl methionine, SAM) for methyl group transfer.[27] Unlike oxonium salts, such species are stable enough to be formed without reacting instantaneously with water, yet have a higher alkylating reactivity than ammonium salts.

Although the focus of the present work is on leaving group ability, it is useful to note that the same two factors of intrinsic reactivity and thermochemistry account for the relative nucleophilicity of the different groups also. For example, phosphines are usually quite good nucleophiles despite their low intrinsic reactivity, because the strong C–P bond means that substitution is usually quite strongly exothermic. Calculated barriers for the reaction $X + CH_3OH_2^+ \rightarrow CH_3X^+ + H_2O$ are shown in Table 2. Because the exothermicity increases in the order ether < sulfide < amine < phosphine, the calculated nucleophilicity follows the well known[28] order $R_3N > R_3P > R_2S > R_2O$. The intrinsically weakest nucleophile, R_3P, has the second lowest barrier to reaction due to forming the most stable products. The ether group, on the other hand, is intrinsically reactive but the reaction is near thermoneutral and hence has a significant barrier.

In summary, the reactivity of sulfonium, ammonium, phosphonium, and oxonium ylides in a range of reactions is to a large part determined by the leaving group ability of the corresponding onium group, and this decreases for both intrinsic and thermochemical reasons in the order O > S > N > P. This means that when comparing reactions of, for example, ammonium and sulfonium ylides, the rate-limiting and selectivity-determining steps in a multistep mechanism may well be different. This insight should be of considerable use in designing new stereoselective synthetic transformations.

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