

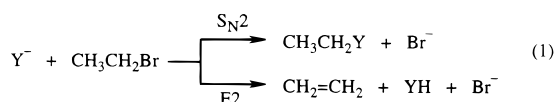
## The Gas-Phase Reactions of Dianions with Alkyl Bromides: Direct Identification of S<sub>N</sub>2 and E2 Products

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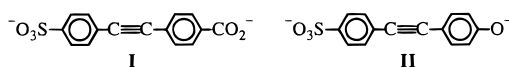
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In recent years there has been great interest in probing organic reaction mechanisms in the gas phase because these studies allow chemists to investigate the intrinsic reactivity of organic substrates in the absence of solvation effects. In addition, gas-phase studies provide a baseline for judging the importance of solvation and ion pairing in condensed phase studies. Unfortunately, one of the classic problems in physical organic chemistry, the competition between substitution and elimination, has proven to be exceptionally difficult to probe in the gas phase. The problem is that both pathways lead to the same ionic product (for example, Br<sup>-</sup> in eq 1) and cannot be distinguished by mass spectrometry.



Isolation and identification of the neutral products in this type of gas-phase reaction is exceedingly difficult and has not proven to be a general technique.<sup>1,2</sup> However, Jones and Ellison<sup>2</sup> have successfully applied this approach to the reaction of methoxide with 1-bromopropane and observed elimination products. Most often the competition between elimination and substitution has been determined by indirect means such as isotope effects or trends in kinetic reactivity.<sup>3,4</sup> In addition, novel substrates have been used which are capable of producing diagnostic products.<sup>5–13</sup> In the present work, we report the direct detection of substitution and elimination products in reactions of simple alkyl halides. The key is the use of dianions containing nucleophilic (Y<sup>-</sup>) and nonnucleophilic (Z<sup>-</sup>) anionic sites. These dianions yield distinctive monoanionic products in reactions with alkyl halides (Scheme 1), and the mechanism is clearly indicated by the alkylation (S<sub>N</sub>2) or protonation (E2) of the reactive site.

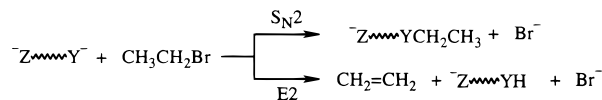
To test this approach, salts of dianions **I** and **II** were synthesized by using a scheme based on sequential Heck reactions of protected aryl bromides.<sup>14</sup> Each dianion employs a sulfonate as the nonnucleophilic site and has a rigid rod unit separating it from the nucleophilic site (carboxylate or phenolate).



Although selective generation of dianions is very difficult in

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### Scheme 1



conventional electron impact sources, electrospray ionization of solutions of the tetrabutylammonium salts of **I** and **II** in acetonitrile ( $\sim 10^{-4}$  M) led to satisfactory dianion signals in a Finnigan LCQ quadrupole ion trap mass spectrometer. With use of a gas handling system previously described,<sup>15</sup>  $10^{-5}$ – $10^{-8}$  Torr<sup>16</sup> of an alkyl bromide was introduced into the helium buffer gas ( $1.75 \times 10^{-3}$  Torr) of the ion trap. After isolating the dianion in the ion trap (notched waveform), reaction times from 100 to 5000 ms were employed before all the ions were ejected to obtain a mass spectrum. To check for secondary reactions, the intensities of the S<sub>N</sub>2 and E2 products were recorded as a function of reaction time.<sup>17</sup> The E2/S<sub>N</sub>2 ratios<sup>18</sup> are reported in Table 1 for a series of alkyl bromides and a typical spectrum is shown in Figure 1. In addition, rate constants were determined for the reactions of **II** by monitoring the dianion signal as a function of reaction time.<sup>19</sup> The overall rate constants as well as the derived E2 and S<sub>N</sub>2 rate constants are listed in Table 2.<sup>20</sup>

Overall, it is clear that both mechanisms are viable for these nucleophiles, and in most cases, mixtures are observed. With respect to alkyl substituents at the α-carbon, the results reveal the expected reactivity trend. The E2/S<sub>N</sub>2 ratio increases in going from 1° to 2° to 3° alkyl bromides. With **II** as the nucleophile, there is a smooth increase in E2 rates and decrease in S<sub>N</sub>2 rates across the series (ethyl ⇒ isopropyl ⇒ *tert*-butyl). For both nucleophiles, there is more elimination with propyl bromide than with ethyl bromide, indicating that a β-methyl group favors the E2 path. The rate data for **II** (Table 2) show that a β-methyl group increases both the S<sub>N</sub>2 and E2 rates, but that elimination gains the greatest benefit and therefore the E2/S<sub>N</sub>2 ratio increases. The effect of a β-methyl group on the E2 and S<sub>N</sub>2 rates is consistent with the results of previous computational<sup>21–23</sup> and experimental<sup>24</sup>

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(14) Both nucleophiles were synthesized via sequential palladium-catalyzed couplings starting from trimethylsilylacetylene and an aryl bromide (ethyl *p*-bromobenzoate for **I** and butyl *p*-bromobenzenesulfonate for **II**). After desilylation, a second palladium-catalyzed coupling was completed with another aryl bromide (butyl *p*-bromobenzenesulfonate for **I** and *p*-bromophenyl acetate for **II**). Deprotection led to salts of **I** and **II**.

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(16) A known ratio of reagent/helium is prepared externally and delivered to the ion trap. Reagent pressures are calculated by multiply this ratio times the helium pressure in the trap (1.75 mTorr) and correcting for differential effusion out of the end-cap holes in the trap. This correction factor is equal to the square root of the mass ratio ( $M_{\text{reagent}}/M_{\text{helium}}$ ).

(17) Other control experiments have shown that the sulfonate is unreactive.

(18) No correction was made for mass discrimination. In the narrow mass range of interest ( $m/z = 270$ – $330$ ), test studies suggest that mass discrimination has only a minor effect.

(19) The reactions of **I** are about an order of magnitude slower than those of **II**. With the present experimental setup, it was not possible to hold **I** in the trap long enough to allow for a sufficient number of half-lives in its reactions.

(20) To test the accuracy of rate measurements in the instrument, the previously studied reactions of 1,1,1,3,3,3-hexafluoro-2-propoxide with ethyl and isopropyl bromide were investigated ( $k = 5.4 \times 10^{-12}$  and  $4.2 \times 10^{-12}$  cm<sup>3</sup>/molecule/s, respectively, in the ion trap). Reasonable agreement was observed and systematic errors were not evident (36% deviation for ethyl and 1% deviation for isopropyl compared to the flowing-afterglow values in ref 4).

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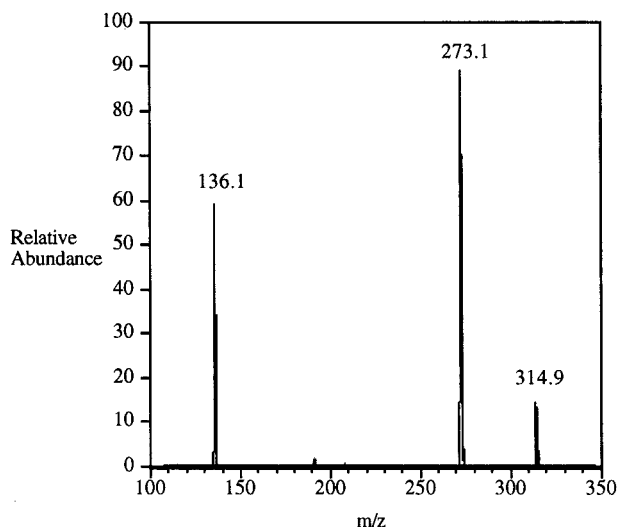
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**Table 1.** E2/S<sub>N</sub>2 Ratios for the Reactions of Dianions with Alkyl Bromides<sup>a</sup>

substrate	E2/S <sub>N</sub> 2	
	I	II
ethyl	<0.01	0.12 ± 0.01
<i>n</i> -propyl	0.11 ± 0.01	0.68 ± 0.02
isopropyl	0.86 ± 0.04	5.9 ± 0.1
<i>sec</i> -butyl	1.1 ± 0.1	7.0 ± 0.1
<i>tert</i> -butyl	>200	>200

<sup>a</sup> Uncertainties are one standard deviation.**Figure 1.** Mass spectrum from the reaction of **II** with isopropyl bromide. The dianion (**II**) appears at  $m/z = 136$ . The protonated (E2) and isopropylated (S<sub>N</sub>2) products appear at  $m/z = 273$  and  $315$ , respectively. The small peak at  $m/z = 192$  is a minor decomposition product formed during the isolation of **II** (**II**-SO<sub>3</sub><sup>-</sup>).**Table 2.** Rate Constants for the Reactions of **II** with Alkyl Bromides<sup>a</sup>

substrate	<b>II</b>		
	$k$	$k(\text{E2})^{b,c}$	$k(\text{S}_{\text{N}2})^b$
ethyl	4.0 ± 0.3	0.4 ± 0.1 (0.2)	3.6 ± 0.2
<i>n</i> -propyl	8.2 ± 0.3	3.3 ± 0.1 (1.6)	4.8 ± 0.2
isopropyl	3.2 ± 0.4	2.7 ± 0.4 (0.5)	0.5 ± 0.1
<i>sec</i> -butyl	13.1 ± 1.5	11.0 ± 1.0 (2.2)	1.6 ± 0.2
<i>tert</i> -butyl	10.8 ± 1.2	11.0 ± 1.0 (1.2)	<0.05

<sup>a</sup> Rate constants in units of 10<sup>-12</sup> cm<sup>3</sup>/molecule/s. Uncertainty listed for rate constants in one standard deviation. Absolute accuracy of rate constants is expected to be ±25%. <sup>b</sup> Obtained by multiplying the overall rate constant by the product fraction. <sup>c</sup> Rate per β-hydrogen is given parenthetically. As a crude approximation, all the β-hydrogens are considered equal in *sec*-butyl.

studies. For example, in the reactions of fluoride with alkyl chlorides, ab initio calculations predict that the E2 and S<sub>N</sub>2 barriers will be reduced by 1.5 and 0.8 kcal/mol, respectively, in going from ethyl to *n*-propyl chloride as the substrate.<sup>22</sup> A similar β-methyl effect is seen when comparing the rate constants for the reaction of **II** with the 2° bromides (*sec*-butyl and isopropyl

bromide). Again, both rate constants increase with the addition of the β-methyl group, but elimination gains the most and a larger E2/S<sub>N</sub>2 ratio is observed. As expected, the 3° bromide gives only elimination.

To compare the two nucleophiles, it would be useful to have a measure of their relative basicity. Unfortunately, it is very difficult to determine the basicity (acidity) of multiply charged ions<sup>25</sup> so we must rely on estimates based on singly charged analogues. Using *p*-methylphenol (ΔH<sub>acid</sub> = 352.2 kcal/mol) and *p*-methylbenzoic acid (ΔH<sub>acid</sub> = 342.1 kcal/mol) for comparison,<sup>26</sup> it is anticipated that the phenolate (**II**) will be the stronger base. Of course electrostatic repulsion in dianions will make them more basic than the singly charged analogues,<sup>27</sup> but this will only have a minor effect on the S<sub>N</sub>2 and E2 reactions because in reaching the transition state, there is a relatively small increase in the charge separation.<sup>28</sup> Higher rate constants as well as a greater preference for elimination also suggest that the phenolate (**II**) is a stronger base than the carboxylate (**I**).

The present results are in general accord with those from previous studies. The work from DePuy and co-workers clearly indicated that oxygen-centered nucleophiles were capable of both pathways and that elimination probably dominates for 2° halides (and possibly for 1° halides with strong bases).<sup>3,4</sup> In our work with 2° bromides, the phenolate (**II**) gives mainly elimination whereas the carboxylate (**I**) gives a roughly one-to-one mixture of substitution and elimination. The difference in behavior is probably related to the weak basicity of **I**. In fact, the E2 reaction of a benzoate with ethyl bromide is virtually thermoneutral so it is only the electrostatic repulsion in **I** that makes the process exothermic (in general, the S<sub>N</sub>2 process is ~10 kcal/mol more exothermic than the E2 process for bromides so substitution is less sensitive to basicity).<sup>26,29</sup> The reactivity trends that we observe with the dianions are also consistent with work reported by Grabowski and co-workers<sup>5,6</sup> on the competition between substitution and elimination in the reactions of alkyl phosphates and sulfites with a series of bases.

In summary, the use of dianion nucleophiles is a powerful new approach that allows for the direct observation of substitution and elimination products in reactions with alkyl halides. We are presently studying a wider range of nucleophiles as well as other organic reactions where singly charged reactants lead to ionic products that do not identify the mechanism.

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