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Reactions of Gas-Phase Salts: Substitutions and Eliminations in Complexes Containing a Dianion and a Tetraalklylammonium Cation

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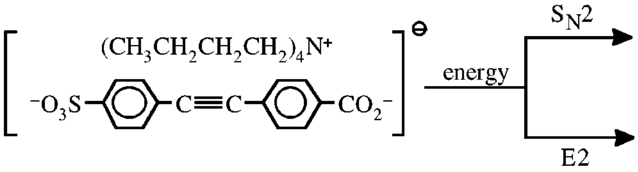
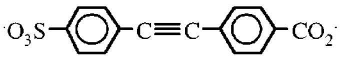
ABSTRACT



Electrospray ionization has been used to generate gas-phase complexes of a dianion (4-carboxy-4′-sulfodiphenylacetylene) with a series of tetraalkylammonium cations. The salt complexes are stable within a quadrupole ion trap but readily react during collision-activated dissociation to give substitution and elimination products (alkylation or protonation of the carboxylate with the loss of a trialkylamine). Ab initio calculations at the MP2/6-31+G(d,p)//MP2/6-31+G(d) level are presented for the corresponding reactions of a model system, acetate + ethyltrimethylammonium.

Electrospray ionization (ESI) techniques have added a new dimension to mass spectrometry and allowed chemists to study a wide range of species that could not be generated by conventional methods.[1−3] For example, multiply charged ions[4,5] and noncovalent complexes[6,7] have been prepared via electrospray. In effect, ESI allows for the direct transfer of ionic species into the gas phase. In this Letter, we report the novel reactions of an organic salt in the gas phase.

As a part of a study of the gas-phase reactions of dianions,[8] we synthesized a diphenylacetylene derivative with two ionizable groups, **1**. When the tetrabutylammonium salt of **1** is dissolved in methanol (~10^{-5} M), the ESI mass spectrum obtained on a Finnigan LCQ quadrupole ion trap contains a peak for the dianion as well as one for the complex of the dianion with one tetrabutylammonium cation. This species (**2**) is a gas-phase salt with a net charge of −1. It can also be viewed as the initial intermediate in the highly exothermic reaction of a dianion with a cation.



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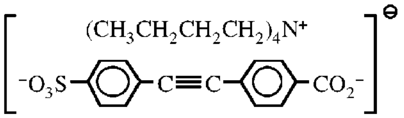

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Although simple salts (i.e., Li^+, Na^+, K^+, etc.) of polyanions are readily formed during ESI, this is an unusual example involving a complex cation with inherent reactivity.

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[1] Striegel, A. M.; Timpa, J. D.; Cole, R. B. *Int. J. Mass Spectrom. Ion Processes* **1997**, *162*, 45.

[2] Fenn, J. B.; Mann, M.; Meng, C. K.; F., W. S.; Whitehouse, C. M. *Science* **1989**, *246*, 64.

[3] Loo, J. A.; Edmonds, C. G.; Smith, R. D. *Science* **1990**, *248*, 201.

[4] Vekey, K. *Mass Spectrom. Rev.* **1995**, *14*, 195.

[5] Williams, E. R. *J. Mass Spectrom.* **1996**, *31*, 831.

[6] Loo, J. A. *Mass Spectrom. Rev.* **1997**, *16*, 1.

[7] Nordhoff, E.; Kirpekar, F.; Roepstorff, P. *Mass Spectrom. Rev.* **1996**, *15*, 67.

[8] Flores, A. E.; Gronert, S. *J. Am. Chem. Soc.* **1999**, *121*, 2627.

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In fact, its existence is notable given that neutralization channels are open (see below).[9]

Although the complex is indefinitely stable in the ion trap, it does undergo reactions during collision-activated dissociation (CAD). Application of an excitation voltage to the trap leads to the formation of two new ions at *m/z* = 301 and 357 in about a 1:2 ratio (Figure 1).[10] These ions correspond to the protonation and alkylation products of dianion **1** and represent novel examples of S_N2 and E2 reactions within a salt complex. These are outlined in Scheme 1. The carboxylate is the only active nucleophile in **1**, and during CAD it attacks at either the α-carbon or β-hydrogen of one of the butyl groups to initiate either the S_N2 or E2 reaction, respectively. The leaving group is tributylamine in each case, and no other products are seen during CAD at moderate energies. Reaction at the sulfonate group can be ruled out by MS^3 experiments on the elimination product (*m/z* = 301). After isolation, CAD on this ion leads to the loss of SO_2, a common fragmentation pattern for arylsulfonate anions (formation of a phenolate).[11,12] In addition, the *m/z* = 357 ion loses butene during MS^3 experiments (a common process for esters with remote charge sites[13]) to give the same *m/z* = 301 ion.

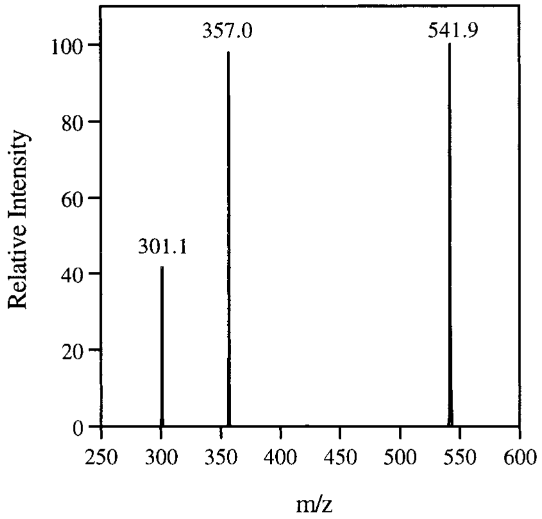
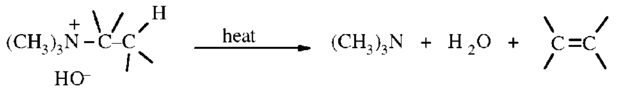


Figure 1. CAD spectrum of the complex of **1** with tetrabutylammonium. The complex is seen at *m/z* = 541.9. Substitution and elimination products are seen at *m/z* = 357.0 and 301.1, respectively. CAD was caused by a 0.68 V excitation for 50 ms.

It should be pointed out that we are not the first to observe an S_N2 reaction in a gas-phase salt complex. Gross and Williams[14] previously reported related S_N2 reactions in cationic complexes between a halide and a bis-tetraalkylammonium dication.

The E2 process for **2** is a gas-phase analogue of the Hofmann elimination,[15] a well-known pyrolytic method of obtaining alkenes from the hydroxide salts of tetraalkylammonium cations. An interesting feature of Hofmann eliminations is their preference for forming the least substituted alkene during the elimination process. In contrast, conventional E2 reactions generally give the most substituted alkene (Saytzev rule[16]). This has been attributed to two factors.[17] First, the reaction is expected to take an E1cb-like pathway with limited double formation in the transition state. As a result, alkene stability is less important and acidity (as well as steric crowding) at the β-carbon plays a significant role in determining the preferred product.[18] Second, it is known that larger leaving groups (i.e., trialkylamine) reduce the preference for Saytzev elimination.[19]



To explore the generality of the complex formation and subsequent CAD reactions, we have prepared complexes of **1** with several other tetraalkylammonium ions. These were generated by adding a small amount of the appropriate tetraalkylammonium salt (~10^{-4} M) to a methanol solution (~10^{-5} M) of the tetrabutylammonium salt of **1**. The results are presented in Table 1. Tetrapropylammonium gives nearly the same distribution as tetrabutylammonium with about a 3:1 preference for the S_N2 pathway. Benzyltriethylammonium gives a substantially different pattern. First, elimination is favored over substitution by a factor of about 2:1 on the ethyl group. Second, the presence of different alkyl groups allows for two S_N2 pathways. Benzylation is favored over ethylation

Scheme 1

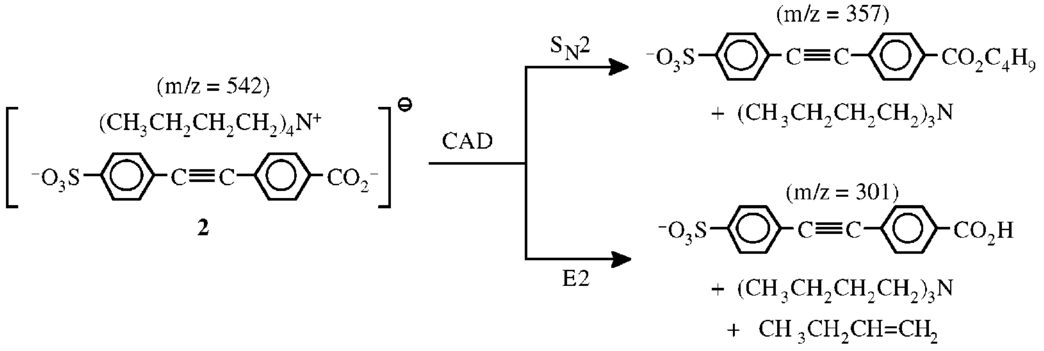


Table 1. Reaction Yields (%) from CAD on the Tetraalkylammonium Complexes of **1**

cation	S_N2	E2
tetrabutyl	70	30
tetrapropyl	75	25
benzyltriethyl	55/15[a]	30
cetyltrimethyl	8/91[b]	1

[a] Percentages of benzylation/ethylation in the S_N2 process. [b] Percentages of cetylation/methylation in the S_N2 process.

by a factor of ~10:1 after correcting for the 3:1 ratio of alkyl groups on the cation. Of course, the preference for benzylation is consistent with known trends in S_N2 reactivity. For example, benzyl iodide is ~100 times more reactive than ethyl iodide in solution.[20] The shift to elimination being the dominant pathway on the ethyl group is not surprising on the basis of known reactivity trends in Hofmann eliminations. For example, Cope showed that ethyl is about 50 times more reactive than *n*-propyl or *n*-butyl in the pyrolysis of quaternary ammonium salts.[21] Cetyltrimethylammonium gives almost exclusively S_N2 reactions at the methyl group. There is a small yield from an S_N2 reaction on the cetyl chain (8%), but almost no elimination is observed. The higher proportion of substitution on the methyl group is expected (methyl halides are about ~100 times more reactive than long-chain alkyl halides in solution),[20] but the small amount of elimination must be related to steric effects involving the large cetyl group. Overall, the results indicate surprising selectivity in the reactions and suggest that subtle factors play a role in determining the preferred pathways.

Although Hofmann elimination generally gives high yields of alkenes,[22] CAD on the tetraalkylammonium salts of **1** gives a substantial amount of substitution. In fact, substitution dominates for the one example of an alkyltrimethylammonium salt (the typical Hofmann substrate). The key difference is probably base strength. The benzoate in **1** is a much weaker (as well as more delocalized) base than hydroxide, and weak (delocalized) bases are known to have a greater tendency to undergo S_N2 reactions.[17,23]

To complement the experimental work and provide insight into the potential energy surface, the GAUSSIAN94 program[24] was used to complete ab initio calculations (MP2/6-31+G(d,p)//MP2/6-31+G(d) level) on a model system, acetate complexed with ethyltrimethylammonium. Although it may seem extreme to model the dianion with acetate, recent work suggests that in reactions with significant intrinsic barriers, dianions can behave much like singly charged analogues.[25] The results in Table 2 are reasonably consistent with our experimental observations. First, the calculated barriers for substitution and elimination (25−30 kcal/mol) are large enough to ensure that the complexes would be stable in the ion trap, but small enough to allow for efficient reactions under CAD conditions. Second, the calculations predict that the barriers to substitution and elimination are fairly similar so competition should be expected. One discrepancy is that the calculated barriers suggest that substitution at the ethyl group should be favored over elimination whereas experimentally there is a 2:1 preference for elimination (see benzyltriethylammonium in Table 1). However, the calculated energy difference is small (1.8 kcal/mol), the experimental system is more crowded than the model system, and elimination has a large entropic advantage[26,27] that is not taken into account in the calculations.[28] Anti elimination is preferred over syn in the calculations,

Table 2. Reaction Energies and Barriers of the Acetate/Ethyltrimethylammonium Complex[a]

process	ΔE	$\Delta E^{\ddagger}$
S_N2 (methyl)	−3.4	25.8
S_N2 (ethyl)	−7.0	26.2
E2 (anti)	9.9	28.0
E2 (syn)	9.9	31.3
dissociation[b]	100.6	

[a] Energies in kcal/mol. Corrected for zero-point energies (scaled by 0.9125).[30] The ester products are optimized in syn conformations. [b] Dissociation to give free acetate and ethyltrimethylammonium.

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(9) Complex **2** is related to gas-phase salt-bridge species, and its reluctance to neutralize can be rationalized in a similar way. For example, see: Lee, S. W.; Kim, H. S.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1998**, *120*, 3188.

(10) In the ion trap, CAD is a multicollision process. Excitation voltages of ~0.7 V were applied for ~50 ms. The branching ratios were relatively insensitive to the applied voltage.

(11) McLuckey, S. A.; Glish, G. L.; Kelley, P. E. *Anal. Chem.* **1987**, *59*, 1670.

(12) The CAD of the $m/z = 301$ ion is the same as that of an authentic sample of the monoanion from **1**.

(13) Katritzky, A. R.; Shipkova, P. A.; Qi, M.; Burton, R. D.; Watson, C. H.; Eyler, J. R.; Karelson, M. *Int. J. Mass Spectrom. Ion Processes* **1998**, *175*, 149.

(14) Gross, D. S.; Williams, E. R. *Int. J. Mass Spectrom. Ion Processes* **1996**, *158*, 305.

(15) Hofmann, A. W. *Ann. Chem.* **1851**, *78*, 253.

(16) Saytzev, A. *Ann. Chem.* **1875**, *179*, 296.

(17) Saunders, W. H., Jr.; Cockerill, A. F. *Mechanisms of Elimination Reactions*; John Wiley & Sons: New York, 1973.

(18) Hanhart, W.; Ingold, C. K. *J. Chem. Soc.* **1927**, 997.

(19) Brown, H. C.; Wheeler, O. H. *J. Am. Chem. Soc.* **1956**, *78*, 2199.

(20) Streitweiser, A., Jr. *Solvolytic Displacement Reactions*; MacGraw-Hill: New York, 1962.

(21) Cope, A. C.; LeBel, N. A.; Lee, H. H.; Moore, W. R. *J. Am. Chem. Soc.* **1957**, *79*, 4720.

(22) Smith, P. A. S.; Frank, S. *J. Am. Chem. Soc.* **1952**, *74*, 509.

(23) Lum, R. C.; Grabowski, J. J. *J. Am. Chem. Soc.* **1992**, *114*, 9663.

(24) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Kieth, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; DeFrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. GAUSSIAN94: Gaussian, Inc., Pittsburgh, PA, 1995.

(25) Gronert, S.; Fong, L.-M. *Int. J. Mass Spectrom.*, in press.

(26) Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219.

(27) Hu, W.-P.; Truhlar, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 860.

(28) Although entropy corrections from frequency calculations are not always reliable, elimination is computed to have a 4.5 eu advantage over substitution in terms of $\Delta S^{\ddagger}$.

(29) Gronert, S. In *Modern Electronic Structure Theory and Applications in Organic Chemistry*; Davidson, E. R., Ed.; World Scientific Publishing: New York, 1998.

but the preference is small relative to other computational studies of E2 reactions.[29] This parallels the results of condensed phase work on Hofmann eliminations where enhanced syn reactivity generally has been observed.[17] Finally, the ab initio results indicate that all of the reactions are close to thermoneutral (±10 kcal/mol) despite the fact that each is a neutralization process. Clearly, the electrostatic attraction in the complex counterbalances the energetic advantages of neutralization. In fact the complexation energy (acetate + ethyltrimethylammonium) exceeds 100 kcal/mol.

In summary, ESI mass spectrometry can be used to generate novel salt complexes and probe the reactivity of ion pairs in the gas phase. In the present example, we have demonstrated a gas-phase analogue of the Hofmann elimination and made an unusual connection between the gas phase and a reaction often run in the solid phase.

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(30) Pople, J. A.; Scott, A. P.; Wong, M. W.; Radom, L. *Isr. J. Chem.* **1993**, *33*, 345.