Stereoselectivity in the Collision-Activated Reactions of Gas Phase Salt Complexes

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The collision-activated dissociations (CAD) of gas phase salt complexes composed of chiral ions were studied in a quadrupole ion trap mass spectrometer. Because both partners in the salt are chiral, diastereomeric complexes can be formed (e.g., RR, RS). Two general types of complexes were investigated. In the first, the complex was composed of deprotonated binaphthol and a chiral bis-tetraalkylammonium dication. CAD of these complexes leads to the transfer of a proton or an alkyl cation to the binaphtholate leading to a singly-charged tetraalkylammonium cation. During CAD, diastereomeric complexes give significantly different product distributions indicating reasonable stereoselectivity in the process. In the second system, the complexes involved a peptide dianion and a chiral tetraalkylammonium cation. These systems may be viewed as very simple models for the interactions of peptides/proteins with small chiral molecules. Again, stereoselectivity was evident during CAD, but the extent was dependent on the nature of the peptide and not observable in some cases. To better understand the structural features needed to achieve stereoselectivity in gas phase salt complexes, representative transition states were modeled computationally. The results suggest that it is critical for the asymmetry of the nucleophile (i.e., anion) to be well represented in the vicinity of its reactive center. (J Am Soc Mass Spectrom 2004, 15, 1509–1516) © 2004 American Society for Mass Spectrometry

The high sensitivity and rapid analysis capabilities of mass spectrometry make it an attractive methodology for solving a wide range of analytical problems. However, stereochemical issues are a challenge because a mass-to-charge ratio provides no direct information with regards to the stereochemistry of a species. Nonetheless, many workers have developed novel approaches for gaining stereochemical information from mass spectrometric data [1, 2]. Much of this work has focused on the development of methods that could be used to determine the enantiomeric purity of a product mixture [3–35]. Like many condensed phase approaches to enantiomeric analysis, the methods rely on complexing the analyte with a substrate of known chirality. This leads to the formation of a pair of diastereomers (assuming that the analyte is not enantiomerically pure). The diastereomers are not equivalent and as a result have different stabilities, kinetic reactivities, and dissociation patterns. These differences can be exploited (i.e., by comparison to data for known standards) and used to determine the enantiomeric purity of a sample. Cooks [3–16], Dearden [7–29], Lebrilla [21–26], Speranza [27–35], and others have provided useful examples of this approach to stereochemical analysis.

Along with methods for analyzing the enantiomeric purity of products, there is a growing need for the development of new reaction processes that are stereoselective. In general, these processes have been probed in the condensed phase, but there is no reason why mass spectrometry could not also be used to screen gas phase reactions for stereoselectivity [35, 36]. An advantage of this approach is that in the solvent-free environment of the gas phase, it is possible to gain a clear understanding of the molecular interactions that lead to stereoselectivity in a chemical transformation. Promising gas phase systems could later be tested in solution.

To explore this possibility, we have turned to a novel gas phase reaction system, salt complexes between doubly and singly charged ions of different polarities. In 1996, Gross and Williams [37] showed that a halide complex of a bis-tetraalkylammonium dication could undergo substitution reactions when subjected to CAD conditions. Later, we showed that complexes of dianions with tetraalkylammonium cations could undergo both substitution (S_N2) and elimination (E2) reactions (Scheme **1**) [38]. This results in the transfer of either an alkyl group (substitution) or a proton (elimination) to the nucleophilic center in the complex (i.e., the carboxylate in Scheme **1**). Moreover, we have shown that these complexes follow the same reactivity patterns that have been observed in condensed phase reactions of analogous species [39].

The salt complexes provide a convenient system for studying gas phase reactivity because the reaction pro-

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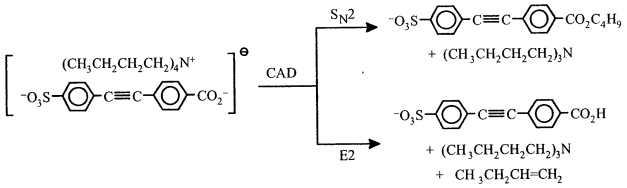


Scheme 1.

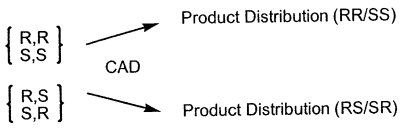
cesses are essentially bimolecular (i.e., intermolecular in the context of a complex), but both of the reagents are introduced via electrospray ionization. As a result, neither reagent needs to be volatile, and it is possible to study reactions between two large, highly functionalized species. Our hypothesis was that if we created salt complexes between chiral partners, the pairs of diastereomers would yield different product distributions during CAD (Scheme **2**). That is, either a different set of products would be formed or the ratio of products would be different. Because these reactions generally produce several products (any of the alkyl groups on the ammonium can be transferred and eliminations can occur on some of them), it seemed likely that variations in the product distribution would be detectable.

In the present study, we show that it is possible to observe stereoselectivity in gas phase chemical transformations using a salt complex system. These results provide a foundation for future work that will emphasize reaction processes that are more relevant to synthetic organic chemistry and offer practical applications.

Methods

All experiments were completed in a Finnigan-LCQ quadrupole mass spectrometer equipped with an electrospray ionization source. Typically the source was operated with electrospray voltages from 3.5–4.0 kV and the heated capillary was held at 150–200 °C. A sample flow rate from 3-10 ul/min was used in the experiments. In general, the salt precursors were dissolved in methanol (10^{-5}–10^{-4} M) and used without further purification. For the CAD experiments a helium background pressure of 1.75×10^{-3} torr was used and tickle voltages from approximately 0.7–1.1 V were employed. As in all ion traps, the CAD is expected to be a multi-collision process. In some cases, the product distributions were measured as a function of tickle voltage and extrapolated to 0 V to eliminate the contribution from secondary fragmentation reactions.

The chiral ammonium salts were produced via Menshutkin reactions of the appropriate enantiomer of N,N-dimethyl-1-phenylethylamine with (5-bromopentyl)trimethylammonium bromide in methanol or with neat methyl iodide. The reaction progress was monitored via mass spectrometry. All solvents and the other reagents were obtained from commercial sources and used without further purification.

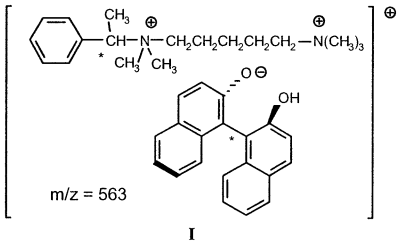


Scheme 2.

All calculations were completed using Macromodel [40], MacSpartan [41], or Gaussian 98 [42]. For the alanine system calculations, a model S_N2 transition state was optimized at the AM1 level. The resulting structure was optimized at the Hartree-Fock level using a 6-31G(d) basis set augmented with standard diffuse functions on the oxygens and nitrogens. This structure then was used for an MP2/6-31 + G(d) single-point calculation. In the E2 transition state searches on the binaphthol system, a Monte-Carlo survey of 10,000 possible structures was completed using the MMFF force-field [43] implemented in Macromodel. Because the force-field is not parameterized for transition state structures, "pre-reaction" structures were surveyed. In these structures, the nucleophilic oxygen was constrained to be within 3.3 Å of the 1-phenylethyl group's β-carbon. This distance does not cause severe steric strain, but forces the nucleophile to be on the path to the transition state. In addition, the dihedral angle defined by the nucleophilic oxygen, β-carbon, α-carbon, and ammonium nitrogen of the dication was constrained to be 180°, the arrangement needed for the generally preferred, antiperiplanar orientation of an E2 transition state [44, 45]. The best structure from the search was modified by stretching the C_β–H and C_α–N bonds to values appropriate for an E2 elimination transition state (1.45 and 1.90 Å, respectively). This structure then was used for an optimization at the AM1 level. The resulting structure was optimized at the Hartree-Fock level using a 3-21G basis set augmented with standard diffuse functions on the oxygens and nitrogens. Finally, the optimized structure was used for a B3LYP single-point calculation employing a 6-31G(d) basis set augmented with standard diffuse functions on the oxygens and nitrogens.

Results and Discussion

Although our initial focus in this project was complexes between a peptide dianion and a tetraalkylammonium cation bearing a chiral group, it is more instructive to begin with a discussion of the binaphtholate system. Binaphthol has been widely used in organic synthesis as a chiral auxiliary and in its deprotonated form, it offers a nucleophilic center, (i.e., oxyanion) in a highly asymmetric environment [46]. Here, the chirality comes from a hindered axis of rotation between the naphthyl groups rather than a stereogenic atom. This system will have the opposite polarity of the one shown in Scheme **1** and therefore, the cation partner must be doubly charged so that overall, the complex has a net charge of +1. To form the chiral dication, a five-carbon chain with



I

Scheme 3.

a pendant trimethylammonium group was added to the R or S enantiomer of N,N-dimethyl-1-phenylethylamine. The binaphtholate salt complex, **I**, is shown in Scheme **3**.There are four possible stereochemical combinations for **I**, and in the text, they will be differentiated by appending to the name the enantiomeric symbols for the dication and anion, respectively (i.e., **I**(R,R)). This salt is capable of numerous reactions during CAD. There are five different alkyl transfer reactions (including two types of methyl transfers) and three different elimination (proton abstraction) reactions. If there is inherent stereoselectivity in the processes, the R and S enantiomer of the cation should not give the same distribution of products when combined with the S enantiomer of the binaphtholate (or vice versa). That is, the chirality of the cation will direct the reactivity of the binaphtholate and alter the preferred site of nucleophilic attack.

When subjected to CAD conditions, **I**(R,R) and **I**(R,S) give the spectra shown in Figure 1. Each spectrum shows the same set of products, but the ratios are not the same, particularly the yield of *m/z* = 173 relative to 218 (the others are nearly unchanged). The structures of the CAD products are shown in Scheme **4**.Four of the products are the result of reactions that occur on the pentyl group that links the charge centers together. At *m/z* = 504 and 414 are alkyl transfer products where the binaphtholate has added to the termini of the pentyl group displacing trimethylamine and N,N-dimethyl-1-phenylethylamine, respectively. The products at *m/z* = 218 and 128 are alkenes that result from elimination reactions (i.e., proton transfer to the binaphtholate) at the ends of the pentyl spacer. Finally, the product at *m/z* = 173 could result from either the transfer of the 1-phenylethyl group to the binaphtholate or an elimination on this group to produce styrene, $C_6H_5CHCH_2$ (i.e., proton transfer to the binaphtholate). The last significant peak in the spectrum, *m/z* = 114, is a secondary fragment from *m/z* = 173 and involves cyclization with the loss of trimethylamine (Scheme **5**).

Because there is a significant secondary fragmentation channel, the CAD branching ratios are dependent on the excitation energy. To correct for the secondary channel, the ratios were measured as a function of the tickle voltage used in the multi-collision CAD. Because the stereoselectivity is most apparent in the ions at *m/z* = 173 and 218, we have focused on them in our analysis. The ratios of these ions are shown in Figure 2

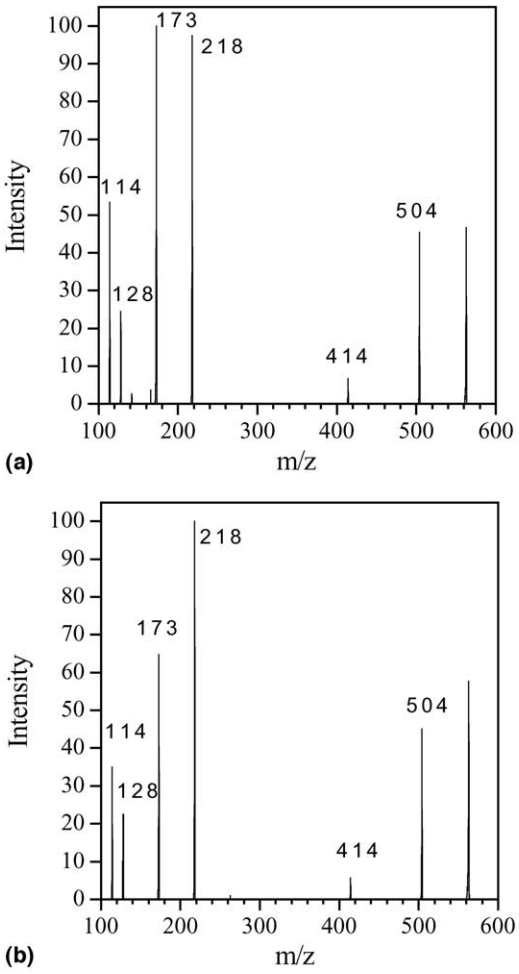
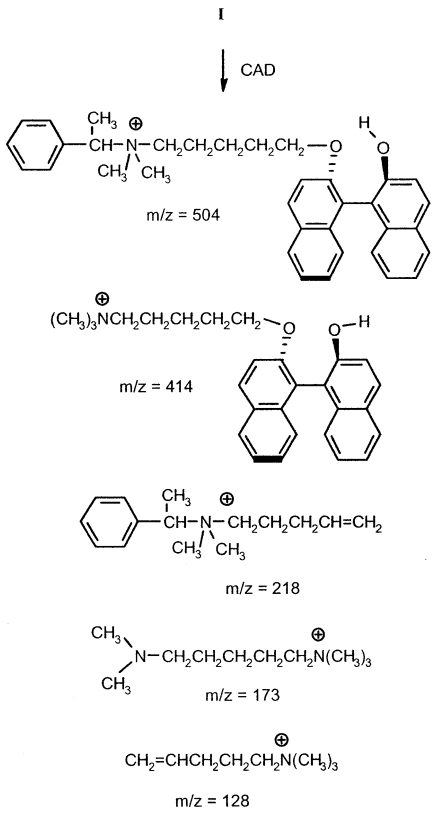


Figure 1. CAD spectra of (**a**) **I**(R,S) and (**b**) **I**(R,R). Parent is at *m/z* = 563. See Schemes **4** and **5** for identities of the peaks.

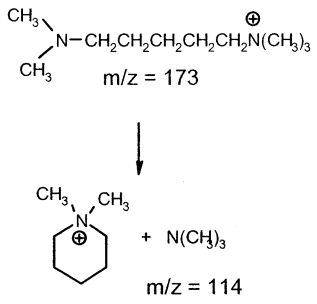
for the four possible stereochemical combinations. In addition, the total CAD yield at each voltage is shown for the (R,S) combination (a nearly identical curve would be obtained with the other complexes). Each point in the graph is the average of at least six measurements. As expected, the data for the enantiomeric pairs, RR versus SS and RS versus SR, are essentially identical. However, it is clear that the diastereomers (e.g., RR versus RS) yield markedly different branching ratios at all CAD voltages. The increase in the relative amount of *m/z* = 173 at lower CAD energies is a result of suppressing the secondary fragmentation channel shown in Scheme **5**. At the approximate onset voltage (0.7 V), there is about a two-fold difference in the ratios produced by the diastereomeric salt complexes. Clearly, these complexes are exhibiting stereoselectivity with respect to the formation of *m/z* = 173.

It is not surprising that the intensity of the peak at *m/z* = 173 would be the most sensitive to the chirality of the cation. This is the only peak in the spectrum that is related to a reaction directly on the chiral center of the 1-phenylethyl group. As noted above, it could result from either the transfer of the 1-phenylethyl group to



Scheme 4.

the binaphtholate or an elimination reaction on this group to give styrene. It is likely a combination of both, but the high yield observed for the other elimination pathway (m/z = 218) suggests that styrene formation might account for the majority of ions at m/z = 173. In any case, the data indicate that the RS and SR combinations allow for more of the reactivity to occur on the phenylethyl group. To explore the factors behind the stereoselectivity, we have modeled the transition state of an E2 reaction on the 1-phenylethyl group. The transition states for the RR and SR diastereomers are shown in Figure 3. They were obtained from a survey of pre-reaction conformers using the MMFF force-field [43] and then were subsequently optimized at the Hartree-Fock level (see Methods section for details). The energies of the structures were also determined by single-point calculations at the B3LYP level. This ap-



Scheme 5.

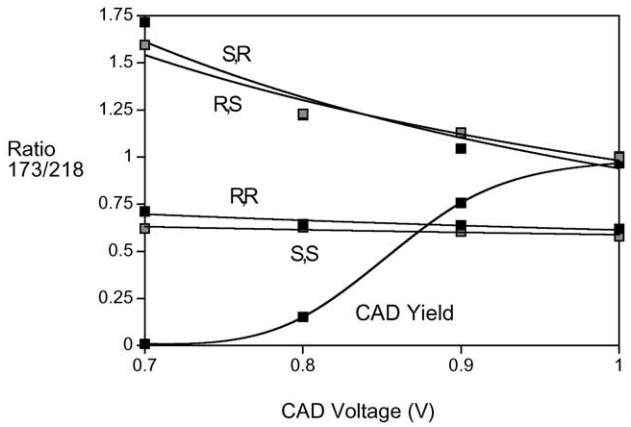


Figure 2. Product ratio of m/z 173 to 218 as a function of the activation voltage. The CAD yield refers to the fraction of the salt complex that dissociates at that voltage. The points are the result of multiple experiments and have standard deviations from 0.01–0.05. The points for the R,S and S,S combinations are shown in gray.

proach is not guaranteed to yield the lowest energy transition states, but provides insight into the factors that lead to the stereoselectivity. The SR structure is preferred at the Hartree-Fock and B3LYP levels by about 2 kcal/mol. The cause of the preference is evident in the steric interactions of the binaphtholate. In the preferred transition state (SR), the neutral naphthol ring suffers no close steric interactions and has what is likely a stabilizing charge-π interaction with the spectator trimethylammonium group of the dication. In contrast, the neutral naphthol ring in the RR transition state suffers from a repulsive interaction with the phenyl group of the dication and is unable to take advantage of the interaction with the trimethylammonium group. Although these are only representative structures, they clearly illustrate how stereoselectivity can be attained in the transition state.

In our second system, a peptide dianion was used as the chiral nucleophile and it was complexed with a chiral tetraalkylammonium cation. This is in direct analogy to the system presented in Scheme **1** with the carboxylates of the peptide dianion acting as nucleophiles. As before, the chiral tetraalkylammonium was obtained by the quaternization of a chiral tertiary amine. Scheme **6** shows a representative example of such a salt complex. The peptide contains three carboxyl groups that are easily ionized, the aspartic acid side chain, the glutamic acid side chain, and the C-terminus, so a dianion is formed readily. Of course electrostatics suggest that ionization would occur preferentially on the aspartic acid and one of the sites on the C-terminal glutamic acid. As in **I**, the chirality of the ammonium cation is provided by a 1-phenylethyl group attached to the nitrogen in either its R or S configuration. During CAD, the N,N,N-trimethyl-1-phenylethylammonium cation potentially can transfer three different groups to the peptide dianion: a methyl

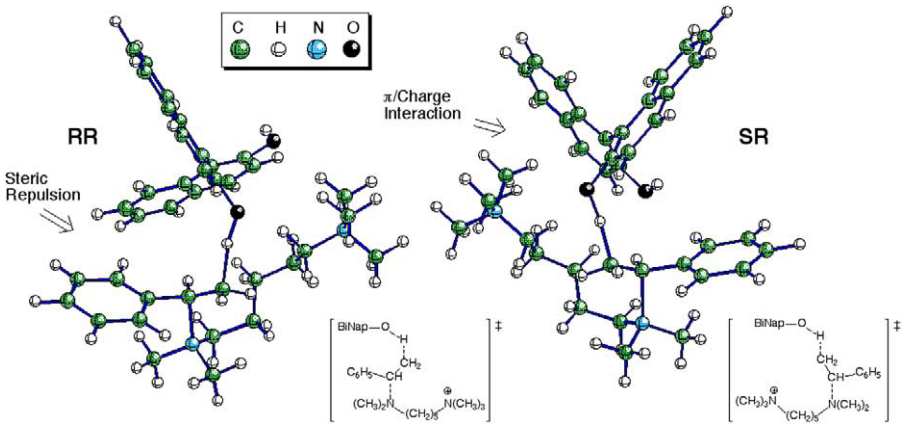
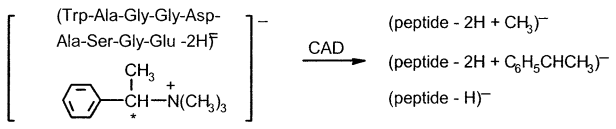


Figure 3. Optimized structures of the E2 transition states for the formation of m/z = 173 from **I**(R,R) and **I**(S,R).

group, a 1-phenylethyl group, or a proton (i.e., elimination on the phenylethyl group to give styrene). Presumably the group is transferred to one of the nucleophilic carboxylates on the peptide dianion.

Spectra obtained for the R and S enantiomers are shown in Figure 4. In both diastereomers, the major pathway is loss of trimethylamine (m/z = 951) indicating transfer of the phenylethyl group to the dianion. The other products correspond to substitution on a methyl group (m/z = 861) and elimination on the phenylethyl group (m/z = 847). The latter product is simply singly deprotonated Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu (i.e., transfer of a proton). Comparing the spectra in Figure 4, it is clear that the yield of m/z = 847 is somewhat dependent on the chirality of the cation. It should be noted that similar differences were observed in multiple spectra taken at different times.

In contrast, the complexes of doubly deprotonated Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe with the chiral cation lead to little evidence of stereoselectivity. The two spectra are very similar and the three channels are observed in approximately equal yields (Figure 5). There is a small difference in the amount of H_2O loss from the complex (m/z = 1207), but this is a very minor channel. Apparently the chirality of the cation has little effect on the product yields despite the fact that the majority of the reactions occur on the chiral, 1-phenylethyl group ($C_6H_5CHCH_3$ and proton transfer). Clearly the asymmetry of the cation should be well represented in reactions occurring on the chiral center, so it appears that this peptide is doing a poor job of exerting its asymmetry on the reaction process. This result appears to be fairly general. In an effort to explore stereoselectivity in these systems, we surveyed the CAD spectra of



Scheme 6.

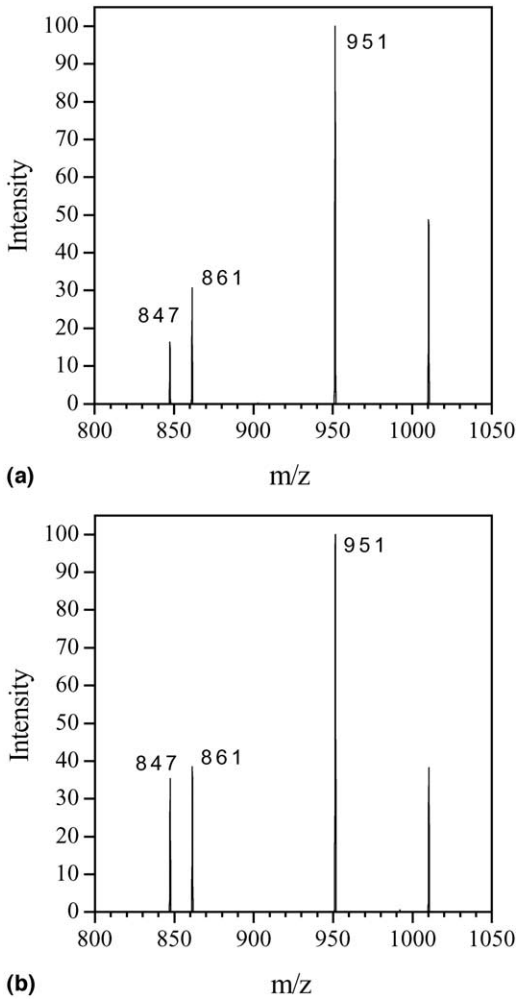


Figure 4. CAD spectra for the complexes of [Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu − 2H]$^=$ with the (**a**) S and (**b**) R enantiomers of the N,N,N-trimethyl-1-phenylethylammonium cation. Parent is at m/z = 1010 and peaks at m/z = 951, 861, and 847 represent the transfer of a 1-phenylethyl cation, a methyl cation, and a proton, respectively, to the peptide dianion.

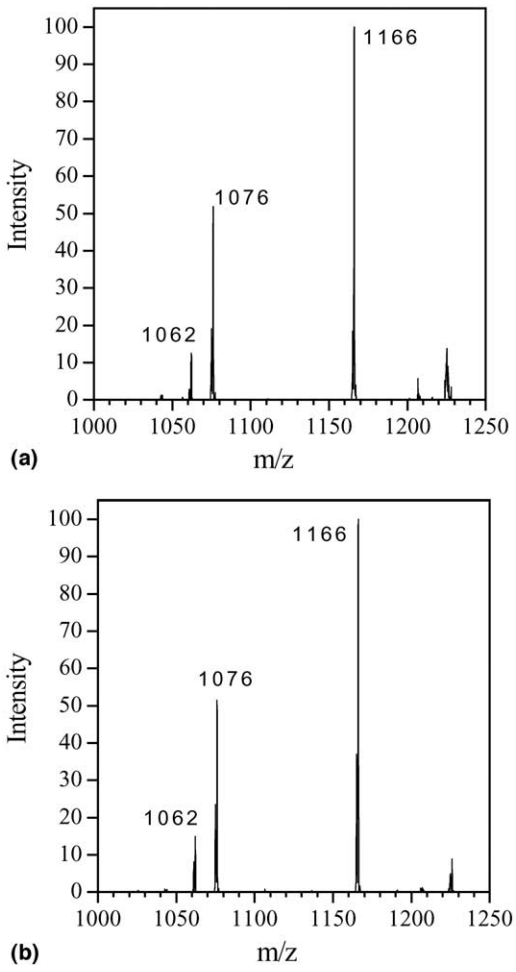


Figure 5. CAD spectra for the complexes of [Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe − 2H]$^{=}$ with the (**a**) S and (**b**) R enantiomers of the N,N,N-trimethyl-1-phenylethylammonium cation. Parent is at m/z = 1225 and peaks at m/z = 1166, 1076, and 1062 represent the transfer of a 1-phenylethyl cation, a methyl cation, and a proton, respectively, to the peptide dianion.

salts containing a variety of peptide dianions (3–9 residues with a variety of amino acids). In most cases, there was only a small difference between the CAD spectra of the complex with the R or S enantiomer of the N,N,N-trimethyl-1-phenylethylammonium cation.

Our work with the peptide complexes suggests that a high degree of stereoselectivity is difficult to attain in these systems. This result can be rationalized by considering the two ways in which a peptide might confer asymmetry to a reaction process. By analogy to an enzyme, the combined chiral centers of the peptide could lead to a secondary structure with an asymmetric binding pocket. Of course this is not a reasonable expectation in a small peptide subjected to CAD conditions. Instead the peptides in these complexes probably rely on local asymmetry near the reaction center to promote stereoselectivity. In the case of a C-terminal carboxylate acting as a nucleophile, the reaction center (carboxylate oxygen) is relatively far from the nearest chiral center, an α-carbon. As a result, van der Waals interactions between the groups on the α-carbon and the substrate (cation) could be weak and have little impact on the relative energies of the R and S transition states. To explore this conjecture, substitution transition states were optimized for a model system, the S_N2 reaction of deprotonated alanine with the N,N,N-trimethyl-1-phenylethylammonium cation (see Methods section for details). The structures for attack on the 1-phenylethyl group of the R and S cations are shown in Figure 6. As we have noted before [39], the transition states of these reactions tend to be relatively loose (ion-pair like [47]) and consequently, the two chiral centers are far apart. In this case, the transition state is exceptionally loose and is best described as a carbocation trapped between the nucleophile and leaving group (S_N1-like). In the figure, the structures are presented as if they were mirror images with the only exception being the orientation of the α-methyl group of the alanine (into the plane in S and out of the plane in R). Because this group is far from the cation's chiral

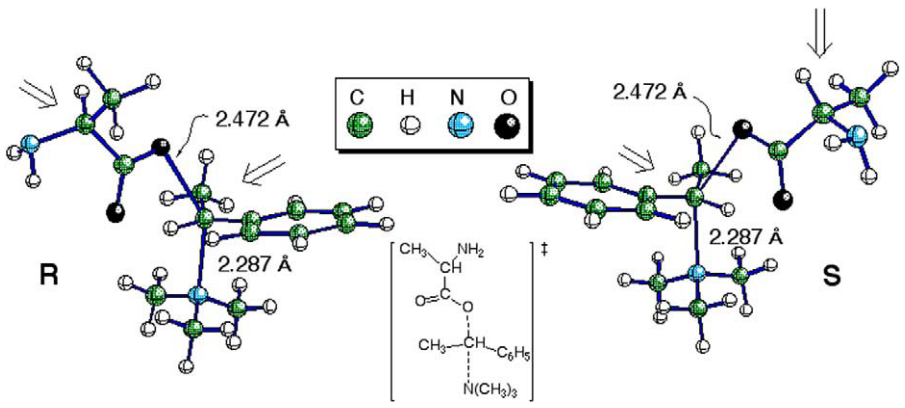


Figure 6. Optimized structures of the S_N2 transitions states for the reaction of deprotonated alanine with the R and S enantiomers of the N,N,N-trimethyl-1-phenylethylammonium cation. Arrows indicate chiral centers. Alanine is at the top and the trimethylamine leaving group is at the bottom. Breaking C–N and forming C–O bond distances are shown.

center, it is not surprising that the energies of the two transition states are very similar. At the MP2/6-31 + G(d,p) level, they differ by less than 0.1 kcal/mol so stereoselectivity is effectively absent. Of course this is a small model system in comparison to a peptide where many other interactions would be possible, but the large separation between the chiral centers indicates that stereoselectivity may not generally be observed in these systems and might be dependent on the presence of some long range interactions with other residues on the peptide. The chiral center is more removed if the side chain of an aspartate or glutamate acts as the nucleophile and the potential for stereoselectivity would be reduced.

Conclusions

Stereoselectivity can be achieved in the CAD of gas phase salt complexes as long as the asymmetry of the nucelophile is well represented near the reactive centers. Salt complexes composed of a peptide dianion and a tetraalkylammonium cation can fail to display stereoselectivity because the chiral centers of the peptide are not close to the nucleophilic oxygen and secondary interactions probably are necessary for stereoselectivity. However, complexes that incorporate a binaphtholate anion and a bis-tetraalkylammonium dication display good stereoselectivity because the bulky naphthalene rings create a highly asymmetric environment near the nucleophilic oxygen. Computational modeling supports this view. These systems differ from those studied in the past because the stereochemistry is controlling the outcome of a chemical transformation of a substrate (i.e., dication) rather than the dissociation of or exchange in a non-covalent complex. Studies are underway in an effort to discover systems that offer greater stereoselectivity in the CAD of gas phase salt complexes.

Acknowledgments

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