exactly as described earlier.[4] However, the workup was quite different: At the end of the indicated time period, dimethyl sulfide (4 equiv) was added to the reaction mixture at -20 °C. After the mixture was stirred for 40 min at -20 °C (CCl_4/dry ice), the cold reaction mixture was added slowly to a vigorously stirred, saturated (~5%) aqueous solution of sodium fluoride (the volume of this NaF solution was about twice the volume of the original reaction mixture) at room temperature. Stirring was continued for the specified time then the aqueous phase was saturated with sodium chloride. The gel-like, precipitated inorganic fluorides were removed by filtration through a pad of Celite, and the phases were separated. The aqueous phase was extracted three more times with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and concentrated to give a mixture of the desired epoxy alcohol and the recovered tartrate diester. Final purification was effected by chromatography on silica gel.[13] In the original procedure the dialkyl tartrate would be removed in a two-phase alkaline hydrolysis step, but here such a step destroys the water-soluble epoxy alcohol. Fortunately, dimethyl tartrate (DMT), diethyl tartrate (DET), and diisopropyl tartrate (DIPT) have quite different R_f values on silica gel (0.1, DMT; 0.27, DET; 0.44, DIPT; hexane:ethyl acetate, 7:3). Chromatographic separation of the epoxy alcohol from the dialkyl tartrate is easy if the appropriate tartrate ester is chosen.

Epoxy alcohol ester **3** was also prepared by an alternate sequence starting from butadiene dimer **9** (Scheme II). This is probably the best current route to this SRS precursor (**3**).

The last example is synthesis of epoxy alcohol **4** and thence (+)-disparlure (Scheme III). The crystallinity of epoxy alcohol **4** greatly simplifies its isolation (no chromatography needed). The final step involves hydrogenation of an α,β-unsaturated epoxide and gives in addition to **5** a ketonic product (ratio of **5** to byproduct is 72:28). The ketone presumably arises by rhodium(I)-catalyzed rearrangement of the unsaturated epoxide in a process similar to that reported by Noyori.[18] The ketone impurity was reduced to an alcohol ($NaBH_4$, EtOH, 15 min) and then easily removed by flash[19] chromatography (silica gel, 2% ether-petroleum ether) to give the pure epoxide **5** in 60% yield from the unsaturated epoxide. We have also produced pure (-)-disparlure [$[\alpha]^{20}_D$ -0.5° (*c* 10, CCl_4)] by this same synthetic sequence (Scheme III) with the obvious exception that (+)-DET was used in the epoxidation step. Both disparalure enantiomers gave appropriate combustion analyses and exhibited spectral and chromatographic properties consonant with literature data.[20] Further proof of structure and absolute configuration was obtained in field tests.[21]

Acknowledgment. We are very grateful to Professors Hisashi Yamamoto and Jiro Tsuji for helpful discussions and providing us with the butadiene dimer **9**. We also thank Professor Ring Cardé and his colleagues for carrying out the field tests of (+)- and (-)-disparlure. Financial support was given by the National Institutes of Health (GM 24551) and by Eli Lilly and Co.

(11) Both (-)- and (+)-diisopropyl tartrate (DIPT) were prepared in about 50-60% distilled yield by the method of Austin (Austin, P. C. *J. Chem. Soc.* **1928**, 1831). When the epoxidation of **7** was performed by using (+)-DIPT, the enantiomer of **2** [i.e., 2(*S*),3(*S*)-epoxybutan-1-ol, $[\alpha]^{24}_D$ -54.5° (*c* 0.24, PhH)] was produced in 40% yield.

(12) We are indebted to Dr. Y. Arai of Ono Pharmaceutical Co. for a generous sample of this allylic alcohol. He prepared it in several steps from propargyl alcohol. When allylic alcohol **8** was subjected to the standard epoxidation conditions and workup,[4] epoxidation occurred but further reaction (apparently involving cyclization to a diol lactone) also took place. For examples of highly selective cyclizations and other rearrangements of epoxy alcohols mediated by titanium(IV) alkoxides, see: Morgans, D. J.; Sharpless, K. B.; Traynor, S. G. *J. Am. Chem. Soc.*, preceding paper in this issue.

(13) On larger scales, and depending on the exact case, vacuum distillation has proven to be an alternative to chromatography for this separation.

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(15) The use of acetonitrile in addition to carbon tetrachloride and water is an important factor in making this modification (Carlsen, P. H. J.; Katsuki, T.; Sharpless, K. B., unpublished results) of the well-known RuO_4-catalyzed olefin cleavage procedure better than those already in the literature. For a 1-mmol scale reaction, we have found that the optimum solvent ratio is 2 mL of CCl_4, 2 mL of CH_3CN, and 3 mL of H_2O.

(16) When the procedure of Ames et al.[17] was performed using 1-bromodecane and the dianion of propargyl alcohol, 2-tridecyn-1-ol was obtained in 90% distilled yield (bp 97-100 °C (0.3 torr)). Partial hydrogenation over 5% Pd-$BaSo_4$, in the presence of synthetic quinoline, in ethanol gave the (*Z*)-allylic alcohol **10** in 96% distilled yield ((bp 85-89 °C (0.1 torr)).

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(21) Our (+)-disparlure was ~10 times more effective than (±)-disparlure as a gypsy moth attractant. Our (-)-disparlure showed negligible activity as a moth attractant.

(22) **Note Added in Proof**: For other efficient routes to chiral, four-carbon epoxy alcohols such as **2** see: Hungerbühler, E.; Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 958. Seebach and Hungerbühler have also written a detailed and stimulating review on the usefulness of tartaric acid for "Syntheses of Enantiomerically Pure Compounds"; this review will appear in a forthcoming book entitled "Modern Synthetic Methods 1980".

Unimolecular Dissociations at Short Times. A Comparison of Angle-Resolved Mass Spectrometry and Field Ionization Kinetics

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The distribution of products arising from unimolecular dissociation of an internally excited molecule is a function of both its internal energy and the observation time.[1] Methods which allow control of these factors provide access to unimolecular rate constants[2] on one hand and give a highly resolved view of the dissociation chemistry on the other. We now show that collision-induced dissociation, done with resolution of scattering angle, gives data which are comparable to that provided by field ionization kinetics (FIK).[3] This method provides good time resolution at lifetimes approaching 10 ps and is proving an effective means of studying unimolecular chemistry;[4] the angle-resolved procedure may have comparable value since collisionally activated molecules can be selected so that they dissociate at times comparable to the fastest observed in FIK while a continuous range of longer lifetimes is also accessible.

In angle-resolved mass spectrometry[5] the collisionally induced dissociation of an ion, m_1^+, to give a product, m_2^+, is monitored as a fuction of the laboratory scattering angle, θ. Large (approximately 10 eV) energy depositions are accessible at scattering angles of ca. 1° for kilovolt energy ions. The methodology has previously been shown to allow selection of the internal energy deposited in an ion [6,7] and thus to serve as a means of obtaining

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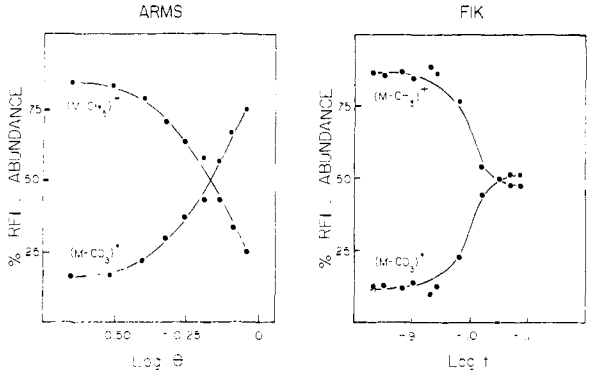
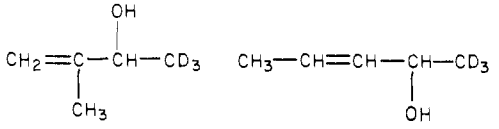


Figure 1. Comparison of the competitive unimolecular dissociations of ionized $CH_2C(CH_3)CH(OH)CD_3$ as followed by field ionization kinetics (FIK) and angle-resolved mass spectrometry (ARMS). The ARMS data are plotted against the laboratory scattering angle, since this quantity tracks the internal energy deposition and hence ion lifetimes.

breakdown curves (mass spectra deconvoluted for internal energy of the parent ion)[9] and of following H/D exchange as a function of internal energy[10] and characterizing structurally isomeric ions.[11]

For this comparison between the time-resolved FIK technique and angle-resolved mass spectrometry, we chose to examine[12] a superficially simple but subtle reaction, methyl loss from the unsaturated alcohols, **1** and **2**. This process occurs by three



1 **2**

distinct mechanisms[14] dependent upon observation time and distinguishable by isotopic labeling. At short times, $<10^{-10.5}$s, ion **1** fragments by $CD_3\cdot$ loss in preference to $CH_3\cdot$ loss. At intermediate times, however ($10^{-10.5}$–10^{-9}s), the loss of $CH_3\cdot$ predominates. At still longer times (including the metastable time region), there is an increase in the loss of $CD_3\cdot$ vs. $CH_3\cdot$, with the loss of $CD_3\cdot$ proceeding by an alternative mechanism from what is nominally the same process occurring at very short times. Figure 1 shows the results of the angle-resolved experiment and the FIK experiment, for isomer **1**. As plotted, the angle-resolved data show the collision-induced dissociations of the molecular ion, yielding $(M - CD_3\cdot)^+$ as a function of the angle through which the ion is scattered. At high angles (i.e., short ion lifetime) the ratio of the loss of $CD_3\cdot$ vs. $CH_3\cdot$ is larger for the angle-resolved technique,

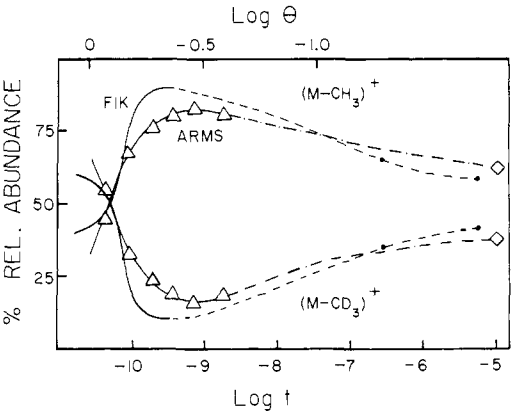


Figure 2. Comparison of FIK and ARMS data for isomer **2**. The abscissa for the angle-resolved data has been scaled to give the best fit to the FIK results.

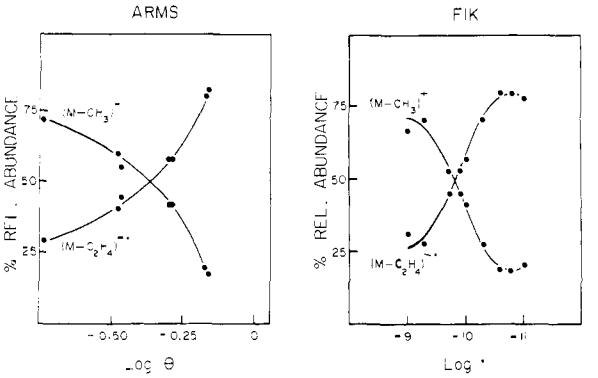


Figure 3. Comparison of the two methods for fragmentations of ionized cyclohexene.

which implies that the time scale accessible to this technique is comparable with or even shorter than FIK. The results for the long-lived metastable ion decompositions in both experiments are in excellent agreement.

Isomer **2** also gave comparable results for both techniques. At 50 ps, near the short time extreme, the ratio of labeled to unlabeled methyl radical loss is 1.21, the same ratio which is reached at the high angle extreme of 0.82°. The FIK and angle-resolved data for this compound are compared in Figure 2. It is especially noteworthy that the angle-resolved results access those internal energies, and correspondingly those times which are intermediate between the longest observable times of the present FIK experiment and the metastable ion time window.

A further illustration of the capabilities of angle-resolved measurements is provided by the cyclohexene molecular ion. This species has been the subject of careful FIK investigation[15] and undergoes two reactions which have very different frequency factors. They are a retro-Diels–Alder reaction, to give what can be thought of as the 1,3-butadiene radical cation (m/z 54), and a multiple hydrogen atom shift followed by elimination of a methyl radical, to give a $C_5H_7^+$ ion (m/z 67). The field ionization kinetics data for these transitions show that at short ion lifetimes the retro-Diels–Alder reaction dominates, while at longer lifetimes the predominant process is the rearrangement–elimination reaction. These findings are also verified by the results obtained from the angle-resolved technique. Figure 3 shows the experimental results for both of the methods.

Ions that undergo collisional activation can have lifetimes, with respect to unimolecular dissociation, ranging from those of the fastest dissociations which occur in the ion source to those corresponding to metastable dissociations occurring within the various field-free regions of a mass spectrometer. It is evident from the

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data presented that resolution of the angle of scatter of kilovolt energy ions after collision with neutral gas molecules provides access to this range of lifetimes. This information had previously only been available via more complex methods. Much in the same way that the "phenomenological" rate constant determined by FIK can be ascribed to the internal energy content of a given molecular ion, we have demonstrated that angle-resolved mass spectrometry has a similar capability of specifying the lifetime[16] of an ion after collisional activation. Most significantly, a wide range of ion lifetimes is available, including those corresponding to the shortest accessible in field ionization kinetics. These findings should facilitate fundamental studies of ion chemistry.

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(16) These ions would not fragment without collisional activation; the total lifetime of the molecular ion is of the order of microseconds, but the lifetime after collisional activation is variable in the range 10^{-11}–10^{-6} s. If isomerization occurs prior to collisional activation, the two techniques would sample the same time interval but do so for ions of different structure.

Observation of Conformationally Distinct Proline Residues in Two Cyclic Peptides by Solid-State Nuclear Magnetic Resonance

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High-resolution ^{13}C NMR spectroscopy of crystalline cyclic peptides allows the comparison of their conformations in the solid state to those assumed in solution. The solid-state NMR spectra have individual ^{13}C resonances at their isotropic chemical shift positions.[1,2] Both intramolecular (conformational) and intermolecular (crystal packing) effects can play important roles in determining the actual magnetic environment of nuclei in solid samples which is reflected in the isotropic chemical shift.[3] In contrast, solution samples have chemical shifts dominated by intramolecular factors, since most intermolecular interactions are averaged out by rapid molecular motions. It is of interest to find examples of molecules where the solid-state NMR chemical shift data can be interpreted in terms of conformational and packing effects separately. Cyclic peptides with solved crystal structures and well-analyzed solution NMR spectra showing defined conformational features are attractive choices for study.

We have obtained ^{13}C NMR spectra of two crystalline peptides with chemical shifts that can be uniquely attributed to molecular conformation, and these are the same effects manifested in the solution spectra. Both of the peptides studied contain two proline residues, and the ^{13}C chemical shifts of proline resonances are indicative of particular conformational states of the peptide.

The cyclic pentapeptide *cyclo*-(D-Phe-Pro-Gly-D-Ala-Pro) has essenitally the same conformation in solution (in a variety of solvents)[4] and crystals.[5] This conformation is stabilized by the two intramolecular hydrogen bonds shown in Figure 1A. The two prolines in the molecule have very different ring geometries; the one involved in the 4 → 1 hydrogen bond (β turn)[6] has a ring conformation similar to that found in many linear peptides with rotational angles $\phi = -64°$ and $\psi = 128°$,[7] while the other has a more unusual conformation with $\phi = -82°$ and $\psi = 59°$, probably because it is residue 2 of the 3 → 1 hydrogen bond (γ turn).[6] This latter local conformation has the carbonyl oxygen of the proline eclipsed with its β-methylene group, resulting in an unusually high-field chemical shift position for the β-carbon resonance.[8,9] This is shown in the solution spectrum of Figure 2B where the arrows point out the 5-ppm difference between the C_β resonances of the two prolines; the upfield shifted β signal is near those from the proline γ carbons.

Figure 2A contains the ^{13}C NMR spectrum of the crystalline cyclic pentapeptide. It is a well-resolved spectrum with aliphatic

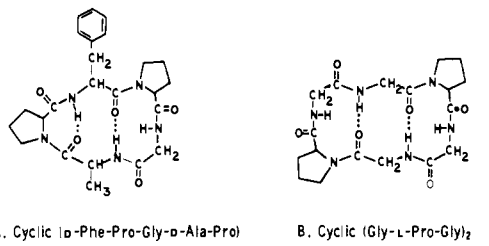

Figure 1. Structures of the two cyclic peptides whose solid-state NMR spectra are discussed. (A) *cyclo*-(D-Phe-L-Pro-Gly-D-Ala-L-Pro), showing 3→1 (γ turn) and 4→1 (β-turn) hydrogen bonding, present in both solution and crystal conformations of this peptide. (B) *cyclo*-(Gly-L-Pro-Gly)$_2$, showing 4→1 (β turn) hydrogen bonding present in the proposed (ref 12) solution conformation. Only one hydrogen bond exists in the conformation observed in crystals.

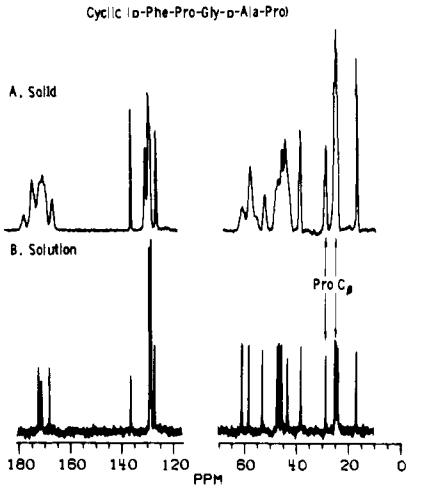

Figure 2. ^{13}C NMR spectra of *cyclo*-(D-Phe-Pro-Gly-D-Ala-Pro) at 38 MHz with chemical shifts relative to external Me_4Si. (A) Polycrystalline peptide sample. This spectrum was obtained on a home-built double-resonance spectrometer from ca. 300 mg of material in an Andrews-Beams rotor spinning at the magic angle. The spectrum is the result of 15 000 single 1-ms cross-polarizations from the protons, recycled every 5 s with 2.5-mT proton decoupling during the 0.1-s acquisition time. To avoid interference from spinning sidebands the spectral region 120–180 ppm is from the sample in a Kel-F rotor spinning at 2.4 kHz while the 0–70-ppm region is from the sample in a Delrin rotor spinning at 3.2 kHz. (B) Peptide in $CDCl_3$ solution. This spectrum was obtained on a Nicolet NT-150 spectrometer with 300 mg of sample in 10-mL volume in a 20-mm tube. It is the result of 9000 accumulations after 90° pulses recycled every 7 s. Square-wave modulated proton decoupling was applied continuously.

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