

be crucial in interpreting the SID studies of 1,3-dioxolane. The conclusion that was reached based on the SID data applies here too, i.e., the formation of ring-opened structure d from 1,3-dioxolane and subsequent isomerization of d to g (and/or f) accounts for the fragmentation behavior. It is important to note that, in agreement with SID data, CAD data do not support the suggestion that the vinyl alcohol structure b makes a significant contribution to the dioxolane-derived ion. The agreement between the surface and gas-phase data also confirms the earlier conclusion that the contributions of $[M + H]^+$ to the SID spectra are not predominant.

Further confirmation that the peak at m/z 29 in the gas-phase ERMS spectra is due to a structure of the type f or g was obtained by recording the ERMS spectrum (5–25 eV collision energy) of the $[C_2H_4O]^+$ ion derived from pyruvic acid. The spectrum was dominated by m/z 29 (at 10 eV, $29^+ = 63\%$, $27^+ = 5\%$, $16^+ = 4\%$, and $15^+ = 4\%$). Even more significantly, the spectrum changed little with collision energy. This is in marked contrast with the behavior of the ions derived from ethylene oxide and dioxolane. These results therefore provide further evidence for isomerization of d to f and g.

Conclusions

The results of the SID and the gas-phase collision experiments (ERMS and ARMS) for $[C_2H_4O]^+$ ions generated from six different precursors agree very well and can be summarized as follows

1. The majority of acetaldehyde, butyraldehyde, and pyruvic acid derived $[C_2H_4O]^+$ ions have the structures a, b, and f, respectively, assigned earlier.

2. The $[C_2H_4O]^+$ ions formed from ethylene oxide have stable structure d, although a fraction isomerize to structure f and g, during collisions with the gaseous or metal target. It is not possible to exclude the presence of some ions with structure c in the stable ion beam.

3. $[C_2H_4O]^+$ ions derived from 1,3-dioxolane and ethylene oxide are identical with those from ethylene carbonate. There is no evidence for a contribution from structure b in the 1,3-dioxolane derived $[C_2H_4O]^+$ ions studied.

This study shows that the ion/surface interaction method can be successfully applied to ion structural problems especially in cases where a mixture of structures is represented. Features of this technique of ion characterization are the following: (i) considerable excitation occurs yielding high-energy ions that fragment by readily interpreted bond cleavage reactions; (ii) it provides results that in many respects are comparable to other methods that are used for structure characterization; however, (iii) reactive collisions occur simultaneously and add a new dimension of information to the daughter spectra recorded. It is also evident that the ability to preclude reactive collisions so as to separate out their contributions to the daughter spectra is desirable. This capability will require the use of surface conditions (e.g., ultra high vacuum conditions) that are not presently available.

Acknowledgment. This work was supported by NSF Grant CHE 8408258 and by the U.S.–Yugoslav Joint Fund for Scientific and Technological Cooperation in cooperation with the National Science Foundation under Grant 514 and by the Science Research Fund of Serbia.

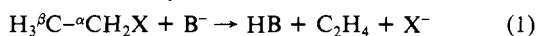
On the Mechanism of Base-Induced Gas-Phase Elimination Reactions of Thioethers

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Abstract: The base-induced gas-phase elimination reactions of diethyl sulfide have been studied by using the method of Fourier transform ion cyclotron resonance mass spectrometry. Reaction with the nitrogen bases NH_2^- , $EtNH^-$, and Me_2N^- preferentially proceeds via an α',β -elimination mechanism, where α' proton abstraction of the sulfide results in the formation of an α -thio carbanion, which undergoes an intramolecular syn elimination to generate the ethyl thiolate anion. Reaction with OH^- , MeO^- , and F^- exclusively proceeds via an E2 mechanism. However, for the reaction with OH^- , rapid exchange is observed within the reaction complex between the α -hydrogens of the sulfide and the hydroxide hydrogen prior to E2 elimination. For the E2 eliminations the α - and β -deuterium isotope and leaving group effects have been determined as a function of the base strength. As in our previous study of the mechanism of base-induced gas-phase elimination reactions of ethers, the isotope and leaving group effect data are interpreted in terms of a variable E2 transition-state structure. Combining the results of our previous study with those of the present study has led to the conclusion that the perturbation of the transition-state character effected by changing the leaving group or the base follows the rules established for condensed phase β -elimination reactions. For the nearly thermoneutral elimination reaction of diethyl sulfide induced by F^- it is concluded that two reaction mechanisms are operative, both characterized by a bent proton transfer: an E2C mechanism involving a two-side attack of F^- on the β -hydrogen and α -carbon of the sulfide, yielding free ethyl thiolate anions and a syn elimination involving a two-side attack of F^- on the β -hydrogen and the leaving group, generating HF solvated ethyl thiolate anions.

Over the years, the scope of concerted base-induced elimination reactions (E2) has proven to be an inexhaustible source for mechanistic studies. The interest in this class of reactions derives from the widely held view that these one-stage processes involve a mechanism in which at the transition state the $C_\beta-H$ and $C_\alpha-X$ bond breaking are electronically coupled, although these bond cleavages need not to be synchronous.



Various workers have pointed out that the $C_\alpha-X$ bond breaking may lag behind hydrogen transfer, or vice versa, a concept which has become known as the "variable transition state".¹ Within this concept refinements are introduced with respect to the geometry of the transition state involving linear proton transfer

(1) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 2nd ed.; Harper and Row: New York, 1981; pp 197–210.

(E2H model),² bent proton transfer with loose covalent B---C_α interaction (E2H-E2C model),³ and even an intermediate type proton transfer (McLennan model).⁴

Finally, the concept of syn and anti elimination reflects the competition between β-hydrogen abstractions characterized by a transition state in which the β-hydrogen and leaving group X are syn or anti periplanar, respectively.¹

Experimental observations indicate that the mechanistic course of the concerted elimination reactions may be determined by many factors such as temperature, the nature of the base, the substrate, and, last but not least, the solvent.

To prevent participation of solvent molecules and/or counterions, polar eliminations have also been studied in the gas phase.⁵⁻¹⁰ Although these studies are still in their infancy, strong indications have already been obtained to suggest that the characteristics of the mechanism of concerted gas- and solvent-phase elimination reactions are very similar. Our previous paper on the subject of gas phase eliminations reactions reported a Fourier transform ion cyclotron resonance (FT-ICR)¹¹ study of the base-induced elimination reactions of simple ethers.¹⁰ On the basis of kinetic isotope, leaving group, and conformational effect measurements we concluded that the concept of the "variable transition state" and of syn and anti elimination may also apply to gas-phase elimination reactions. However, in order to generalize more the applicability of these concepts in the gas phase, we now have extended our study to the base-induced elimination reactions of simple thioethers.

Analogous to the previous study, the approach in this work has been to estimate the extent and type of bond changes in proceeding from reactants to the activated complex by relating measured kinetic isotope and leaving group effects with the kinetic isotope effect model calculations, performed by Saunders,¹²⁻¹⁴ for base-induced elimination reactions.

Experimental Section

Experiments were performed with our homemade Fourier transform ion cyclotron resonance mass spectrometer.¹⁵ The experimental procedures were as described in a previous paper on a related study.¹⁰

In addition, CH₃O⁻ was formed via proton abstraction from CH₃OH by NH₂⁻, generated by dissociative capture of 4.5 eV electrons by NH₃. F⁻ was generated via dissociative capture of 6.0 eV electrons by CF₄.

The gas-phase acidity differences between CH₃CH₂SH and CD₃C₂H₂SH and between CH₃CH₂SH and CH₃CD₂SH were determined from the equilibrium isotopic product distribution of the OH⁻/CH₃CH₂SH/CD₃CH₂SH and OH⁻/CH₃CH₂SH/CH₃CD₂SH reaction systems, respectively. The standard deviation after three independent experiments was in both bases ±0.04 kcal/mol.

(2) (a) Bunnet, J. F. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 225; *Angew. Chem.* **1962**, *74*, 73]. (b) Bartsch, R. A.; Bunnett, J. F. *J. Am. Chem. Soc.* **1968**, *90*, 408.

(3) Parker, A. J.; Ruane, M.; Biale, G.; Winstein, S. *Tetrahedron Lett.* **1968**, 2113. (b) Biale, G.; Cook, D.; Lloyd, D. J.; Parker, A. J.; Stevens, I. D. R.; Takahashi, J.; Winstein, S. *J. Am. Chem. Soc.* **1971**, *93*, 4735.

(4) McLennan, D. J. *Tetrahedron* **1975**, *31*, 2999.

(5) (a) Ridge, D. P.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 637. (b) Sullivan, S. A.; Beauchamp, J. L. *Ibid.* **1977**, *99*, 5017. (c) Sullivan, S. A.; Beauchamp, J. L. *Ibid.* **1976**, *98*, 1160.

(6) van Doorn, R.; Jennings, K. R. *Org. Mass Spectrom.* **1981**, *16*, 397.

(7) DePuy, C. H.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1981**, *103*, 5034.

(8) DePuy, C. H.; Beedle, E. C.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1982**, *104*, 6483.

(9) Bierbaum, V. M.; Filley, J.; DePuy, C. H.; Jarrold, M. F.; Bowers, M. T. *J. Am. Chem. Soc.* **1985**, *107*, 2818.

(10) de Koning, L. J.; Nibbering, N. M. M. *J. Am. Chem. Soc.* **1987**, *109*, 1715.

(11) (a) Comisarow, M. B. *Anal. Chim. Acta* **1985**, *178*, 1. (b) Marshall, A. G. *Acc. Chem. Res.* **1985**, *18*, 316. (c) Nibbering, N. M. M. *Mass Spectrometry, Specialist Periodical Reports*; Rose, M. E., Ed.; The Royal Society: London, **1985**, Vol. 8, Chapter 6, p 141. (d) Gross, M. L.; Rempel, D. L. *Science (Washington, D.C.)* **1984**, *226*, 261. (e) Wanczek, K.-P. *Int. J. Mass Spectrom. Ion Proc.* **1984**, *60*, 11. (f) Laude, D. A.; Johlman, C. L.; Brown, R. S.; Weil, D. A.; Wilkins, C. L. *Mass Spectrom. Rev.* **1986**, *5*, 107.

(12) Saunders, W. H., Jr. *Chem. Scr.* **1975**, *8*, 27.

(13) Saunders, W. H., Jr. *Chem. Scr.* **1976**, *10*, 82.

(14) Saunders, W. H., Jr. *J. Chem. Soc., Chem. Commun.* **1973**, 850.

(15) (a) For hardware, see: Dawson, J. H. J. *Lect. Notes Chem.* **1982**, *31*, 33]. (b) For software, see: Noest, A. J.; Kort, C. W. F. *Comput. Chem.* **1982**, *6*, 111.

Materials. Most of the chemicals used were commercially available. The asymmetrically labeled diethyl sulfides CD₃CD₂SEt, CD₃CH₂SEt, and CH₃CD₂SEt were prepared from the correspondingly labeled ethyl bromides or iodides by reaction with ethanethiol in an aqueous solution of potassium hydroxide.

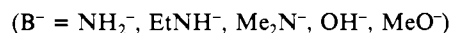
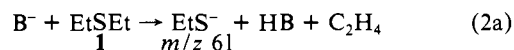
CH₃CD₂Br was commercially available. CD₃CH₂Br was synthesized by a Grignard reaction of CD₃MgI with diiodomethane, and CD₃CD₂Br was obtained from bromination of commercially available C₂D₅OD with PBr₃. C₂D₅SC₂D₅ was prepared by reaction of C₂D₅Br with Na₂S in aqueous solution. Finally, CD₃CH₂SH and CH₃CD₂SH were obtained from reaction of the correspondingly labeled ethyl bromides with thiourea in aqueous solution and subsequent addition of potassium hydroxide to the reaction mixture.

All diethyl sulfides and ethanethiols were purified by preparative GC before use (the diethyl sulfides: column OV 17, temperature 70 °C; the ethanethiols: column OV 17, temperature 40 °C).

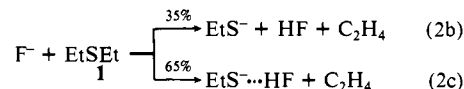
For all the labeled compounds the label content was better than 98%.

Results and Discussion

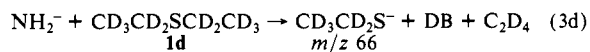
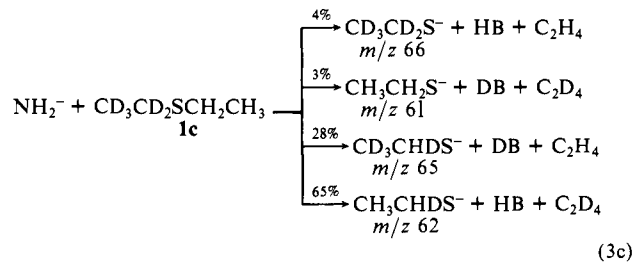
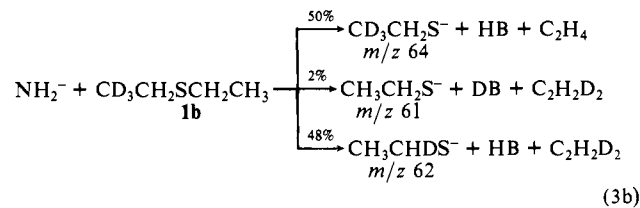
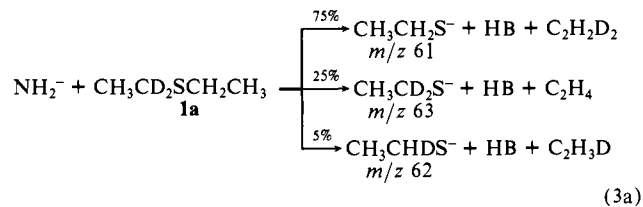
Reactions of Diethyl Sulfide with a Base. Reaction of NH₂⁻, EtNH⁻, Me₂N⁻, OH⁻, and MeO⁻ with EtSEt (**1**) results exclusively in the formation of the ethyl thiolate anion as shown by eq 2a.



Reaction of F⁻ with EtSEt, however, generates both free and HF solvated ethyl thiolate anions (eq 2b and 2c). The formation of the ethyl thiolate product ion appears to be not straightforward in all cases, as has been revealed by studying the reactions with specifically deuterium labeled diethyl sulfides.

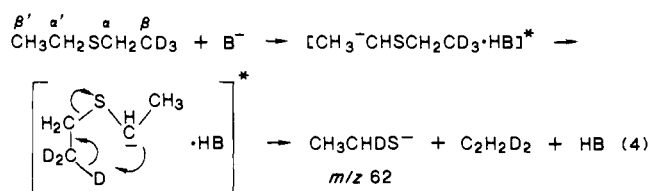


Reaction with Nitrogen Bases. Reaction of NH₂⁻, EtNH⁻, and Me₂N⁻ with the specifically labeled sulfides **1a-d** reveals that a hydrogen shift from the β-carbon to the α'-carbon may occur prior to the isolation of the thiolate anion from the reaction complex (eq 3a-d). This hydrogen shift, which is apparent from the



formation of the thiolate anions with *m/z* 62 and *m/z* 65 can be

explained by the following eq 4. Since the measured gas-phase



acidity of MeSMe is 393 ± 2 kcal/mol,¹⁶ which is at least 2.7 kcal/mol lower than the gas-phase acidity of the weakest nitrogen base used, Me_2N^- ,¹⁷ the first step of the above mechanism is assumed to be an exothermic proton transfer, resulting in the formation of an α -thio carbanion. The α -thio carbanion, being a relatively strong base itself, now undergoes an intramolecular syn elimination, where a proton is transferred from the β -carbon to the α' -carbon.

This process, known as an α',β -elimination, has also been observed as an extremely slow condensed phase reaction between diethyl ether and alkyl lithium compounds.¹⁸ The proton-transfer step is irreversible within the reaction complex, as follows from reaction 3d where no hydrogen incorporation is found in the product ion which would be the result of deuterium/hydrogen exchange of the nitrogen base and the substrate prior to the elimination step. It should be noted that for all reactions traces of deprotonated sulfides are observed in addition to the thiolate anions.

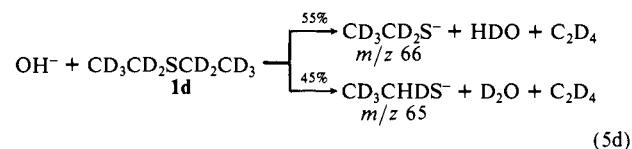
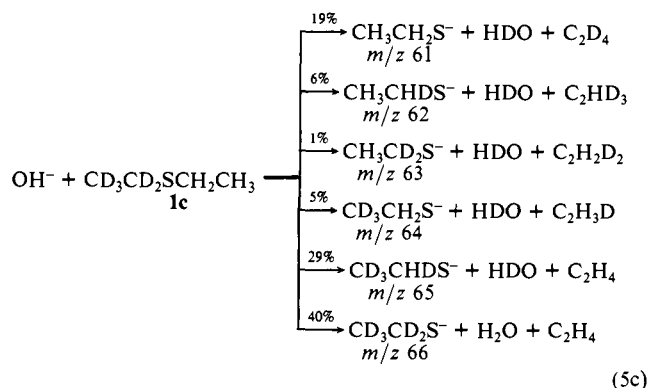
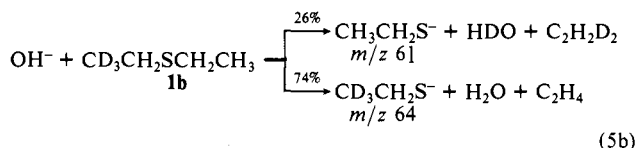
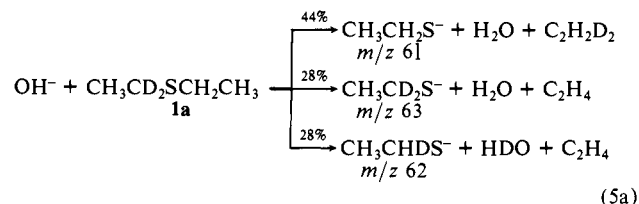
In the reaction with sulfide **1a** both the deprotonated and deuterated sulfides have been isolated from the reaction mixture by means of a notch ejection pulse¹⁹ and subsequently subjected to a collision-induced dissociation (CID) experiment.²⁰ Upon collision the $(\text{M}-\text{H})^-$ ion selectively loses $\text{C}_2\text{H}_2\text{D}_2$, whereas the $(\text{M}-\text{D})^-$ ion selectively loses C_2H_4 , which confirms the α',β -elimination mechanism.

Since none of the nitrogen bases are found to react with MeSMe other than by proton abstraction,¹⁶ it can be excluded that the ethyl thiolate anions are also formed via a displacement reaction ($\text{S}_\text{N}2$) on the α -carbon. Consequently, the thiolate anions can only be formed via either a direct E2 or an α',β -elimination mechanism.

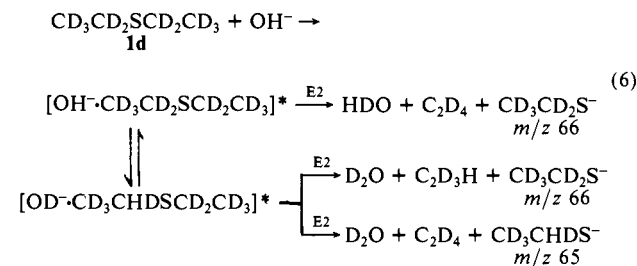
Unfortunately, the contributions of the two reaction channels for sulfide **1a** and **1b** cannot be determined accurately because the thiolate anions with m/z 61 and 64, respectively, may originate from both direct and α',β -elimination. Since both direct and α',β -elimination are expected to suffer from deuterium isotope effects,^{9,10} the branching ratio does not immediately follow from the relative ion intensity measurements. For the sulfide **1c** this problem does not occur and from the intensities of the m/z 61, 66 and m/z 62, 65 ions, respectively, it follows that the contribution of the direct elimination in the reaction with NH_2^- is only about 7% (see eq 3c).

Reactions of EtNH^- and Me_2N^- with the sulfides **1a-c** exhibit results analogous to the reactions of the amide ion. For these two bases the contribution of the direct E2 reaction channel is also about 7%.

Reaction with Hydroxide. Reaction of OH^- with the specifically labeled sulfides **1a-d** results in a slightly different overall picture than seen for the reactions of the nitrogen bases (eq 5a-d). Striking in this respect is the absence of the thiolate product ion with m/z 62 in the reaction mixture of OH^- and sulfide **1b** (eq 5b), implying that for the reaction with OH^- no α',β -elimination mechanism is operative. As a consequence the product ions with m/z 62 and m/z 62, 63, 64, 65 in the reactions with substrates **1a** and **1c**, respectively, must be formed via an alternative



mechanism. The nature of this mechanism follows from the results of the reaction between OH^- and sulfide **1d**, where it is observed that a practically complete, statistical exchange between the hydroxide hydrogen and the α -deuterium atoms of the sulfide has occurred prior to the E2 elimination reaction (eq 6). On the basis



of this observed statistical distribution of deuterium and hydrogen atoms in the thiolate product ion it can be concluded that the reaction complex must be relatively long lived and that the E2 reaction channel is slow relative to the hydrogen/deuterium exchange. In view of this, the product distribution in the reactions of OH^- with sulfides **1a** and **1c** are best explained by a fast hydrogen/deuterium exchange followed by a slow E2 reaction rather than by proton abstraction followed by α',β -elimination.

Reaction with Methoxide and Fluoride. Reactions of MeO^- and F^- with the specifically deuterium labeled sulfides **1a-d** exclusively generate thiolate anions formed via a direct E2 elimination mechanism. No subsequent α' -proton abstraction and β -hydrogen shift have been observed, implying that also for the reaction of diethyl sulfide with MeO^- and F^- no competition exists between the E2 and α',β -elimination mechanism. The latter may not be surprising, since the proton-transfer step required for the α',β -elimination is estimated to be at least 12 kcal/mol endothermic.²¹

(21) Heats of formation of reactants and products have been calculated from the data in ref 17 and 22. The gas-phase acidity $\Delta H^\circ_{\text{acid}}$ of EtSEt is estimated to be less than 3 kcal/mol lower than that of MeSMe (see ref 16).

(16) Ingemann, S.; Nibbering, N. M. M. *Can. J. Chem.* **1984**, *62*, 2773.

(17) Bartmess, J. E.; McIver, R. T. *Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1979, Vol. 2, Chapter 11, p 87. Moylan, C. R.; Bauman, J. I. *J. Phys. Chem.* **1984**, *88*, 3175.

(18) Maercker, A.; Demuth, D. *Liebigs Ann. Chem.* **1977**, 1909.

(19) (a) Noest, A. J.; Kort, C. W. F. *Comput. Chem.* **1983**, *7*, 81. (b) Kleingeld, J. C.; Nibbering, N. M. M. *Tetrahedron* **1983**, *39*, 4193.

(20) (a) Cody, R. B.; Burnier, R. C.; Freiser, B. S. *Anal. Chem.* **1982**, *54*, 96. (b) Carlin, T. J.; Freiser, B. S. *Anal. Chem.* **1983**, *55*, 571.

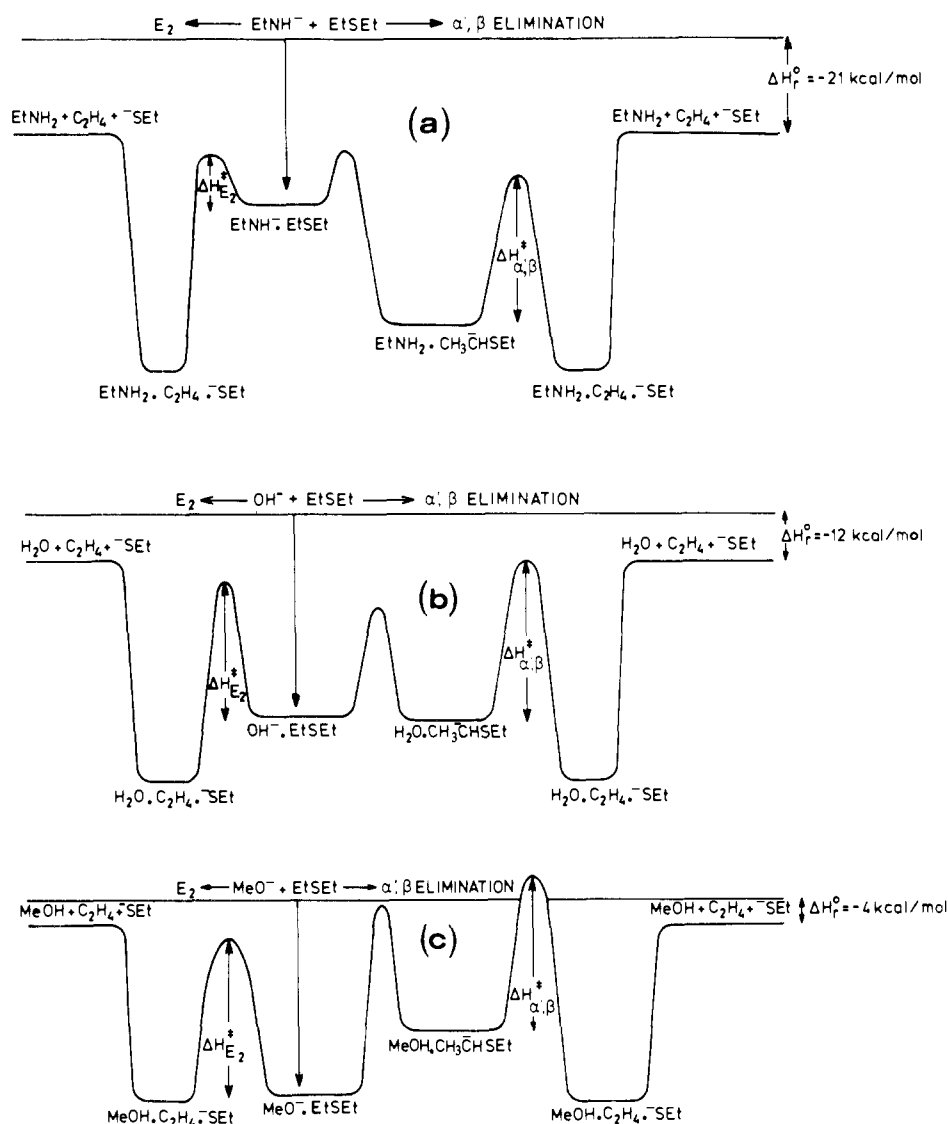


Figure 1. Outline of the energy profiles for the reactions between diethyl sulfide and (a) EtNH⁻, (b) OH⁻, and (c) MeO⁻.

Again, a displacement reaction mechanism (S_N2) for the formation of the thiolate anion can be excluded, since both MeO⁻ and F⁻ are observed not to react with MeSMe.

E2 vs α',β-Mechanism. On the basis of the product distributions of the reactions of the used bases with the deuterium-labeled sulfides and the heats of formation^{17,22} of the reactants and products, a qualitative picture of the potential energy profiles for the gas-phase reactions of EtNH⁻, OH⁻, and MeO⁻ with diethyl sulfide is presented, which may rationalize the observations.

In Figure 1a it is shown that the collision complex [EtNH⁻·EtSEt]* may undergo an E2 as well as an α-proton abstracting reaction. The barriers of these two reaction channels are considered to be about equally high, compatible with the observation that for this reaction system E2 elimination is in competition with α',β-elimination. Furthermore, the irreversible proton transfer, indicated by the absence of hydrogen/deuterium exchange, suggests that the barrier toward α',β-elimination (ΔH_{α,β}[‡]) is lower than the barrier toward proton back transfer, implying that the proton transfer step is rate determining for the α',β-elimination reaction channel.

Figure 1b shows a relatively low barrier for the proton-transfer reaction, which enables a fast equilibrium between the reaction complexes [OH⁻·EtSEt]* and [H₂O·EtSCH₃]*, in agreement

with the observed hydrogen/deuterium exchange. Consequently, the bottleneck for the α',β-elimination is the reaction barrier itself characterized by the activation energy ΔH_{α,β}[‡]. This intrinsic activation energy ΔH_{α,β}[‡] is expected to be relatively insensitive with respect to the strength of the used base, because ΔH_{α,β}[‡] is associated with an unimolecular reaction of deprotonated diethyl sulfide. Nevertheless, this barrier must be significantly higher than the barrier toward E2 elimination, characterized by the activation energy ΔH_{E₂}[‡], since OH⁻ is found to react with diethyl sulfide exclusively via an E2 mechanism.

Figure 1c shows that the energy of the proton-transfer barrier exceeds the energy of the reactants as a consequence of which the endothermic proton transfer within the [MeO⁻·EtSEt] reaction complex cannot occur. Therefore, the only energetically accessible reaction channel is the E2 elimination.

Isotope and Leaving Group Effects. For the E2 reactions of the isotopic isomers of diethyl sulfide **1a-d** the overall kinetic isotope effects have been measured. The results of these measurements are listed in Table I. Intramolecular isotope effects $k_H/k_D(\text{CH}_3\text{CD}_2\text{SCH}_2\text{CH}_3)$, $k_H/k_D(\text{CD}_3\text{CH}_2\text{SCH}_2\text{CH}_3)$, and $k_H/k_D(\text{CD}_3\text{CD}_2\text{SCH}_2\text{CH}_3)$ are determined from the ratio of the isotopic thiolate products ions in the reaction of a base with CH₃CD₂SCH₂CH₃, CD₃CH₂SCH₂CH₃, or CD₃CD₂SCH₂CH₃, respectively. Intermolecular isotope effects $k_H/k_D(\text{C}_4\text{H}_{10}\text{S}/\text{C}_4\text{D}_{10}\text{S})$ are determined from the ratio of the isotopic thiolate product ions in the reaction of a base with a 1:1 mixture of C₂H₅SC₂H₅ and C₂D₅SC₂D₅. Unfortunately, for the reactions

(22) The heats of formation of the neutrals have been calculated or taken from the following: Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley Interscience: New York, 1976.

Table I. Overall Kinetic Isotope Effects Associated with the Reaction between B⁻ and Diethyl Sulfide

| B ⁻ | PA (B ⁻), ^a kcal/mol | CH ₃ CD ₂ SCH ₂ CH ₃ ^b k _H /k _D | CD ₃ CH ₂ SCH ₂ CH ₃ ^b k _H /k _D | CD ₃ CD ₂ SCH ₂ CH ₃ ^b k _H /k _D | C ₂ D ₅ SC ₂ D ₅ /C ₂ H ₅ SC ₂ H ₅ ^b k _H /k _D |
|------------------|--|---|---|---|---|
| HO ⁻ | 391 | | 2.85 ± 0.05 | | |
| MeO ⁻ | 381 | 1.03 ± 0.05 | 2.50 ± 0.44 | 2.51 ± 0.23 | 2.42 ± 0.04 |
| F ^{-c} | 371 | 1.18 ± 0.06 | 1.64 ± 0.04 | 1.99 ± 0.11 | 2.39 ± 0.03 |
| F ^{-d} | 371 | 0.94 ± 0.02 | 1.98 ± 0.03 | 1.86 ± 0.09 | 2.81 ± 0.04 |

^a Proton affinity data taken from ref 17. ^b Given error is the standard deviation over eight or more independent experiments. ^c Reaction of F⁻ generating thiolate anions. ^d Reaction of F⁻ generating HF solvated thiolate anions.

induced by the nitrogen bases the overall isotope effects of the E2 eliminations cannot be determined from the isotopic thiolate product ion ratio, because the E2 mechanism is in competition with the α',β-elimination (see reactions 3a-c). Similarly, for the hydroxide base the kinetic overall isotope effect is only determined for the reaction with CD₃CH₂SCH₂CH₃ since all other sulfides studied may lose their α-deuterium label in a fast hydrogen/deuterium exchange reaction with OH⁻ prior to E2 elimination (see reactions 5a, c, and d).

As mentioned in a previous section, reaction of F⁻ with diethyl sulfide yields free as well as HF solvated thiolate anions. For the formation of both of these elimination products the overall kinetic isotope effects have been measured. The overall measured kinetic isotope effects are the combined result of individually operating isotope effects such as the following: the primary (prim.) β-isotope effect, k_H/k_D(prim. H_β), referring to the relative rates of βH and βD abstraction by the base; the secondary (sec.) β-isotope effect, k_H/k_D(sec. H_β), corresponding to a decrease in E2 reaction rate upon substitution of the two remaining βH's by D; the secondary α-isotope effect, k_H/k_D(sec. H_α), corresponding to a decrease in E2 reaction rate upon substitution of both αH's by D, and finally a leaving group effect, k(SCH₂CH₃)/k(SCD₂CH₃) and k(SCH₂CH₃)/k(SCD₂CD₃), corresponding to a decrease in E2 reaction rate upon replacing H's by D's in the leaving ethyl thiolate group, by which the basicity increases and consequently the leaving ability of the thiolate group decreases.

The contributions to the measured overall isotope effects from these primary and secondary isotope and leaving group effects can now be evaluated by solving the following set of equations.

$$k_H/k_D(\text{CH}_3\text{CD}_2\text{SCH}_2\text{CH}_3) = \frac{k_H/k_D(\text{sec. H}_\alpha)}{k(\text{SCH}_2\text{CH}_3)/k(\text{SCD}_2\text{CH}_3)} \quad (7a)$$

$$k_H/k_D(\text{CD}_3\text{CH}_2\text{SCH}_2\text{CH}_3) = \frac{k_H/k_D(\text{prim. H}_\beta) \times k_H/k_D(\text{sec. H}_\beta)}{k(\text{SCH}_2\text{CH}_3)/k(\text{SCH}_2\text{CD}_3)} \quad (7b)$$

$$k_H/k_D(\text{CD}_3\text{CD}_2\text{SCH}_2\text{CH}_3) = \frac{k_H/k_D(\text{prim. H}_\beta) \times k_H/k_D(\text{sec. H}_\beta) \times k_H/k_D(\text{sec. H}_\alpha)}{k(\text{SCH}_2\text{CH}_3)/k(\text{SCD}_2\text{CD}_3)} \quad (7c)$$

$$k_H/k_D(\text{C}_4\text{H}_{10}\text{S}/\text{C}_4\text{D}_{10}\text{S}) = \frac{k_H/k_D(\text{prim. H}_\beta) \times k_H/k_D(\text{sec. H}_\beta) \times k_H/k_D(\text{sec. H}_\alpha) \times k(\text{SCH}_2\text{CH}_3)/k(\text{SCD}_2\text{CD}_3)}{k(\text{SCH}_2\text{CH}_3)/k(\text{SCD}_2\text{CH}_3)} \quad (7d)$$

In order to solve this set of four equations, involving six unknown quantities, simplification is required. To this end the individual contributions of k_H/k_D(prim. H_β) and k_H/k_D(sec. H_β) are combined in k_H/k_D(H_β) representing the total kinetic effect upon replacing all three β-H's by D. Furthermore, k(SCH₂CH₃)/k(SCH₂CD₃) is neglected (taken to be unity) since no significant gas-phase acidity difference δΔH⁰_{acid} between CH₃CH₂SH and CD₃CH₂SH could be detected from equilibrium measurements,²³ implying that β-hydrogen replacement by deuterium does not affect significantly the acidity of ethyl mercaptan and therefore the leaving group ability of the ethyl thiolate group.

Consequently, k_H/k_D(SCD₂CD₃) is taken to be equal to k_H/k_D(SCD₂CH₃). Indeed, a leaving group effect may be expected upon substituting the α-hydrogens by deuterium, since CH₃CD₂SH

Table II. Kinetic Isotope and Leaving Group Effects Associated with the Reaction between B⁻ and Diethyl Sulfide^d

| B ⁻ | k _H /k _D (H _β) ^a | k _H /k _D (sec. H _α) ^a | k(SCH ₂ CH ₃)/k(SCD ₂ CH ₃) ^a |
|------------------|---|--|--|
| MeO ⁻ | 2.43 ± 0.10 | 1.01 ± 0.07 | 0.98 ± 0.05 |
| F ^{-b} | 1.68 ± 0.08 | 1.30 ± 0.06 | 1.10 ± 0.02 |
| F ^{-c} | 1.98 ± 0.05 | 1.16 ± 0.05 | 1.23 ± 0.02 |

^a Errors calculated from the standard deviation in Table I. ^b Reaction of F⁻ generating thiolate anions. ^c Reaction of F⁻ generating HF solvated thiolate anions. ^d Calculated from the data in Table I.

has been measured to be 0.33 kcal/mol less acidic than CH₃C-H₂SH in the gas-phase.²³

On the basis of the above considerations eq 7a-d can be simplified to eq 8a-d.

$$k_H/k_D(\text{CH}_3\text{CD}_2\text{SCH}_2\text{CH}_3) = \frac{k_H/k_D(\text{sec. H}_\alpha)}{k(\text{SCH}_2\text{CH}_3)/k(\text{SCD}_2\text{CH}_3)} \quad (8a)$$

$$k_H/k_D(\text{CD}_3\text{CH}_2\text{SCH}_2\text{CH}_3) = k_H/k_D(\text{H}_\beta) \quad (8b)$$

$$k_H/k_D(\text{CD}_3\text{CD}_2\text{SCH}_2\text{CH}_3) = \frac{k_H/k_D(\text{H}_\beta) \times k_H/k_D(\text{sec. H}_\alpha)}{k(\text{SCH}_2\text{CH}_3)/k(\text{SCD}_2\text{CH}_3)} \quad (8c)$$

$$k_H/k_D(\text{C}_4\text{H}_{10}\text{S}/\text{C}_4\text{D}_{10}\text{S}) = \frac{k_H/k_D(\text{H}_\beta) \times k_H/k_D(\text{sec. H}_\alpha) \times k(\text{SCH}_2\text{CH}_3)/k(\text{SCD}_2\text{CH}_3)}{k(\text{SCH}_2\text{CH}_3)/k(\text{SCD}_2\text{CH}_3)} \quad (8d)$$

In Table II the calculated k_H/k_D(H_β), k_H/k_D(sec. H_α), and k(SCH₂CH₃)/k(SCD₂CH₃) are listed. In doing so, k_H/k_D(H_β) has been calculated by solving eq 8a,c,d rather than by directly taking the measured value k_H/k_D(CD₃CH₂SCH₂CH₃) (see eq 8b). In this way it can be shown that the values for k_H/k_D(H_β), calculated from the measured values for k_H/k_D(CH₃CD₂SCH₂CH₃), k_H/k_D(CD₃CD₂SCH₂CH₃), and k(C₄H₁₀S)/k(C₄D₁₀S) are in excellent agreement with the directly measured values for k_H/k_D(H_β) (see Table I). This demonstrates the validity of the used method to determine the individual α- and β-deuterium isotope and leaving group effects.

Variation of Energy. The translational energy dependence of the E2 elimination has been studied in the reaction of F⁻ with CD₃CH₂SCH₂CH₃. To this end, F⁻ has been isolated from the reaction mixture by means of a notch ejection pulse¹⁹ and subsequently translationally excited, by applying a pulse with the cyclotron resonance frequency of F⁻ to the transmitter plates of the FT-ICR cell, after which F⁻ has been allowed to react with CD₃CH₂SC₂H₅. By varying the energy level of the radio frequency pulse, both isotope effects k_H/k_D(H_β) [SEt] and k_H/k_D(H_β) together with the product ratio [HF⁻SEt]/[SEt] have been determined as a function of the translational energy E_{kin} of F⁻, where E_{kin} is calculated from eq 9²⁴

$$E_{\text{kin}} = \frac{q^2 V_{\text{RF}}^2 t^2}{8md^2} \quad (9)$$

where q is the ion charge, V_{RF} is the energy level of the radio frequency pulse in volts peak-to-peak, t is the irradiation time,

(23) See Experimental Section.

(24) Kleingeld, J. C. Thesis, University of Amsterdam, The Netherlands, 1984.

Table III. Translational Energy Dependence of the Reaction between F^- and $CD_3CH_2SCH_2CH_3$

| E_{kin} (eV) [F^-] | $k_H/k_D(H_\beta)$ [^-SEt] ^a | $k_H/K_D(H_\beta)$ [$HF \cdot SEt$] ^a | [$HF \cdot SEt$]/ [^-SEt] ^a |
|-----------------------------|--|---|---|
| 0.0 | 1.61 ± 0.03 | 2.00 ± 0.04 | 1.87 ± 0.02 |
| 1.9 | 1.64 ± 0.02 | 1.98 ± 0.03 | 1.81 ± 0.02 |
| 7.7 | 1.60 ± 0.04 | 2.00 ± 0.05 | 1.78 ± 0.01 |
| 17.3 | 1.69 ± 0.04 | 1.95 ± 0.06 | 1.76 ± 0.09 |

^a Given error is standard deviation over three experiments.

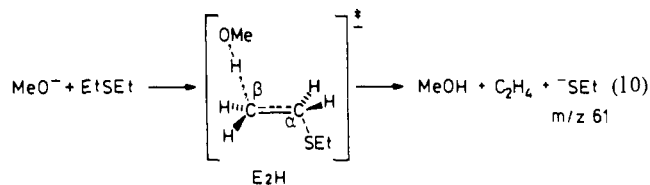
m is the ion mass, and d is the distance between the transmitter plates.

The results in Table III show that up to a translational energy of 17.3 eV both isotope effects $k_H/k_D(H_\beta)$ [^-SEt] and $k_H/K_D(H_\beta)$ [$HF \cdot SEt$] and the product ratio [$HF \cdot SEt$]/[^-SEt] are found to be constant within the experimental error. These observations are not consistent with the idea that the elimination proceeds via one E2 transition state where the reaction complex partly dissociates to form either free or HF solvated thiolate anions. In such a mechanism it is expected that partial dissociation of the elimination reaction complex, i.e., the product ratio, would be very sensitive toward the translational energy of the base. Therefore, the significantly different and translational energy independent isotope effects associated with the free and HF solvated thiolate anion formation are better rationalized in terms of two uncoupled competing elimination mechanisms involving two distinct transition states.

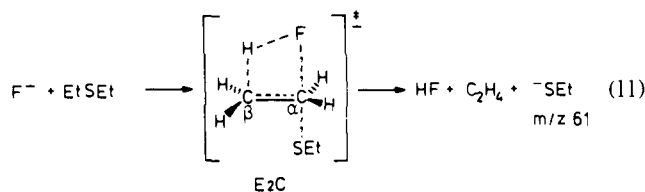
Transition-State Geometry. In our previous study¹⁰ of the mechanism of base-induced gas-phase elimination reactions of ethers, α - and β -deuterium isotope and leaving group effects were determined as a function of the base strength and rationalized in terms of a variable transition state by fitting the data qualitatively with kinetic isotope effect model calculations of Saunders.¹²⁻¹⁴ These calculations performed for the OH^-/C_2H_5X ($X = Br, Cl, SC_2,$ and NC_3) system describe the relationship between the various isotope effects and the $C_\beta-H$ and $C_\alpha-X$ bond order in the transition state and include tunnel corrections and temperature dependencies.¹³ As in the previous paper it must be stated that the temperature of the isolated gas-phase reaction complex cannot be measured, so that a quantitative fit of our data is not possible. However, since the present results indicate that the observed isotope effects are relatively insensitive toward variation of the translational energy of the base (see Table III), at least a qualitative picture of the geometry of the transition states of the elimination reactions can be offered by interpreting the isotope effect data.

Saunders calculations indicate that a maximum combined β -deuterium isotope effect of about 9.5 and 5 at temperatures of 5 and 95 °C, respectively, corresponds to a symmetric linear arrangement for the base, β -hydrogen and β -carbon in an E2H transition state. These values drop sharply when going from a symmetrical to an asymmetrical linear proton transfer transition-state structure. In the present study such a sharp decrease of the combined β -deuterium isotope effects is observed with decreasing base strength (see Tables I and II). Therefore, following Hammond's postulate²⁵ the values of $k_H/K_D(H_\beta)$ of 2.85 and 2.50, for OH^- and MeO^- , respectively, are associated with E2H transition states in which the β -hydrogen is more than half transferred for the reaction with OH^- and almost completed for the reaction with MeO^- . In addition, reaction of MeO^- shows no significant α -deuterium, $k_H/k_D(sec. H_\alpha)$, and leaving group effect, $k(SC_2H_5)/k(SCD_2CH_3)$ (see Table II), implying that the transition state has little olefinic character and a minimally stretched $C_\alpha-S$ bond, which is indicative for an E1cb-like mechanism (eq 10).

Reaction of F^- yielding free thiolate anions shows an extremely low β -deuterium isotope effect $k_H/k_D(H_\beta)$ of 1.68. Moreover, the extremely large α -deuterium isotope effect $k_H/k_D(sec. H_\alpha)$ of 1.30 for this reaction does not seem compatible with an E2H mechanism for which in the condensed phase maximum α -deu-



terium isotope effects have been found in the order of 1.05,^{26,27} where Saunders calculated a maximum α -deuterium isotope effect of 1.1, associated with a $C_\alpha-X$ bond order of 0.9! Even displacement reactions (S_N2) on primary carbon in the condensed phase in general are found to show α -deuterium isotope effects which only run from about 0.95 up to 1.04 per deuterium.²⁷ In view of this an E2H mechanism for the gas-phase reaction of F^- with diethyl sulfide is very unlikely. Alternatively, the isotope effect data are best explained in terms of an E2C-like mechanism,³ involving a bent proton transfer and covalent interaction of F^- with the α -carbon (eq 11).



For this model Saunders predicted a maximum β -deuterium isotope effect of about 2.6, while our value of 1.68, according to his calculations, corresponds to a $C_\beta-H$ bond order in an E2C-like transition state of 0.65.¹² Moreover, the temperature dependences for the E2C model are predicted to be less marked than for the E2H model.¹³ In agreement with these calculations maximum β -deuterium isotope effects have been observed for E2C eliminations in the condensed phase, which are in the order of three.²⁸ Especially interesting in this respect are the studies of Kwart²⁹ concerning the elimination reactions of $C_6H_5CH_2CHBrCOOEt$ induced by weak bases. By applying the criterion of temperature dependence of the kinetic isotope effects (TDKIE)³⁰ it was established that the elimination reactions involved a bent proton transfer with $C_\beta-H-B$ angles of less than 100° in agreement with the E2C model. Since these elimination reactions, like in the present study, were found to be accompanied by extremely large α -deuterium isotope effects of the order of 1.25 per deuterium, it indeed appears that large α -deuterium isotope effects are characteristic for E2C mechanisms. In the condensed phase E2C eliminations are generally favored in aprotic solvents, for substrates with a good leaving group, and are promoted by weak bases which are also relatively strong C-nucleophiles (in S_N2 reactions).³¹ In this respect the present gas-phase study shows a similarity, since the thiolate anion is known as a good leaving group in the gas phase, while F^- as a relatively weak gas-phase base is known to be a better C-nucleophile in gas-phase S_N2 reactions than, for instance, the stronger base MeO^- .³²

Compared to the reaction of F^- generating free thiolate anions, the reaction of F^- with diethyl sulfide yielding HF solvated ethyl thiolate anions shows a relatively larger β -deuterium isotope effect of 1.98, a much smaller α -deuterium isotope effect of 1.16, and an extraordinarily large leaving group effect of 1.23 (see Table II). The larger β -deuterium isotope effect of 1.98 indicates that

(26) Fry, A. *Chem. Soc. Rev.* **1972**, *1*, 163.

(27) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley-Interscience: New York, 1980.

(28) (a) Biale, G.; Parker, A. J.; Stevens, I. D. R.; Takahashi, J.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2235. (b) Cook, D.; Hutchinson, R. E. J.; MacLeod, J. K.; Parker, A. J. *J. Org. Chem.* **1974**, *39*, 534.

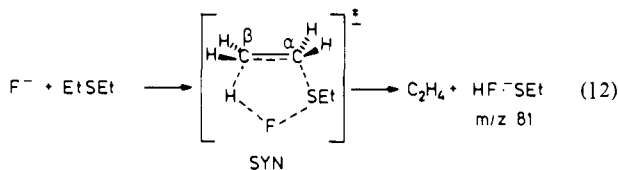
(29) (a) Kwart, H.; Gaffney, A. *J. Org. Chem.* **1983**, *48*, 4502. (b) Kwart, H.; Gaffney, A.; Wilk, K. A. *J. Org. Chem.* **1983**, *48*, 4509.

(30) Kwart, H. *Acc. Chem. Res.* **1982**, *15*, 401.

(31) (a) Beltrame, P.; Biale, G.; Lloyd, D. J.; Parker, A. J.; Ruane, M.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2240 and references cited therein. (b) Parker, A. J.; Ruane, M.; Palmer, D. A.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2228.

(32) Albritton, D. L. *Atomic Data and Nuclear Tables*; Academic Press, Inc.: New York, **1978**; Vol. 22, no. 1, pp 1-101.

the C_β -H-F bond angle must be larger than in the discussed E2C model. On the other hand, the extraordinarily large leaving group effect of 1.23 suggests that the leaving group in the transition state is involved in both bond breaking and bond formation, which points to interaction of the leaving group and the base in the transition state. In the previous paper similar isotope and leaving group effects were obtained for the elimination reaction of diethyl ether induced by OH^- and producing water solvated ethoxide anions.¹⁰ It was argued that this reaction could best be described by a syn elimination with a cyclic transition-state structure. Following the same argumentation the formation of the HF solvated thiolate anions is also considered to proceed via a syn elimination mechanism (eq 12). This mechanism strongly favors solvated thiolate



anion formation because of the interaction of F^- and the leaving thiolate group in the transition state as a consequence of which no reorganization of the reaction complex is required in order to stabilize $\text{HF} \cdot \text{SEt}$. This is in contrast with the E2H and E2C mechanisms where solvation of this thiolate anion can only be achieved after a considerable reorganization of the reaction complex.

Conclusions

It appears that the results of the present study confirm our conclusion from the previous study,¹⁰ that the concept of the variable transition state structure is applicable to base-induced elimination reactions in the gas phase. Perturbations in transition-state character effected by changing the leaving group or the base seem to follow the rules established for condensed phase β -elimination reactions.³³ That is, from both the present and the previous study it follows that increasing the base strength not only enhances the carbanionic character of the transition state but also causes the transition state to shift toward the reactant side of the reaction coordinate. Both effects also find expression if the leaving

ability of the leaving group is improved, as follows from comparison of the mechanisms of the reactions of OH^- with diethyl ether and diethyl sulfide. A more reactantlike transition state is to be expected upon substitution of the ethoxy by an ethyl thiolate group. However, the enhancement of the carbanionic character is more difficult to rationalize, unless it is assumed that development of negative charge on the β -carbon is better stabilized by sulfur than by oxygen.

Another interesting conclusion which follows from combination of the results of the present study with those of the previous study¹⁰ is that, as the overall exothermicity of the elimination reactions becomes very small, the E2H mechanism, characterized by a linear proton transfer, is superseded by a mechanism, which is characterized by a bent proton transfer and a two-side attack of the base on the substrate. This is illustrated by the reactions of OH^- with diethyl ether and F^- with diethyl sulfide. For both reaction systems the free ethoxide and free ethyl thiolate anion formation, respectively, are close to thermoneutral.^{16,21} Evidently, as a result of this, the E2H mechanism in the reaction of OH^- with diethyl ether has to compete with a syn elimination mechanism in which a bent proton transfer and interaction of the incoming base with the leaving group in the transition state promotes the formation of water solvated ethoxide anions. Moreover, the E2H mechanism in the reaction of F^- with diethyl sulfide is completely superseded by elimination mechanisms involving a bent proton transfer. These are the E2C mechanisms, characterized by a two-side attack of F^- on the β -hydrogen and the α -carbon and a syn elimination mechanism characterized by a two-side attack on the β -hydrogen and the leaving group, analogous to the syn elimination mechanism which is operative in the OH^- /diethyl ether reaction system.

In summary, the exothermicity of the elimination reactions appears to be a selection criterion for the elimination mechanisms, where the entropically favored linear proton transfer mechanism (E2H) is preferred for relatively highly exothermic elimination reactions, whereas the enthalpy favored bent proton transfer mechanisms with rigid transition states (E2C and syn) are preferred in the case of slightly endothermic elimination reactions.

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Registry No. $\text{S}(\text{C}_2\text{H}_5)_2$, 352-93-2; D_2 , 7782-39-0.

(33) Thornton, E. R. *J. Am. Chem. Soc.* 1967, 89, 2915.

Direct Examination of Chemical Kinetic Laws by Visual Imagery. 3.[†] Association of Latex Particles Modified with Antigens and Antibodies

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Abstract: Association processes of latex particles modified with antigen (human serum albumin, HSA) and antibody (anti-HSA immunoglobulin G) are examined by direct visual observation and by a spectrophotometric method. By direct visual observation using an ultramicroscope connected to an image-processing system, the rate constant of the dimeric association process of polymer latex particles carrying 16 000 antigens or antibodies is estimated to be $1.3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ at 25 °C, which is smaller than that of the association reaction of oppositely charged polymer latex particles ($1.9 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$), but is larger than the rate constant of the association reaction between an antigen and an antibody ($1.9 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$). The activation parameters of the interlatex reaction system are also estimated.

Latex particles have been extensively used in clinical assays as carriers of antigens or antibodies to detect complementary antibodies or antigens in biological samples by the agglutination method.¹ Many reports have been published on practical con-

ditions of clinical assays using polymer latices. This agglutination phenomenon of latex particles, however, has not yet been clarified

(1) (a) Rembaum, A.; Yen, S. P.; Cheong, E.; Wallace, S.; Molday, R. S.; Gordon, I. L.; Dreyer, W. J. *Macromolecules* 1976, 9, 328. (b) Crane, L. J. *Clin. Chem.* 1981, 27, 697. (c) Bernard, A. M.; Moreau, D.; Lauwerys, R. *R. Ibid.* 1982, 28, 1167.

[†] Part 1: see ref 3a; part 2, see ref 3b.