This represents a minor part of the five-membered ring effects seen in this study.

Another factor lowering the energy of the spiro or monocyclic sulfuranes relative to their acyclic analogs is related to possible repulsive interactions between the π electrons of the equatorial aryl rings and the apical substituents. These would be minimized in the geometry of the spiro system, with the planes of the aryl rings perpendicular to the equatorial plane. The complete X-ray structures of **3** and **9**, which will be presented in a later paper, provide a basis for bond length comparisons supporting this interpretation over an alternative explanation for the lack of reactivity of monocyclic and spirobicyclic sulfuranes which might invoke some steric inhibition of resonance interactions between the annelated aromatic rings and the product sulfonium sulfur.[55]

(55) Phosphoranes show parallel reductions in reactivity upon inclusion of the phosphorus in a five-membered ring (or in two such rings in a spirophosphorane). For a recent review with leading references, see P. Gillespie, F. Ramirez, I. Ugi, and D. Marguading, *Angew. Chem., Int. Ed. Engl.*, 12, 91 (1973). For analogies in selenium chemistry, see H. J. Reich, *J. Amer. Chem. Soc.*, **95**, 964 (1973).

The reduced reactivity of derivatives of the monocyclic sulfurane **14** opens the way to isolation of sulfuranes with new apical ligand functionality. Further work now underway will probe for applications of these derivatives as reagents in organic synthesis.

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Supplementary Material Available. A complete listing of carbon-13 nmr spectroscopic data is to be found in the table which will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-3155.

Association and Solvation Reactions of Protonated Gaseous Amino Acids

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Abstract: High-pressure mass spectrometric measurements were made to determine the thermodynamic values of the gas phase solvation of protonated amino acids (valine and proline) by individual molecules of several solvents. The enthalpies of monomolecular solvation by both hydrogen-bonding solvents H_2O and NH_3 and a nonhydrogen-bonding solvent CH_3NO_2 are found to be in the range of 20 ± 2 kcal/mol. The exothermicities of the gaseous association reactions of protonated and neutral entities for valine and proline are found to be of similar magnitude (~20 kcal/mol).

Reversible association reactions of protonated ions with neutral molecules of the type

$$MH^+ + M \rightleftharpoons M_2H^+ \quad (1)$$

and the association of ions with gaseous solvent molecules of the type

$$X^+ + \text{solvent} \rightleftharpoons X^+ \text{ solvent} \quad (2)$$

have been investigated extensively recently using high-pressure mass spectrometric techniques.[1-4] The results are providing a better understanding of the intrinsic properties of ionic reactions, as in the gas phase such reactions are observed in the absence of liquid solvent effects.[5] To date, investigations of gaseous ion–solvent interactions have been limited to the reactions of small ions, mainly of inorganic interest.

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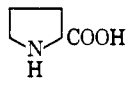
In the present study we have investigated the association of protonated ions of the amino acids valine ($(CH_3)_2CHCH(NH_2)COOH$) and proline



with neutral molecules of valine and proline, with the proton-bonding solvents H_2O and NH_3, and with the nonproton-bonding solvent CH_3NO_2. In addition to their intrinsic interest as ion–molecule interactions, the energetics of the solvation reactions of protonated amino acid molecules are of potential interest in the physical chemistry of protein conformation, while the association reactions may be of potential interest in exobiological processes.

Experimental Section

The scope of quantitative mass spectrometric gaseous ionic studies is limited at the present time to compounds of relatively high volatility. Problems of volatility restricted our studies in amino acids to those reported. The low volatility of these compounds also renders the pressure of the vapor of such samples in the ion source inde-

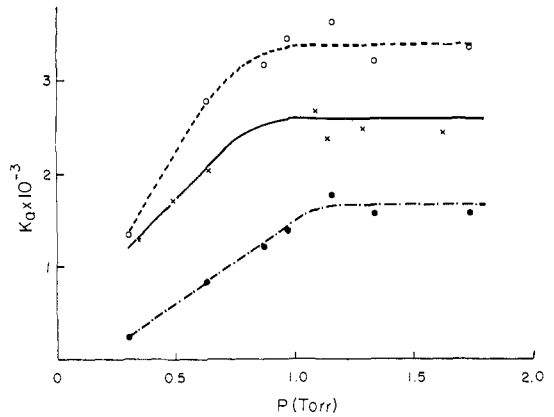


Figure 1. The dependence of the observed equilibrium constant of the solvation reactions $K_a = 760(I_{ValH^+ \cdot solvent}/I_{ValH^+}P_{solvent})$ on the total source pressure: (a) ×, solvent = H_2O, T = 385°K; (b) ○, solvent = NH_3; T = 463°K; (c) ●, solvent = CH_3NO_2; T = 463°K. Ordinate scale to be multiplied by 10 for graph c.

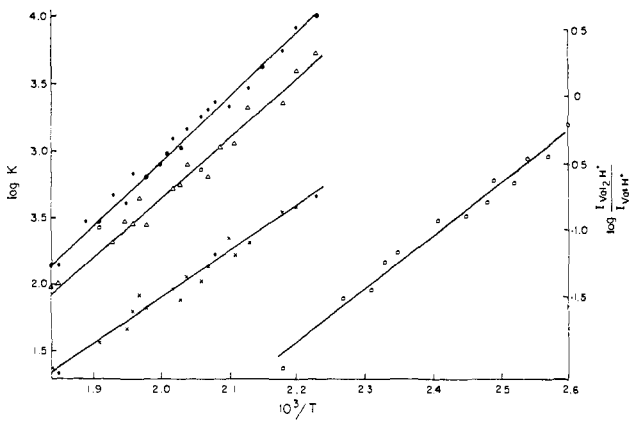


Figure 2. Sample van't Hoff plots for association and solvation reactions: (a) ×, $ValH^+ + Val \rightleftharpoons Val_2H^+$; (b) ○, $ValH^+ + H_2O \rightleftharpoons ValH^+ \cdot H_2O$; (c) ●, $ValH^+ + NH_3 \rightleftharpoons ValH^+ \cdot NH_3$; (d) △, $ValH^+ + CH_3NO_2 \rightleftharpoons ValH^+ \cdot CH_3NO_2$. In graph a I_{ValH^+}/I_{ValH^+}, rather than K_a *vs.* $10^3/T$, is plotted as P_{Val} is unknown. The ordinate scale on the right-hand side relates to graph a.

terminable, thereby imposing some restrictions and uncertainties on the experimentally available data for the association reactions (eq 1), but not for the solvation reactions, as will be discussed below. Quantitative studies on the thermodynamics of ion–molecule reactions of compounds of comparably low volatility have not been reported previously.

In the present studies high-pressure chemical ionization mass spectrometric methods were applied, using the Rockefeller Chemical Physics mass spectrometer.[6] The major reactant gas was *i*-C_4H_{10}, and it constituted 90–100% of the reactant mixture. The solvent gases (NH_3, H_2O, and CH_3NO_2) were added to the *i*-C_4H_{10} in amounts between 2 and 10%. The mixtures of the solvent gases with *i*-C_4H_{10} were made up with quantitative accuracy so that the partial pressures of the solvents in the ionization chamber could be accurately calculated from the experimentally measured total pressures. The total source pressure was kept at 1.4 Torr, except where otherwise specified. The amino acids were introduced into the flow of the reactant mixture 40 cm upstream from the ion source, using a glass probe heated to 140°. The temperature of the probe was kept constant during the course of each experiment in order to maintain a constant pressure of the amino acid vapor. Constancy of the pressure of the amino acid vapor in the ion source was confirmed by the observations that the ratios $I_{MH^+}/I_{i\text{-}C_4H_9^+}$ and $I_{M_2H^+}/I_{MH^+}$ remained constant at constant source conditions for time periods which were considerably longer than the time required for a typical experiment. The ratios $I_{M_2H^+}/I_{MH^+}$ are dependent on the pressure of the amino acids, as $I_{M_2H^+}/I_{MH^+} = KP_M$, where K is the equilibrium constant of the association reactions of the type given in eq 1.

For some of the studies the mass spectrometer was operated in a pulsed mode, which permitted an examination of the variation of the apparent equilibrium constant with the residence time in the ionization chamber of the ions involved in the equilibria. The modifications to the mass spectrometer to permit operation in this pulsed mode will be described in greater detail in another publication,[7] but for the sake of completeness a brief description is required here. Using appropriate pulse generators, pulses were applied to the electron gun and to the focus electrodes in the ion gun. The electron gun pulse produces ions in the ionization chamber during a time span of a few microseconds, and the focus electrode pulse constitutes a gate which permits ions to pass into the mass analyzer. By varying the delay time of the focus electrode pulse with respect to the electron gun pulse, ions with different residence times in the ionization chamber are allowed to pass into the mass analyzer and be detected. The technique is for practical purposes identical with those described by Henchman and coworkers[8] for low-pressure investigations of ion–molecule reactions and by Kebarle[9] and coworkers for high-pressure studies. In the pulsed mode of operation the mass spectrometer sensitivity is much reduced; consequently, our pulsed studies were restricted to reactions of the more volatile of the two amino acids, valine, and to conditions where the equilibrium concentrations of the ions MH^+ and $MH^+ \cdot$solvent are of comparable magnitudes.

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Results and Discussion

Equilibrium constants for the solvation reaction (eq 2) were calculated as

$$K_a = \frac{I_{MH^+ \cdot solvent}}{I_{MH^+}P_{solvent}} \quad (3)$$

where $I_{MH^+ \cdot solvent}$ = peak intensity of the solvated ion, I_{MH^+} = peak intensity of the unsolvated protonated ion, and $P_{solvent}$ = pressure of solvent in atmospheres.

The presence of equilibrium in the solvation reactions under our experimental conditions was in part established by the dependence of the equilibrium constants on the total source pressure. The results for the solvation reaction of $ValH^+$ are shown in Figure 1. $ProH^+$ behaved similarly. In these studies K_a shows an increase with increasing total source pressure up to P = 1.2 Torr. The increase in K_a results from the increase of the number of ion–molecule collisions as well as from the increase of the residence time of the ions with increasing pressure. In the present experiments K_a obtains a constant value at $P \cong 1.2$ Torr, indicating that equilibrium has been obtained in the solvation reactions. The presence of equilibrium in the solvation reactions was also tested by varying the pressure of the solvent by about an order of magnitude about the solvent pressure at which the temperature studies (*vide infra*) were conducted. The results showed no significant dependence of K on the pressure of the solvent; for example, the values of log K_{385} for the reaction $ValH^+ + H_2O \rightleftharpoons ValH^+ \cdot H_2O$ were measured as 3.29 at P_{H_2O} = 0.016 Torr, 3.32 at P_{H_2O} = 0.230 Torr, and 3.27 at P_{H_2O} = 0.620 Torr. The latter pressure of H_2O vapor in the ion source was used in the temperature studies. The total source pressure was kept constant at 1.4 Torr in the composition studies. The results constitute evidence that the ratios $I_{MH^+ \cdot solvent}/I_{MH^+}P_{solvent}$ are determined by equilibrium rather than kinetic effects in our experiments. Values of ΔG_{300}, enthalpies, and

Table I. Thermodynamic Values for Association and Solvation Reactions in Protonated Gaseous Valine and Proline[a]

Reaction	ΔG_{300}, kcal mol^{-1}	ΔH, kcal mol^{-1}	ΔS, cal mol^{-1} deg^{-1}
$ValH^+ + Val \rightleftharpoons Val \cdot H^+ \cdot Val$		-20.7 ± 2.0	
$ProH^+ + Pro \rightleftharpoons Pro \cdot H^+ \cdot Pro$		-20.0 ± 2.0	
$ValH^+ + Pro \rightleftharpoons Val \cdot H^+ \cdot Pro$		-23.4 ± 2.0	
$ProH^+ + Val \rightleftharpoons Pro \cdot H^+ \cdot Val$		-21.0 ± 2.0	
$ValH^+ + H_2O \rightleftharpoons ValH^+ \cdot H_2O$	-8.4 ± 2.0	-19.3 ± 1.0	-36.3 ± 3.0
$ProH^+ + H_2O \rightleftharpoons ProH^+ \cdot H_2O$	-7.7 ± 2.0	-18.9 ± 1.0	-36.8 ± 3.0
$ValH^+ + NH_3 \rightleftharpoons Val \cdot H^+ \cdot NH_3$	-12.6 ± 2.0	-20.9 ± 1.0	-28.8 ± 3.0
$ProH^+ + NH_3 \rightleftharpoons Pro \cdot H^+ \cdot NH_3$	-11.9 ± 2.0	-20.6 ± 1.0	-28.9 ± 3.0
$ValH^+ + CH_3NO_2 \rightleftharpoons ValH^+ \cdot CH_3NO_2$	-12.4 ± 2.5	-19.8 ± 1.5	-27.8 ± 4.0
$ProH^+ + CH_3NO_2 \rightleftharpoons Pro \cdot H^+ \cdot CH_3NO_2$	-11.0 ± 2.5	-17.5 ± 1.5	-21.6 ± 4.0

[a] Error estimates are based on maximum deviation from the mean of values obtained in replicate experiments.

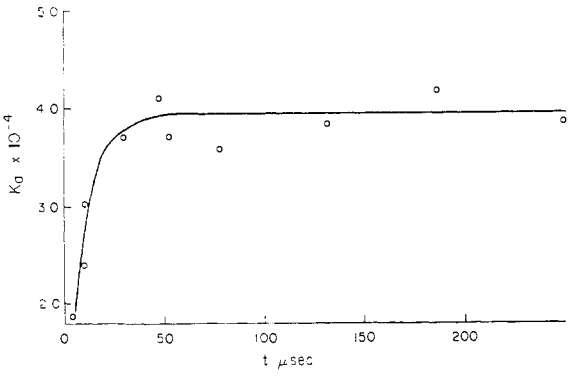

Figure 3. The dependence of $K_a = I_{ValH^+ \cdot H_2O}/I_{ValH^+}P_{H_2O}$ on reaction time at 328°K. P_{total} = 1.2 Torr, P_{H_2O} = 0.028 Torr.

entropies for the solvation reactions, obtained from the van't Hoff plots of log K *vs.* $10^3/T$ (Figure 2), are reported in Table I.

The validity of the thermodynamic values and of the assumption of equilibrium in the solvation reactions was further tested in the study of the behavior of the apparent equilibrium constant $K_a = I_{MH^+ \cdot solvent}/I_{MH^+}P_{solvent}$ as a function of reaction time. The behavior of K_a for the reaction

$$ValH^+ + H_2O \rightleftharpoons ValH^+ \cdot H_2O \qquad (4)$$

is shown in Figure 3. We take the invariance with time of K_a, *i.e.*, the ratio $I_{ValH^+ \cdot H_2O}/I_{ValH^+}$, as evidence that equilibrium has been obtained. The equilibrium constant corresponding to the time invariant portion of Figure 3 is $K = 4.0 \times 10^4$ (T = 328°K) (standard state = 1 atm). From the thermodynamic values for this reaction listed in Table I we calculated the value $K = 8.80 \times 10^4$ (328°K), and the agreement between these two values lies within the error limits of the thermodynamic values.

Equilibrium constants for the solvation of $ValH^+$ by NH_3 and CH_3NO_2 at 460°K were determined by similar methods from the time invariant portions of the plots of K_a *vs.* reaction time. The values obtained were $K = 3.2 \times 10^3$ and 1.6×10^3 for NH_3 and CH_3NO_2, respectively. The values calculated from the thermodynamic data of Table I are 4.5×10^3 and 2.2×10^3, again in good agreement within the experimental error limits.

The satisfactory agreement between the equilibrium constant values obtained with continuous ionization (K_a invariant with pressure) and with pulsed ionization (K_a invariant with time) provides strong evidence that the systems had achieved equilibrium.

As discussed above, the pressure of the amino acids in the ion source may be assumed constant through each experiment, but its value is not known. Consequently, $I_{M_2H^+}/I_{MH^+}$ *vs.* $10^3/T$ was plotted for these reactions. The value of the enthalpy, but not the entropy, for these reactions may be obtained from these plots since

$$\Delta H = -\frac{1}{R}\frac{d \ln K}{d\ 1/T} = -\frac{1}{R}\frac{d \ln (I_{M_2H^+}/I_{MH^+})(1/P_M)}{d\ 1/T} = -\frac{1}{R}\left(\frac{d \ln I_{M_2H^+}/I_{MH^+}}{d\ 1/T}\right)_{P_M} \qquad (5)$$

Values of ΔH for the association reactions are also shown in Table I.

Tests using the variation of pressure are not applicable to the establishment of equilibrium in the association reactions $MH^+ + M \rightleftharpoons M_2H^+$, since we do not know the actual pressure of the amino acid nor can we be sure that it would remain constant if the pressure of reactant gas mixture were varied. The existence of equilibrium in the reaction is implied, however, by the linearity of the van't Hoff plots and by the fact that the values of the enthalpy of the association reactions proved to be independent of the complexity of the reaction systems from which these values were obtained. For example, the value of ΔH for the reaction $ValH^+ + Val \rightleftharpoons Val_2H^+$ was measured as -21.1 kcal/mol in a reaction system of Val + i-C_4H_{10}, involving only one significant equilibrium reaction, and as -20.1 kcal/mol in a reaction system of Val + Pro + NH_3 + CH_3NO_2 + i-C_4H_{10}, which can be shown to involve 15 significant simultaneous association, solvation, and proton transfer equilibria. The lack of dependence of the equilibrium constants and of the thermodynamic values obtained from this on the complexity of the reaction system is a consequence of the principle of microscopic reversibility as applied to gaseous ion chemistry.

The enthalpies of the association reactions (Table I) are comparable to, although slightly lower than, the enthalpies of the association reactions between protonated and neutral gaseous amine molecules.[3] Comparison of the enthalpies of solvation of the $ValH^+$ and $ProH^+$ shows no significant differences. It is interesting that the enthalpies of solvation of both ions by the solvents H_2O and NH_3 which are considered as hydrogen bonding in solution are quite comparable in magnitude to the enthalpies of solvation by the nonhydrogen-bonding CH_3NO_2. It should be noted, however, that in the gas phase all of these solvents may serve as proton acceptors.

The thermodynamic parameters of the interactions

of charged amino acid residues with solvent clusters of various sizes, from single molecules to full solvent, are an essential factor in the determination of biophysically important phenomena, such as the changes in the extent of solvation and in the pK values of amino acid residues upon conformational changes in proteins in protonating environments.[10,11] We think that the quantitative determination by mass spectrometric studies of solute–solvent interactions for ions of biologically important compounds will provide information relevant to the energetics of such ions in their biological environments. Similarly the information available from mass spectrometric studies on the energies of interaction between protonated and nonprotonated amino acids may be helpful in the understanding of the role of such interactions on the determination of protein conformation.

Association complexes of the type ValH$^+$·Val, etc., were shown by Leclerq and Desiderio[4] to form preferentially in a "head-to-tail" configuration and to decompose in several condensation processes including the loss of H_2O, presumably leading to the production of protonated dipeptides. Association reactions of the types investigated in this study may therefore constitute the first step in reactions leading to the abiotic synthesis of large molecules of potential biogenetic significance, under ionizing conditions that are frequently assumed in environments of interest in biogenetic and exobiological studies.

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Displacement Reactions of Neopentyl-*1-d* Tosylate without Rearrangement and Optical Rotatory Dispersion Spectra of Chiral Compounds with Four Different Groups of Either C_{3v} or $C_{\infty v}$ Symmetry Attached to a Central Carbon[1,2]

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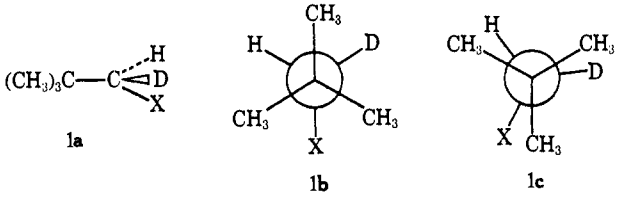
Contribution from the Chemistry Department, Stanford University, Stanford, California 94305. *Received August 7, 1973*

Abstract: (*S*)-Neopentyl-*1-d* tosylate in hexamethylphosphoramide solvent undergoes substitution with inversion and without detectable rearrangement by a number of nucleophiles (F^-, Cl^-, Br^-, I^-, CN^-, N_3^-, SH^-, and CH_3^- [as $(CH_3)_2CuLi$]) to give good yields of chiral neopentyl-*1-d* derivatives. Thus in hexamethylphosphoramide solvent neopentyl tosylate undergoes the normal SN2 substitutions without rearrangement and with inversion of configuration. The syntheses of these neopentyl compounds (Me_3CC^*HDX, X = F, Cl, Br, I, CN, N_3, SH, and CH_3) and derivatives (X = NH_2, $^+NMe_3$, SO_3H) are described. Compounds of this series display an unusually simple conformational symmetry and are therefore of special interest from an ORD standpoint. (*R*)-Neopentyl-*1-d* derivatives with X = F, Cl, Br, I, $^+NH_3$, $^+NMe_3$ and the configurationally related (*S*)-2,2-dimethylbutane-*3-d* (X = CH_3), in which the X substituents have either C_{3v} or $C_{\infty v}$ symmetry, gave plain negative ORD curves while (*R*)-neopentyl-*1-d* derivatives with X = SH, SO_3, NH_2, and CN gave plain positive curves down to approximately 350 nm. (*R*)-Neopentyl-*1-d* azide has a substantial optical rotation: $[\alpha]^{20}D$ +3.2° (neat); ORD maximum $[\phi]^{20}_{305}$ +41° (cyclohexane). Its CD maximum $[\theta]^{20}_{288}$ +30 (methylcyclohexane–isopentane) is unshifted at 77°K and has only slightly higher intensity.

In the course of studying the SN2 displacement reactions of chiral neopentyl-*1-d* tosylates and halides[2,3] we realized that molecules with structure **1a** constitute a group of chiral compounds which are conformationally very simple and potentially interesting for experimental and theoretical ORD studies. Each substituent on the chiral carbon considered separately and viewed along the bond axis to the chiral carbon possesses either C_{3v} symmetry (*tert*-butyl, $^+NMe_3$, CH_3, $^+NH_3$, SO_3^-) or $C_{\infty v}$ symmetry (H, D, halogen, CN, S^-). The major conformational variable for neopentyl compounds with such substituents with $C_{\infty v}$ symmetry is the rotation between the three indistinguishable staggered forms (**1b**) over the three indistinguishable eclipsed barriers (**1c**).[4] There is also



1a **1b** **1c**

the rotation of each C_{3v} symmetrical methyl group which makes up the *tert*-butyl group itself. (Dynamic displacements of bond angles and bond distances are

(1) We gratefully acknowledge support of this study by the National Science Foundation (NSF GP 27448) and the USPHS (NIH ROIGM 19554).
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