the experimental value is only about 10 J mole^{-1} deg^{-1}. However, since the configurational integrals were equated in deriving the formula, this lack of agreement is not unexpected.

If one accepts Swain and Bader's value for the isotope effect on the heat of solution of the fluoride ion, the data in Table III lead to values of +732, +1548, +506, +459, and +462 J mole^{-1} for the Na^+, Cl^-, $MeSO_3^-$, ϕSO_3^-, and TOS^- ions respectively.

The fluoride ion is the only singly charged ion for which a negative contribution to the isotope effect has been observed, and hence is the only such ion for which the librational frequency of the solution is greater than that of pure water. This singular behavior of the fluoride ion does not imply that there is any discontinuity in the properties of the halogens, since plots of the ionic contributions to the thermodynamic properties against the ionic radius or its reciprocal are smooth curves (7).

It is interesting to note that the isotope effect on the heats of hydration of the sulfonates does not vary much with the size of the anion. We have not calculated the corresponding change in librational frequency for the sulfonates since in order to have done so we would have had to introduce further assumptions regarding the extent of coordination. However, it does appear that in all cases these ions tend to decrease the amount of water structure, the disruptive effect being greater in D_2O than in H_2O. This is in line with the positive entropies of transfer (H_2O to D_2O) deduced by Greyson from measurements of the ion exchange membrane potentials for a number of chlorides (9).

Provided that the solute–solvent interaction in the transition state for the solvolysis of alkyl halides and sulfonates in water is proportional to that in the final state, the isotope effects reported in this paper support the hypothesis (10) that it is the initial state solvation shell rather than that in the transition state which is the major factor in determining kinetic solvent isotope effects since the latter do not vary in the same manner as do the enthalpy changes.

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ACYLGUANIDINES AS INTERMEDIATES IN PEPTIDE SYNTHESES

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In our investigation of new peptide syntheses we considered the properties of guanidine as a carboxyl-activating group.

Acylguanidines (I), according to the literature (1, 2), can be prepared by the action of guanidine (liberated from its salt by sodium alkoxide) on the esters of carboxylic

acids. It seemed to us that these compounds should be very prone to proton-catalyzed aminolysis as outlined in eq. [1], since they have, indeed, distinctly basic properties (3).

[1] $$\underset{\text{(I)}}{\mathrm{RCNHCNH_2}} \xrightarrow{H^+} \underset{\text{(II)}}{\left[\mathrm{RCNHCNH_2}\right]^+} \xrightarrow{NH_2R'} \mathrm{RCNHR'} + \left[\mathrm{NH_2CNH_2}\right]^+$$

The positively charged intermediate (II) should then suffer nucleophilic attack by amines to yield the expected amide. The reaction could conceivably be carried out in aqueous or mixed aqueous–organic solvents. Furthermore, the trend of the reaction should be towards the formation of the resonance-stabilized guanidinium ion, thus facilitating the formation of the amide bond.

In a preliminary attempt to verify these assumptions we were successful in preparing acylguanidines of hippuric acid, benzyloxycarbonylglycine, benzyloxycarbonyl-DL-alanylglycine, formyl-L-valine, formyl-L-phenylalanine, and tosyl-L-proline from their corresponding ethyl or methyl esters. The yields in these reactions were fair to good and the substances could be obtained in crystalline form.

These guanidine compounds were then caused to react with either ethyl or benzyl glycinate in water or water–dimethylformamide solution at pH 8 to give ethyl hippurylglycinate, benzyl benzyloxycarbonylglycylglycinate, ethyl benzyloxycarbonyl-DL-alanylglycylglycinate, ethyl formyl-L-valylglycinate, ethyl formyl-L-phenylalanylglycinate, and ethyl tosyl-L-prolylglycinate, respectively, with fairly good yields.

It therefore seems that this is a feasible method for the synthesis of peptides and that optical activity can be retained in these reactions. The scope and limitation of this method are at present under investigation.

EXPERIMENTAL

All melting points were taken on a Fisher–Jones apparatus and are uncorrected.

Benzyloxycarbonylglycylguanidine

Methyl benzyloxycarbonylglycinate (6.1 g; 0.0274 mole) was treated with a solution of 0.0435 mole of free guanidine in 20 ml of absolute ethanol. The ester dissolved and the solution was left to stand at room temperature for several hours. After precipitation was complete, the material was filtered off and dried. The yield was 5.5 g (80.4%); the compound could be recrystallized from either nitromethane or ethanol – ethyl acetate and it melted at 152°.

Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.8; H, 5.6. Found: C, 52.9; H, 5.9.

Similarly prepared were the following.

Hippurylguanidine

This compound was obtained in 87.6% yield. It was recrystallized from dioxane and melted at 182°.

Anal. Calcd. for $C_{10}H_{12}N_4O_2$: C, 54.5; H, 5.4. Found: C, 54.6; H, 5.6.

Benzyloxycarbonyl-DL-alanylglycylguanidine

This compound was obtained in 51% yield. It was recrystallized from ethanol and melted at 175–176°.

Anal. Calcd. for $C_{14}H_{19}N_5O_4$: C, 52.4; H, 5.9. Found: C, 52.6; H, 5.9.

Formyl-L-valylguanidine

This compound was obtained in 74% yield. It was recrystallized from *n*-butanol and melted at 162–164°; $[\alpha]_D^{25}$ +2.8° (*c*, 1.8 in absolute ethanol).

Anal. Calcd. for $C_7H_{14}N_4O_2$: C, 45.1; H, 7.5; N, 30.1. Found: C, 45.3; H, 7.8; N, 29.9.

Formyl-L-phenylalanylguanidine

This compound was obtained in 69% yield. It was recrystallized from *n*-butanol and melted at 153°; $[\alpha]_D^{25}$ +27.2° (*c*, 1.6 in absolute ethanol).

Anal. Calcd. for $C_{11}H_{14}N_4O_2$: C, 56.4; H, 6.0; N, 23.9. Found: C, 56.1; H, 6.3; N, 23.9.

Tosyl-L-prolylguanidine

This compound was obtained in 79% yield. It was recrystallized from absolute ethanol and melted at 187–188°; $[\alpha]_D^{25}$ −174° (*c*, 0.8 in absolute ethanol).

Anal. Calcd. for $C_{13}H_{18}N_4O_3S$: C, 50.4; H, 5.8; N, 18.0. Found: C, 50.5; H, 6.1; N, 18.3.

Ethyl Benzyloxycarbonylglycylglycinate

A solution of 1.25 g (0.005 mole) of benzyloxycarbonylglycylguanidine in 5 ml of dimethylformamide was added to an aqueous solution of 0.7 g (0.005 mole) of ethyl glycinate hydrochloride, the pH of which was adjusted to 8 with alkali. The resultant clear solution was stirred at room temperature overnight and then evaporated on a water bath (40°) under reduced pressure (0.4 mm Hg). The residue was treated with water until crystallization occurred, then filtered, and air dried to yield 1.35 g (90%) of white solid which was recrystallized from ethyl acetate and melted at 80° (lit. m.p. 80° (4)).

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.1; H, 6.1. Found: C, 57.0; H, 6.2.

Similarly prepared were the following.

Ethyl Hippurylglycinate

This was obtained in 76% yield. It was recrystallized from water and melted at 117° (lit. m.p. 117° (5)).

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.1; H, 6.1. Found: C, 59.0; H, 6.2.

*Ethyl Benzyloxycarbonyl-*DL*-alanylglycylglycinate*

This was obtained in 50% yield. It was recrystallized from ethanol–water and melted at 110° (lit. m.p. 113° (6)).

Anal. Calcd. for $C_{17}H_{23}N_3O_6$: C, 55.9; H, 6.3. Found: C, 56.0; H, 6.4.

*Ethyl Formyl-*L*-valylglycinate*

This was obtained in 71% yield. It was recrystallized from ethyl acetate – petroleum ether and melted at 155° (lit. m.p. 156–157° (7)).

Anal. Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.2; H, 7.8; N, 12.2. Found: C, 52.1; H, 7.9; N, 12.4.

*Ethyl Formyl-*L*-phenylalanylglycinate*

This was obtained in 82% yield. It was recrystallized from water and melted at 132°; $[\alpha]_D^{25}$ +4.6° (*c*, 1.6 in absolute ethanol) (lit. m.p. 131–132°; $[\alpha]_D^{26}$ +4.4° (7)).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.5; H, 6.5; N, 10.1. Found: C, 60.3; H, 6.6; N, 10.6.

*Ethyl Tosyl-*L*-prolylglycinate*

This was obtained in 68% yield. It was recrystallized from hexane – ethyl acetate (2:1) and melted at 84–86°; $[\alpha]_D^{25}$ −115.8° (*c*, 4.5 in absolute ethanol).

Anal. Calcd. for $C_{16}H_{22}N_2O_5S$: C, 54.3; H, 6.2; N, 7.9. Found: C, 54.4; H, 6.1; N, 8.0.

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SYNTHESIS OF 5-BENZAMIDO-5-DEOXY-D-XYLOPYRANOSE

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The synthesis of the *N*-acetyl (1, 2) (I, R = $COCH_3$) and the *N*-benzyl (3) (I, R = CH_2Ph) derivatives of 5-amino-5-deoxy-D-xylopyranose (4) (I, R = H) and of the corresponding furanose compounds has been described (1–4). Recently we attempted the preparation by reported procedures of the acetobromo derivative of 5-acetamido-5-deoxy-D-xylopyranose (I, R = $COCH_3$) but were unsuccessful. The synthesis of the benzamido derivative of 5-amino-5-deoxy-D-xylopyranose (I, R = COPh) was therefore undertaken in the hope that this would yield, after *O*-benzoylation, a benzoylbromo sugar.