in pure water. The pD values were obtained by adding 0.40 to the pH meter reading.[44]

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Characterization of the Solvent Dependence of the Nonbonded Atom Interaction Energy by the Stereoselectivity of Asymmetric Reactions

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Abstract: The stereoselectivity of bromide displacement from D- or L-α-bromophenylacetic acid (BPAA) or its methyl ester (MBPA) by L-tyrosine ethyl ester or L-proline derivatives was measured in water and in aqueous solutions of methanol, dioxane, urea, and $NaNO_3$. The results were interpreted in terms of the difference in the free energies of the diastereomeric transition states which reflect nonbonded atom interaction energies in the various solvent media. The stereoselectivity was found to be much higher for processes involving the conformationally rigid proline derivatives, and, in the case of the proline amide reaction in water solution, it exhibited large temperature coefficients which had opposite signs for the reaction with BPAA and MBPA. A much smaller temperature dependence of stereoselectivity was observed in aqueous solutions containing methanol or dioxane as cosolvents. At 35 °C, reactions of L-proline derivatives with L-MBPA were always faster than those with the D isomer, although conformational analysis shows that the transition-state complex formed from L-MBPA is sterically more hindered. Large additions of methanol or dioxane always sharply reduced the stereoselectivity but in some systems the stereoselectivity passed through a maximum on addition of small concentrations of these cosolvents. Addition of urea and of $NaNO_3$ had generally little effect on the stereoselectivity.

In calculating the potential energies characterizing the various conformations accessible to synthetic polymers, it is generally assumed that the role of the solvent has to be taken into account only insofar as it affects dipole–dipole interaction energies.[2] Such interactions have been shown to be particularly important in predicting the unperturbed dimensions of polypeptides.[3] Yet, while this approach has led to valuable results in a variety of systems, it has clearly some important limitations. A striking demonstration of the anomalies that may be encountered is provided by the study of the trans–gauche conformational equilibrium of 1,2-dichloroethane.[4a] This is a particularly simple case, and the conventional analysis would have predicted that the fraction of the molecules in the gauche conformation should increase with an increasing dielectric constant of the solvent. Such a correlation is, in fact, observed with a number of media, but in benzene and dioxane solution the content of the gauche conformer is much higher than expected from the dielectric constant of these solvents. This

suggests that specific solvation effects, which we cannot account for theoretically, may have an important perturbing effect on the conformational distribution of solute molecules. (The solvent dependence of the equilibrium between the diaxial and diequatorial forms of *trans*-1,2-dibromocyclohexane exhibits a similar anomaly in that toluene behaves like a solvent of much higher dielectric constant.[4b])

The situation is even more complex if we consider aqueous solutions. Here the "local effective dielectric constant" in the vicinity of an organic solute should be much smaller than the bulk dielectric constant of water.[5] It is not easy to obtain a reliable estimate of this effective dielectric constant, and although its value should depend on the spacing of the interacting dipoles, this feature would render computations so complex that is is never considered. Moreover, additional effects would be expected due to hydrogen bonding and the related formation of "hydrophobic bonds" between nonpolar residues inserted into an aqueous medium.[6] In the case of poly(L-proline), the explicit consideration of hydrogen bonding of the macromolecule to the aqueous solvent medium was shown to change, in a striking manner, the dependence of its energy on its conformation.[7a] Data of conformational equilibria in aqueous solution are extremely rare. One of the few studies of this type is the NMR investigation of choline, its derivatives, and related substances by Feeney.[7b]

It would appear that the physical situation is so complicated that a search for new experimental approaches to the determination of nonbonded atom interaction energies of solutes in aqueous media is imperative if our understanding of this problem is to be significantly advanced. In the present work we have tried to use for this purpose the stereoselectivity of asymmetric reactions. If the L and D isomers of reagent A react with the L isomer of reagent B, the second-order rate constants k_{LL} and k_{LD} are related, according to the theory of absolute reaction rates, by

$$k_{LL}/k_{LD} = \exp[-(\Delta G^{\ddagger}_{LL} - \Delta G^{\ddagger}_{LD})/RT] \qquad (1)$$

where $\Delta G^{\ddagger}_{LL}$, $\Delta G^{\ddagger}_{LD}$ are the standard free energies of activation of the two processes. However, since the solution of the reagents is highly dilute so that solute-solute interactions can be neglected, the free energy of the ground state is independent of the configuration of reagent A. Thus we have

$$k_{LL}/k_{LD} = \exp[(G^{\ddagger}_{LD} - G^{\ddagger}_{LL})/RT] \qquad (2)$$

so that the stereoselectivity ratio k_{LL}/k_{LD} reflects the difference in the standard free energies of the diastereomeric transition states. This expression was originally used by Prelog[8] who assumed that $G^{\ddagger}_{LD} - G^{\ddagger}_{LL}$ reflects the difference in the steric hindrance characterizing the two diastereomeric transition states. However, the stereoselectivity of asymmetric reactions was later found to be solvent dependent in a number of cases,[9] and this dependence may be used to study the effect of the solvent medium on the nonbonded atom interaction energies of the transition states.

The investigation reported in this paper uses this principle in a study of the solvent dependence of the stereoselectivity of bromide displacement from L- or D-α-romophenylacetic acid and their methyl esters by the amine group of L-tyrosine ethyl ester and various derivatives of L-proline. The aqueous solvent medium was perturbed by addition of methanol, dioxane, urea, or sodium nitrate.

Experimental Section

Reagents. Racemic α-bromophenylacetic acid (Aldrich Chemical Co.) was resolved by crystallization of the brucine salt from methanol. The acid isolated from the salt ($[\alpha]^{20}D = +149°$ in water solution) is the L (or *S*) isomer, since a dextrorotary product is obtained by treatment of (−)-mandelic acid (which has the D (or *R*) configuration[10]) with phosphorus pentabromide,[11] which involves an inversion of the asymmetric center. The D (or *R*) isomer ($[\alpha]^{20}D = -143°$) was obtained from the mother liquor by repeated crystallization. To obtain the optical isomers of the methyl esters of α-bromophenylacetic acid, (*S*)- and (*R*)-mandelic acid was converted to the methyl ester and treated with phosphorus pentabromide. The oily product was distilled at 105–107 °C and 10 Torr. Optical activities (methanol solutions) were $[\alpha]^{20}D = -29.9°$ and +30.1° for the L and D isomers, respectively (where the configurations were opposite to those of the parent mandelic acid). Derivatives of L-proline prepared by standard procedures had the following $[\alpha]^{20}D$ values: methyl ester, −45°; ethyl ester, −39°; isopropyl ester, −21°; amide, −73°; dimethylamide, −63°. L-Tyrosine ethyl ester (Eastman Kodak) had $[\alpha]^{20}D = +20.5°$, mp 104–6 °C.

Kinetics. The bromide displacement from α-bromophenylacetic acid and its methyl ester was studied in thermostated aqueous solutions buffered at pH 7 using 0.05 M phosphate buffer and in such buffer solutions containing various added cosolvents. The progress of the reaction was followed by running aliquots into 6 M nitric acid solution at −10 °C and determining bromide by the Volhard method. The stereoselectivity of the reaction was obtained from k_{LL}/k_{LD}, the ratio of the rate constants characterizing the reaction of the L nucleophile with the L and D bromo derivative, respectively. All reactions involving proline derivatives and methyl α-bromophenylacetate were run in duplicate, k_{LL}/k_{LD} was obtained from the average k_{LL} and k_{LD} vaues, and a statistical analysis of 35 duplicate runs showed that the value of k_{LL}/k_{LD} is subject to an uncertainty (two standard deviations) of ±3%.

Product Characterization. In the case of the reaction of L-proline amide with methyl α-bromophenylacetate, the product was isolated and subjected to elemental analysis. The result C 63.7, H 6.93, N 10.58 compares with C 64.1, H 6.87, N 10.7 for $C_{14}H_{18}O_3N_2$ of the structure

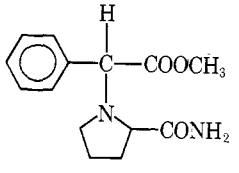

Table I. Rate Constants and Stereoselectivity of the Reactions Between D- or L-Methyl α-Bromophenylacetate and L-Tyrosine Ethyl Ester at 35 °C

Medium	k_{LD}, M^{-1} min^{-1}	k_{LL}, M^{-1} min^{-1}	k_{LL}/k_{LD}	$G^{\ddagger}_{LD} - G^{\ddagger}_{LL}$, cal/mol
Water	0.240	0.242	1.00	0
20% Dioxane	0.192	0.220	1.15	90
40% Dioxane	0.162	0.207	1.28	150
20% Methanol	0.284	0.301	1.06	40
40% Methanol	0.188	0.220	1.17	100
6 M Urea	0.702	0.785	1.12	70
0.5 M $NaNO_3$	0.247	0.256	1.04	20

Results

Reaction of Methyl α-Bromophenylacetate with L-Tyrosine Ethyl Ester. Results obtained with this reaction in water and in aqueous solution containing methanol, dioxane, urea, or sodium nitrate are listed in Table I. The reaction exhibits no significant stereoselectivity in water, but on addition of methanol, dioxane, or urea the LL reaction becomes slightly faster than the LD process. Addition of 0.5 M sodium nitrate has a very small effect on the stereospecificity.

Reaction of α-Bromophenylacetic Acid with L-Proline Amide. Results obtained for this reaction in water and in aqueous solution containing 40 vol % methanol are listed in Table II. In all cases, the LL reaction is much faster than the LD reaction. Beyond this, the most striking observation is the rapid decrease of the k_{LL}/k_{LD} ratio with increasing temperature if the reaction is carried out in water. In 40% methanol,

Table II. Rate Constants and Stereoselectivity of the Reaction Between D- or L-α-Bromophenylacetic Acid and L-Proline Amide at 35 °C

Medium	Temp, °C	k_{LD}, M^{-1} min^{-1}	k_{LL}, M^{-1} min^{-1}	k_{LL}/k_{LD}	$G^{\ddagger}_{LD} - G^{\ddagger}_{LL}$, cal/mol	$E^{*}_{LD} - E^{*}_{LL}$, cal/mol
Water	15	0.110	0.332	3.02	670	
	25	0.506	1.06	2.09	450	+6100
	35	1.97	3.11	1.58	280	
40% Methanol	15	0.312	0.713	2.29	500	
	25	0.647	1.39	2.15	470	+900
	35	1.29	2.64	2.05	440	

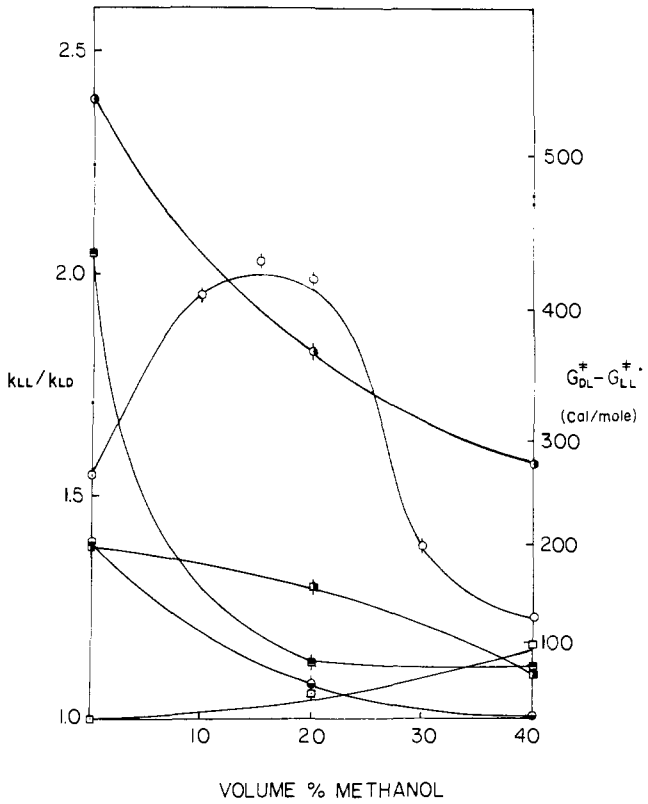

Figure 1. Effect of methanol addition on the stereoselectivity of bromide displacement from methyl α-bromophenylacetate by L-tyrosine ethyl ester (□) and the following L-proline derivatives: amide (◑), dimethylamide (◒), methyl ester (▣), ethyl ester (◧), isopropyl ester (○).

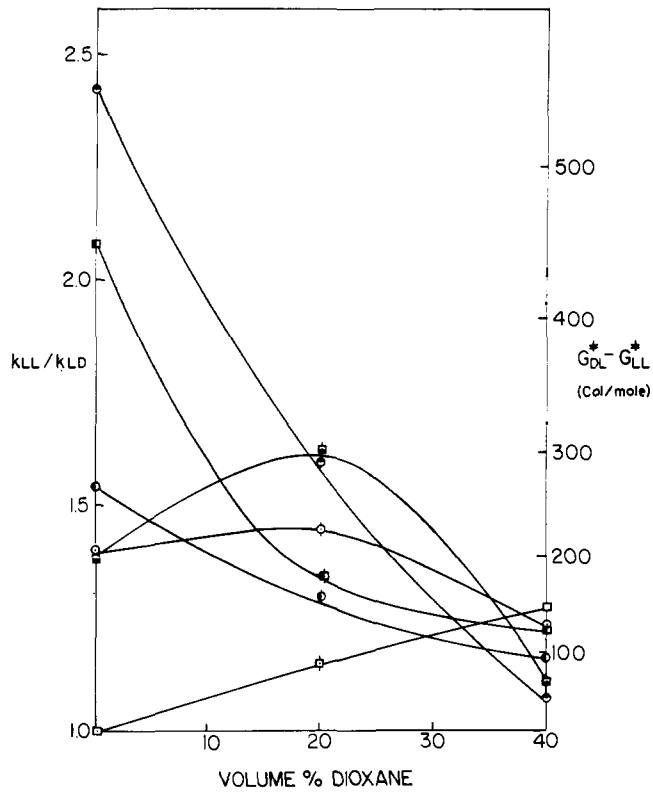

Figure 2. Effect of dioxane addition on the stereoselectivity of bromide displacement from methyl α-bromophenylacetate by -tyrosine ethyl ester (□) and the following amide derivatives: amide (◓), dimethylamide (○), methyl ester (◧), ethyl ester (▣), isopropyl ester (◑).

this ratio shows only a very slight variation with temperature.

Reaction of Methyl α-Bromophenylacetate with L-Proline Derivatives. Table III lists the results obtained with the reaction of methyl α-bromophenylacetate with L-proline amide. The most striking feature is the strong temperature dependence of the stereoselectivity in water solution where the k_{LL}/k_{LD} ratio increases with increasing temperature, in contrast with the decrease observed in the case of the analogous α-bromophenylacetic acid reaction. The temperature dependence of k_{LL}/k_{LD} for the methyl α-bromophenylacetate reaction is sharply reduced by addition of methanol and almost eliminated by addition of dioxane to the aqueous medium.

A summary of k_{LL}/k_{LD} values obtained for the reaction of methyl α-bromophenylacetate with various L-proline derivatives at 35 °C in water and aqueous solutions of methanol, dioxane, urea, and $NaNO_3$ is presented in Table IV and Figures 1 and 2. The following points may be made:

(a) At 35 °C, the LL reaction is invariably faster than the DL reaction.

(b) The addition of 0.5 M $NaNO_3$ is without significant effect on the stereoselectivity.

(c) The addition of 6 M urea is without significant effect in three of the reactions. However, it leads to a sharp increase of k_{LL}/k_{LD} for the reaction of L-proline ethyl ester and a similar sharp decrease of k_{LL}/k_{LD} for the reaction of L-proline methyl ester.

(d) Addition of methanol or dioxane may produce one of two effects: (1) In most cases, the stereoselectivity decreased gradually with increasing cosolvent concentration. (2) In some cases, the stereoselectivity first increased on cosolvent addition, passed through a maximum and then declined. This pattern was observed in the reaction of proline dimethylamide and proline ethyl ester on addition of dioxane and in the reaction of proline isopropyl ester on addition of methanol.

Conformational Analysis

Any tentative interpretation of the experimental results requires a consideration of the probable conformations of the diastereomeric transition states. We have attempted to obtain this information for the transition state formed in the reaction of L-proline derivatives with the two enantiomeric forms of α-bromophenylacetic acid or its methyl ester, as represented schematically in Figure 3. Since the stereoselectivity of the

Table III. Rate Constants and Stereoselectivity of the Reaction of D- or L-Methyl α-Bromophenylacetate with L-Proline Amide at 35 °C

Medium	Temp, °C	k_{LD}, M^{-1} min^{-1}	k_{LL}, M^{-1} min^{-1}	k_{LL}/k_{LD}	$G^{\ddagger}_{LD} - G^{\ddagger}_{LL}$, cal/mol	$E^{*}_{LD} - E^{*}_{LL}$, cal/mol
Water	15	0.73	0.669	0.865	−90	
	25	1.13	1.65	1.46	230	−8800
	35	1.59	3.82	2.39	530	
20% Methanol	25	1.07	1.49	1.39	200	
	35	1.44	2.63	1.82	590	−4800
40% Methanol	15	0.832	0.755	0.907	−70	
	25	1.31	1.60	1.22	120	−4500
	35	2.03	3.20	1.57	270	
20% Dioxane	25	1.10	1.78	1.62	290	
	35	1.31	2.09	1.60	290	+200
40% Dioxane	25	1.37	1.55	1.13	70	
	35	1.98	2.11	1.07	40	+100

Table IV. Medium Effects on k_{LL}/k_{LD} for Reactions of Methyl α-Bromophenylacetate with L-Proline Derivatives at 35 °C

	L-Proline derivatives				
Medium	Amide	Dimethyl amide	Methyl ester	Ethyl ester	Isopropyl ester
Water	2.39	1.40	2.05	1.39	1.55
20% Methanol	1.82	1.08	1.13	1.30	1.99
40% Methanol	1.57	1.01	1.12	1.10	1.23
20% Dioxane	1.60	1.45	1.34	1.62	1.30
40% Dioxane	1.07	1.23	1.22	1.11	1.17
6 M Urea	2.25	1.37	1.32	2.58	1.46
0.5 M $NaNO_3$	2.41	1.33	2.14	1.38	1.59

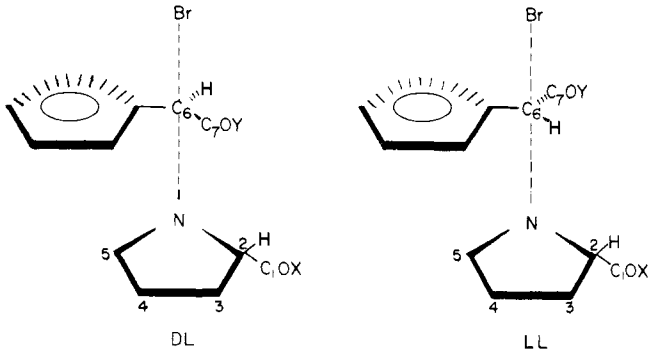

Figure 3. The diastereomeric transition states in the bromide displacement from α-bromophenylacetic acid or its methyl ester by L-proline derivatives.

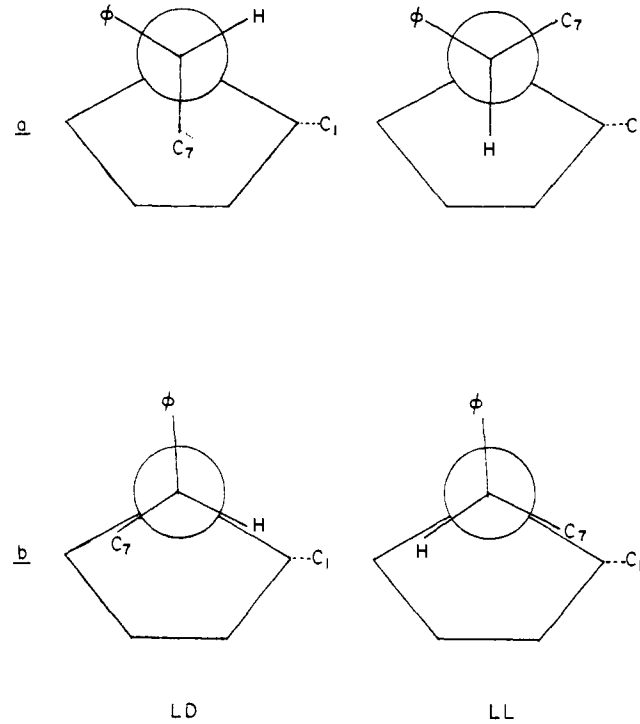

Figure 4. Newman projections along N-C(6) of the diastereomeric transition states in the bromide displacement from α-bromophenylacetic acid or its methyl ester by L-proline derivatives: (a) conformation with phenyl group trans to N-C(2); (b) conformation with maximum distance between phenyl group and proline ring.

reaction was found to depend on the esterification of α-bromophenylacetic acid and the nature of the proline substituent, the distance between the C(1) and C(7) carbons was assumed to be significant.

Two conformations of special interest are represented in a Newman projection on Figure 4 with the C(6)-N bond in the line of sight. If the bulky phenyl group were trans to the bond connecting the nitrogen to its largest substituent C(2) (conformation a), the C(1)-C(7) distance would be 5.24 and 4.60 Å for the LD and LL transition states, respectively. If the phenyl group were trans to the bisector of the C(5)-N-C(2) angle, so as to maximize its distance from the proline ring, the eclipsed conformation b would be obtained for which the C(1)-C(7) distance was computed as 4.75 and 4.12 Å for the LD and the LL transition states, respectively. (We assumed that the proline ring has the same geometry as in proline crystals,[12] that the bonds to the proline nitrogen are tetrahedral, and that the partial N-C(6) bond, lying trans to C(1)-C(2), has a length of 2.5 Å. The bonds connecting C(6) to hydrogen, C(7), and the phenyl group were assumed to lie in a plane perpendicular to N-C(6) with bond angles of 120°. The C(6)-C(7) bond length was taken as 1.53 Å.) It is reasonable to expect the conformation of the transition state

complex to be intermediate between a and b, so that the C(1)-C(7) distance is shorter for the LL than for the LD diastereomer. It may be noted that the difference in this distance in the two diastereomeric transition states is rather insensitive to the assumed length of the N-C(6) partial bond.

Discussion

We should like to emphasize that while the solvent effect on the k_{LL}/k_{LD} ratio has a precise physical significance, the effect of cosolvents on the individual reaction rates is of no interest in the context of this investigation. This is so because we have no knowledge about the effect of the solvent medium on the ionization of the amino groups which act as nleophiles in the reactions we have investigated. Beyond this, a change in the solvent medium affects the activity of both the ground states of the reagents and the transition-state complex,[13] introducing uncertainties into interpretations of kinetic data. Both these complications are eliminated if we concentrate our attention on the k_{LL}/k_{LD} ratio of reaction rates, which depends only on the difference in the free energies of the two diastereomeric transition states. This difference may be obtained with very high precision; an uncertainty of ±3% in k_{LL}/k_{LD} corresponds to an uncertainty in $G^{\ddagger}_{LL} - G^{\ddagger}_{LD}$ of only ±20 cal/mol.

The analyses of the stereoselectivity of asymmetric reactions by Prelog[8] and by Cram and Elhafez[14] assumed that valid predictions may be made on the basis of the relative size of substituents attached to an asymmetric center. It was here postulated that the process resulting in less steric interference would take place at a higher rate. As we shall see, this generalization leads to incorrect predictions for a number of the reactions we have studied.

In general, it would be expected that stereoselectivity is enhanced by conformational rigidity of the interacting species. With reagents which are conformationally mobile, some of the conformers may favor the LL and others the LD reaction, so that the observed average stereoselectivity should be relatively small. We have noted this effect in comparing the stereoselectivities when the conformationally mobile tyrosine ethyl ester and the rigid proline derivatives were used as nucleophiles. For instance, in Table I the largest value of k_{LL}/k_{LD} is 1.28, while Table IV lists a number of reactions for which the k_{LL} rate is more than twice as large as k_{LD}. We have concentrated our study on the reactions of the rigid proline derivatives since the significance of the results can be more easily analyzed.

The conformational analysis of the diastereomeric transition states formed by the proline derivatives with methyl α-bromophenylacetate shows that the LL species should be more sterically hindered. Yet, Table IV shows that at 35 °C the LL reaction is invariably faster so that the LL diastereomer must have a lower free energy. It would be tempting to ascribe this striking result to hydrophobic bonding between the ester group of methyl α-bromophenylacetate and the proline substituent. This interpretation would lead to the prediction that addition of organic cosolvents or of urea generally reduces the stereoselectivity. The hydrophobic bonding (which is endothermic) should also be enhanced by an increase in temperature. The data are, however, found to deviate in important respects from the pattern expected on the basis of this simple model. The following points may be made:

(a) While the addition of 40% methanol or dioxane always reduces the k_{LL}/k_{LD} ratio below the value observed in water, additions of smaller proportions of these cosolvents were found in three cases to lead to an enhancement of the stereoselectivity. This unexpected phenomenon suggests that a mixed solvent medium is highly favorable for the solvation of the transition-state complex.

(b) Urea addition, which was expected to reduce stereoselectivity by destroying the water structure, was found to have no significant effect in three of the five systems studied. In one case it increased and in one it reduced the k_{LL}/k_{LD} ratio.

(c) The stereoselectivity is more pronounced in the reaction with proline amide than with the proline esters, and it is greatly reduced when the amide hydrogens are substituted by methyl groups. This could mean that hydrogen bonding between the amide group and the ester carboxyl of methyl α-bromophenylacetate plays a role in stabilizing the transition state.

(d) Since hydrophobic bonding becomes more pronounced with an increase in temperature, the k_{LL}/k_{LD} ratio increased sharply for the reaction of proline amide with methyl α-bromophenylacetate. However, the opposite temperature coefficient of k_{LL}/k_{LD} was found for the proline amide reaction with α-bromophenylacetic acid. The acid is fully ionized at pH 7, and if there is an attractive interaction between the carboxylate and the amide group, it must be due to exothermic hydrogen bonding rather than endothermic hydrophobic bonding.

(e) Salt addition would have been expected to accentuate attractive interactions between nonpolar residues in the transition state complex formed by methyl α-bromophenylacetate and proline esters. Yet, 0.5 M $NaNO_3$ was without significant effect on the stereoselectivity of the reaction.

We may conclude that the study of the solvent dependence of the stereoselectivity of asymmetric reactions is a highly sensitive method for the study of the solvent dependence of nonbonded atom interaction energies. A variety of unexpected phenomena were observed in this study which do not lend themselves to any simple interpretation.

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References and Notes

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