A Thermodynamic Study of Solute–Solvent Interactions Using Gas–Liquid Chromatography. The Interaction of Chloroalkanes with the Carbonyl Bond

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Abstract: Standard enthalpies and entropies of solution from the vapor phase to the infinitely dilute solution in *n*-eicosane and in dinonyl ketone have been measured for eight alkanes and sixteen chloroalkanes at 60 °C using gas–liquid chromatography. The induction interaction between the carbon–chlorine bond and a methylene chain is −1.1 kcal/mol; for 1,1- and α,ω-dichloroalkanes, it is −1.6 and −1.9 kcal/mol, respectively. The orientation energy between the carbon–chlorine bond(s) and the carbonyl group increases in the order: 1-chloro, 1,1-dichloro, α,ω-dichloro; representative values are −2.1, −2.9, and −3.5 kcal/mol. Dissolved polar solutes spend most of their time in the immediate neighborhood of the solvent dipoles.

Introduction

The use of the gas chromatograph in studies of thermodynamic properties of solution is an approach which is capable of yielding very fundamental data concerning liquid phase interactions considerably more quickly and easily than traditional calorimetry. Furthermore, as experience is gained in the technique, confidence in the reliability and significance of the results is growing, and it promises to add significantly to the store of experimental data required for building theories of the liquid state.

Advantages of the results obtained using gas–liquid chromatography (GLC) as exemplified by the experiments described in this paper may be enumerated as follows: (1) Since the initial state for the solute is the ideal vapor, and the final state is infinite dilution in solvent, they are not encumbered with solute–solute interactions. (2) They involve homologous series; i.e., the role of the nonpolar part of the solute may be isolated. (3) They involve polar as well as nonpolar interactions, in every combination; i.e., polar solute–polar solvent, polar solute–nonpolar solvent, etc. The lack of experimental data for polar systems is a widely lamented hindrance to progress in our understanding of liquid systems. (4) The use of a single solvent dipole in a long chain of methylene groups minimizes dipole–dipole interaction in the solvent, simplifying interpretation of the results. (5) They allow quantitative estimation of the three contributions to the enthalpy of solution: nonpolar (dispersion), dipole-induced dipole (induction), and dipole–dipole (orientation) energies.

In brief, comparison of specific retention volume (V_g), enthalpy, and entropy of solution of, e.g., chloroalkanes in an *n*-paraffin solvent with the same properties for alkanes of similar geometry exposes the role of the carbon–chlorine bond in interactions with the solvent hydrocarbon chains. In addition, if the same solutes are studied in a similar solvent containing a single dipole, transfer properties from the nonpolar to the polar solvent reflect the role of the solvent dipole in interactions with solute molecules. The present study concentrates on the carbon–chlorine dipole (~2 D), since the chlorine atom and a methyl group have similar volumes and polarizabilities. This ensures that differences in polar and nonpolar counterparts will arise primarily as a result of dipolar effects rather than geometric ones. Solutes have been chosen from the 1-chloroalkane, 1,1-dichloroalkane, and α,ω-dichloroalkane, as well as normal and 2-methylalkane families. The solvent pair is *n*-eicosane and and dinonyl ketone.

Experimental Section

Retention times were measured on an apparatus designed to max-imize precision and constructed in this laboratory. The essential features include a thermostated flow controller, minimized dead space between injection and detection, a column bath constant to 0.01 °C, and a flowmeter[10] which measures the time required for a slug of air to travel through a calibrated volume. The detector was a Gow-Mac thermal conductivity cell, Model 10-952. Temperatures were measured with a MINCO platinum resistance thermometer calibrated against a certified Leeds & Northrup model. Specific retention volumes were calculated from adjusted retention times using the equation of Littlewood, et al.[1] Each solute was injected four times at each temperature in order to allow estimation of the standard deviation in each V_g, and the rigorous, weighted least-squares method described by Wentworth[2] was used to fit the data to linear equations relating ln V_g to reciprocal temperature. Reproducibility of V_g values was typically 0.1–0.2% for a given run, providing enthalpy and entropy of solution values with standard deviations of about 1%.

The eicosane (C_{20}) was purchased from Chemical Samples Co., the dinonyl ketone (DNK) from Aldrich Co. Both were analyzed by high temperature GLC and were better than 99.5% pure by this method. All solutes were used as received from suppliers except 1,1-dichloropentane, which was synthesized from valeraldehyde[3] and purified by simple distillation.

The liquid phases were supported on Chromosorb W (AW, DMCS, 45/60 mesh) and packed in ¼-in. copper tubing. Use of columns of 10 and 20% liquid loading gave results within experimental error; several were made up of various lengths and weight loadings to provide convenient retention times for both low and high boiling solutes. Injections were of the order of 0.1 μmol; elution peaks were symmetrical, and there was no dependence of retention time on sample size.

Results

Table I contains the constants for the linear fits, temperature range of the data, V_g at 60 °C, and enthalpy and entropy of solution in C_{20} and DNK for the solutes studied. Table II contains enthalpy and entropy of transfer at infinite dilution from C_{20} to DNK, as well as the concomitant percentage change in V_g at 60 °C. This last column is a more readily visualizable equivalent of the Gibbs energy of transfer.

The solution properties refer to the process: solute vapor (1 atm, ideal) → pure liquid solute (hypothetical; infinitely dilute solution in solvent as reference). The equations relating V_g to solution properties and the advantages to this way of presenting the thermodynamic data have been discussed.[4]

Discussion

Eicosane as Solvent. All five homologous series exhibit a linear relationship between the enthalpy of solution and carbon number[11] (Figure 1), and all are characterized by the same methylene increment, 1.1 kcal/CH$_2$. Since interaction energies are sensitive functions of distance, this is evidence that the methylene group enjoys essentially the same volume in which

Table I. Retention Data and Associated Thermodynamic Properties of Solution[a]

Solute	A	−B	t range, °C	$V_g^{60°}$	−ΔH°	−ΔS°
			n-Eicosane Solvent			
n-Pentane	2.9948	5.0929	55–66	49.23	5.95	18.8
n-Hexane	3.5505	5.7827	57–70	130.9	7.08	20.3
n-Heptane	4.1252	6.5519	56–68	340.5	8.22	21.8
n-Octane	4.6829	7.2824	61–71	874.8	9.36	23.3
2-Methylpentane	3.3232	5.3970	61–71	97.33	6.66	19.5
2-Methylhexane	3.8952	6.1810	60–70	247.4	7.79	21.1
2-Methylheptane	4.4306	6.8516	60–70	631.1	8.85	22.4
1-Chloropropane	3.0433	5.0917	55–65	57.01	6.05	18.8
1-Chlorobutane	3.5432	5.5930	55–65	154.8	7.04	19.8
1-Chloropentane	4.0899	6.2581	56–68	410.9	8.15	21.1
1-Chlorohexane	4.6888	7.1081	61–70	1060	9.37	22.9
1-Chloroheptane	5.3423	8.1086	64–72	2771	10.70	24.9
1,1-Dichloroethane	3.0216	4.8303	58–68	69.37	6.03	18.3
1,1-Dichloropropane	3.6692	5.7073	56–68	201.6	7.31	20.0
1,1-Dichlorobutane	4.1502	6.2308	56–68	506.1	8.27	21.1
1,1-Dichloropentane	4.7799	7.1823	61–71	1294	9.56	23.1
Dichloromethane	2.7676	4.6244	55–65	39.76	5.50	17.9
1,2-Dichloroethane	3.3160	5.1350	55–65	123.8	6.59	18.9
1,3-Dichloropropane	3.9261	5.8259	56–68	387.2	7.82	20.3
1,4-Dichlorobutane	4.5647	6.6434	56–69	1162	9.09	21.9
1,5-Dichloropentane	5.0949	7.1988	64–72	3276	10.20	23.1
Chloroform	3.2388	5.0895	60–72	102.7	6.50	18.9
Carbon tetrachloride	3.5654	5.4150	60–72	197.8	7.14	19.6
			Dinonyl Ketone Solvent			
n-Hexane	3.4621	5.7159	61–73	107.4	6.95	20.3
n-Heptane	4.0099	6.4266	61–74	273.1	8.05	21.7
n-Octane	4.5705	7.1857	70–82	687.7	9.24	23.4
n-Nonane	5.0737	7.7601	74–84	1754	10.18	24.4
2-Methylpentane	3.2604	5.4074	63–73	79.77	6.56	19.7
2-Methylhexane	3.7716	6.0230	63–73	199.9	7.57	20.9
2-Methylheptane	4.3319	6.7805	70–80	503.9	8.76	22.6
1-Chloropropane	3.2290	5.3391	61–74	77.73	6.49	19.5
1-Chlorobutane	3.7537	5.9387	61–74	206.1	7.53	20.7
1-Chloropentane	4.3389	6.7477	70–81	531.7	8.77	22.5
1-Chlorohexane	4.8689	7.3973	70–81	1364	9.83	23.9
1-Chloroheptane	5.3718	7.9785	73–84	3449	10.89	25.2
1,1-Dichloroethane	3.4826	5.6304	61–73	124.4	6.99	20.1
1,1-Dichloropropane	4.0987	6.5129	74–82	327.0	8.32	22.2
1,1-Dichlorobutane	4.5628	7.0324	74–82	783.3	9.25	23.2
1,1-Dichloropentane	5.0645	7.5881	70–84	2026	10.23	24.3
Dichloromethane	3.3858	5.7043	61–73	86.37	6.80	20.2
1,2-Dichloroethane	3.8601	6.0477	61–74	254.4	7.75	20.9
1,3-Dichloropropane	4.5576	6.9125	71–84	869.4	9.23	22.9
1,4-Dichlorobutane	5.1353	7.5044	71–84	2724	10.37	24.1
1,5-Dichloropentane	5.6768	8.0539	75–84	7989	11.49	25.3
Chloroform	3.9933	6.5355	65–77	233.0	8.04	22.0
Carbon tetrachloride	3.6544	5.6140	65–77	211.7	7.37	20.2

[a] $\ln V_g = A(10^3/T) + B$, ΔH° in kcal/mol, ΔS° in cal/mol deg.

to move in all five series. This observation is in accord with the similar van der Waals volumes of alkyl chlorine atoms (11.6) and methyl groups (13.7)[5] and the nonbranched nature of the alkyl chains in question.

The displacement of the chloride lines above those of the alkanes in Figure 1 is due to their ability to induce a dipole into the solvent methylene chain and interact attractively with it. Thus this displacement may be considered the induction energy between the carbon–chlorine dipole and a methylene chain. Because the 1,1-dichloro series exhibits a terminal branching of sorts, the 2-methylalkanes are to be used as their nonpolar counterparts; the other chloroalkanes are geometrically similar to the normal alkanes. In this regard, it should be pointed out that methylene chloride may be considered the first member of either the 1,1- or the α,ω-dichloro series. The latter is the logical choice, since the molecular geometry does not change in going to the next higher homologue. Methylene chloride and 1,2-dichloroethane may be considered "linear"; 1,1-dichlo-

roethane is "branched". The plots of solution enthalpy vs. carbon number are consistent with this assignment.

On the assumption that the dispersion energy of the chlorine atom is equivalent to that of a methyl group,[6] the following estimates are obtained for induction energies: −1.1 kcal/mol for 1-chloroalkanes; and −1.6 and −1.9 kcal/mol, respectively, for 1,1- and α,ω-dichloroalkanes. Earlier estimates for the induction energy of 1-chloroalkanes were −1.0[7] and −0.8[6] kcal/mol, the latter based on an independent method using the properties of pure liquids.

The significantly larger, but not doubled, value for the di-chloro relative to the monochloro series indicates that conformations exist in the former which allow both chlorine atoms to interact with solvent chains simultaneously, but not with full effectiveness. It is noteworthy that in spite of varying degrees of conformational freedom, and the odd–even alternation in terminal chlorine positions, the plot for the α,ω-dichloro series is quite linear; i.e., the sequential insertion of methylene groups

Table II. Transfer Properties from Eicosane to Dinonyl Ketone

Solute	ΔH°_{tr}	ΔS°_{tr}	% change in V_g
n-Hexane	0.13	0.0	−18.0
n-Heptane	0.17	0.1	−19.8
n-Octane	0.12	−0.1	−21.4
2-Methylpentane	0.10	−0.2	−18.0
2-Methylhexane	0.22	0.2	−19.2
2-Methylheptane	0.09	−0.2	−20.2
1-Chloropropane	−0.44	−0.7	36.3
1-Chlorobutane	−0.49	−0.9	33.1
1-Chloropentane	−0.62	−1.4	29.4
1-Chlorohexane	−0.46	−1.0	28.7
1-Chloroheptane	−0.19	−0.3	24.5
1,1-Dichloroethane	−0.96	−1.8	79.3
1,1-Dichloropropane	−1.01	−2.2	62.2
1,1-Dichlorobutane	−0.98	−2.1	54.8
1,1-Dichloropentane	−0.67	−1.2	56.6
Dichloromethane	−1.30	−2.3	117
1,2-Dichloroethane	−1.16	−2.0	106
1,3-Dichloropropane	−1.41	−2.6	125
1,4-Dichlorobutane	−1.28	−2.2	134
1,5-Dichloropentane	−1.29	−2.2	144
Chloroform	−1.54	−3.1	127
Carbon tetrachloride	−0.23	−0.6	7.0

Figure 2. Solution entropy in eicosane vs. the number of carbon atoms in the solute (symbols have same meaning as in Figure 1).
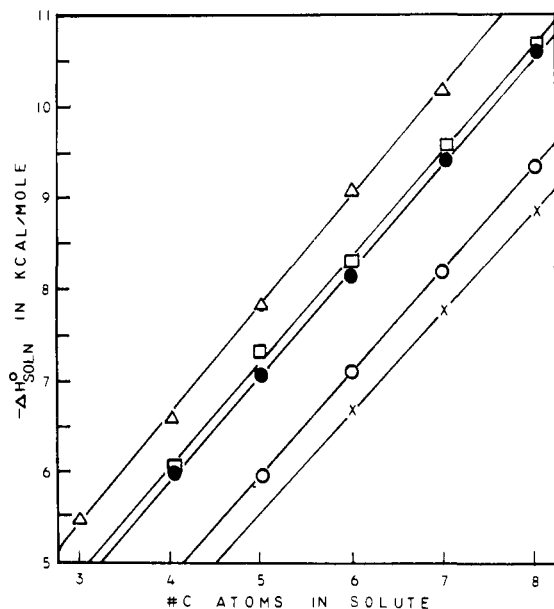

Figure 1. Solution enthalpy in eicosane vs. the number of carbon atoms in the solute: (X) 2-methylalkanes; (O) n-alkanes; (●) 1-chloroalkanes; (□) 1,1-dichloroalkanes; (△) α,ω-dichloroalkanes.

has no measurable effect on the induction interactions of the terminal dipoles with the solvent. Though there is some scatter in the data, the difference in induction energies for 1,1- and α,ω-dichloroalkanes appears real. The former configuration suffers the disadvantage that the second Cl atom must induce a dipole into matter which is already somewhat distorted by the first one; the latter configuration enjoys an added attraction of some 0.2 to 0.3 kcal/mol due to the relatively independent motion of its terminal dipoles.

Solution entropies in eicosane are plotted in Figure 2. The scatter in the values for the polar solutes makes a comparison of slopes difficult; it is probable that the least-squares lines shown in the figure have slopes within experimental error of that for the n-alkanes.

Entropies of solution are significantly more negative for the polar solutes; comparison of the 1-chloroalkanes with the n-alkanes containing one more carbon atom reveals a difference of about 1.1 eu on the average. This may be interpreted as the
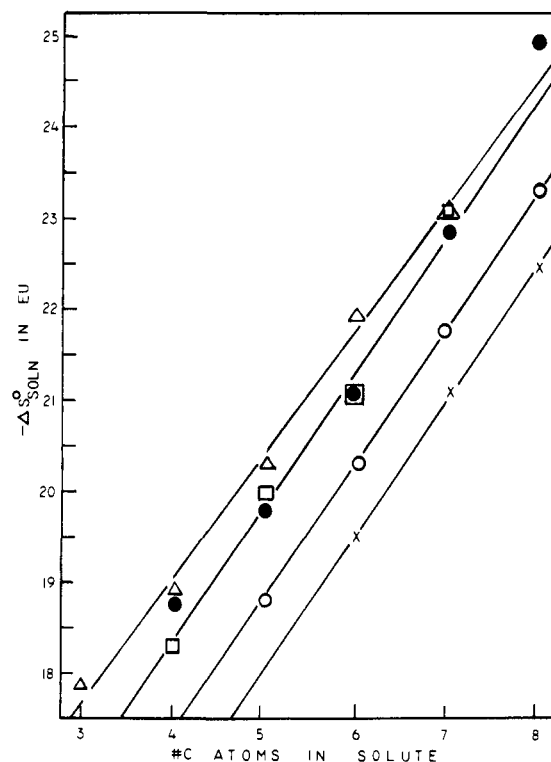
entropy decrease brought about by the dipole–induced dipole interaction between the C–Cl dipole and a methylene chain.

Introduction of a second chlorine atom leads to further decrease in entropy of solution values. While the most negative values are observed for the α,ω series, it must be kept in mind that the geometry of the 1,1 series is responsible for a positive contribution to its solution entropy relative to that of a straight-chain solute. If that contribution is equal to the difference between the values for the n-alkanes and the 2-methylalkanes, the entropy changes observed for the dipole-induced dipole interactions of the dichloroalkanes amount to about 1.5–2.0 eu. This is a sizable ΔS, capable of changing the equilibrium vapor pressure of solute by a factor of 2.

Dinonyl Ketone as Solvent. Linear relationships between enthalpy of solution and carbon number are again observed in DNK (Figure 3). The significantly greater spread between the polar and nonpolar solutes in Figure 3 compared to Figure 1 is ascribable to the presence of the carbonyl dipole in DNK. In addition to the dispersion and induction attraction present in C_{20}, the polar solutes engage in dipole–dipole interactions between the C–Cl dipole(s) of the solute and the C=O dipole of the DNK.

The plots of entropy of solution in DNK (Figure 4) differ from those in eicosane in essentially the same features as the enthalpy plots for the two solvents. These differences are discussed in the next section.

Transfer Properties from Eicosane to Dinonyl ketone. The transfer properties refer to the removal of a single solute molecule from the C_{20} environment and its immersion into the DNK environment. The average values of transfer enthalpy for all of the alkanes is 0.14 ± 0.04 kcal/mol, i.e., a small input of energy is required. Martire and Riedl[8] observed a value of 0.35 kcal/mol for the transfer of three n-alkanes from n-heptadecane to dioctyl ketone, in reasonable agreement with this result.

The entropies of transfer of the alkanes are within experimental error of zero; their longer retention time in C_{20} is clearly an enthalpy effect. The presence of the carbonyl group
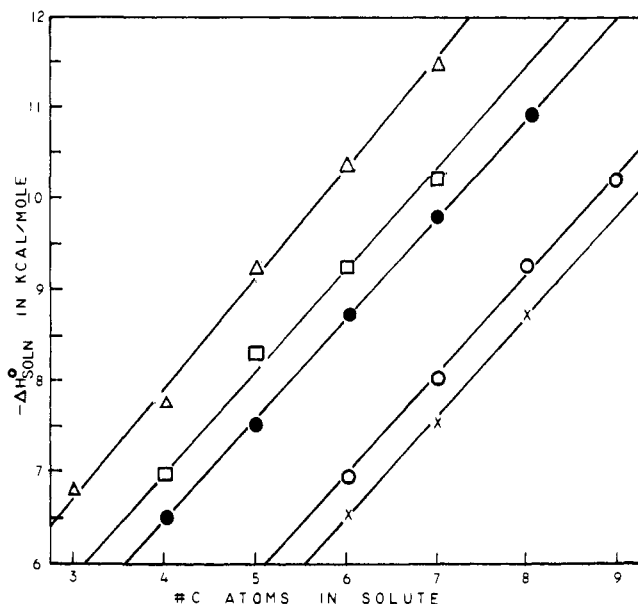
Figure 3. Solution enthalpy in DNK vs. the number of carbon atoms in the solute (symbols have same meaning as in Figure 1).

in the DNK presumably makes it more difficult for a nonpolar solute to make room for itself therein. Earlier estimates of the induction energy between a carbonyl group and a methylene chain were 1.1 kcal/mol;[6] apparently the alkanes do not disrupt this interaction by more than about 20%.

All of the chloroalkanes display negative values for both enthalpy and entropy of transfer, becoming more negative from 1-chloro to 1,1-dichloro to α,ω-dichloro compounds. If we consider that the alkane value of 0.14 kcal/mol represents a dispersion contribution and subtract it from each of the chloroalkane values to isolate the polar contribution, we get the following averages for enthalpy of transfer: 1-chloro, −0.58; 1,1-dichloro, −1.05; α,ω-dichloro, −1.43 kcal/mol. A second chlorine on the same terminal carbon thus considerably enhances the ability of the molecule to engage in dipolar interactions with the solvent. However, when the second chlorine is added to the opposite end of the solute molecule, its effect is still greater, being half again as large as that of the first chlorine atom added. It is not clear whether this extra attraction in the α,ω series is simply the result of a greater ability of independent dipoles to accommodate themselves to the field of a single carbonyl group, or the possibility of simultaneous interaction with carbonyl groups of different solvent molecules. We will return to this matter later in the paper.

There is some question regarding the type of polar interaction responsible for these transfer enthalpies. It is clear from the results in C_{20} that the induction energy with a methylene chain of a single C-Cl dipole is about −1.1, and that for the dichloro dipoles, about −1.6 and −1.9 kcal/mol. However we do not know the extent to which the polar solutes are prevented from engaging in induction interactions with the nonpolar side chains of DNK by their participation in orientation interactions with the carbonyl dipole.

There are two extreme possibilities, with the actual situation probably lying somewhere between them: (1) the induction contribution is the same for all solutes in both C_{20} and DNK. In this case the transfer enthalpies are equal to the orientation energies between solute and solvent. (2) The dipole-dipole interaction is strong enough to tie up all of the solute dipoles and prevent their engaging in induction interactions. In this case the induction energies in C_{20} disappear in DNK, and are replaced by orientation energies. This assumption leads to orientation values as follows: 1-chloro, −1.7; 1,1-dichloro, −2.8; α,ω-dichloro, −3.2 kcal/mol.
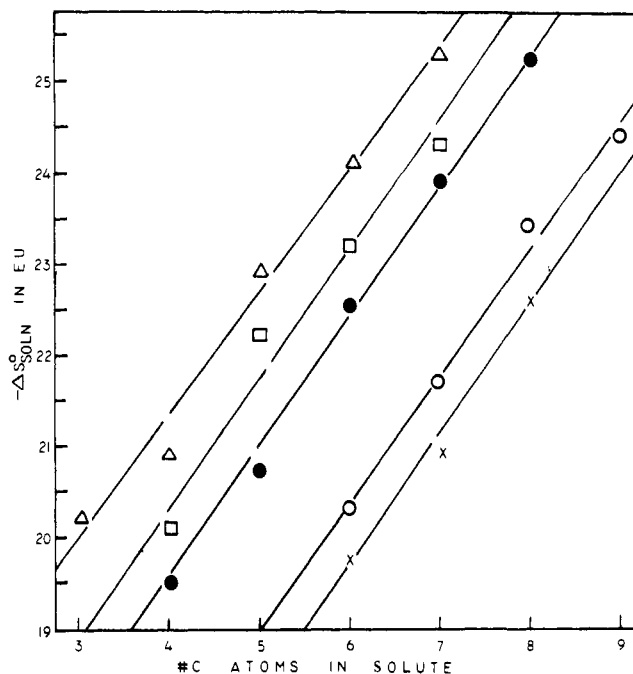

Figure 4. Solution entropy in DNK vs. the number of carbon atoms in the solute (symbols have same meaning as in Figure 1).

These two cases leave a wide range of uncertainty for the contribution of orientation energies to the enthalpy of solution. We can obtain an independent estimate of the orientation energy using experimentally measured quantities if we accept the following assumptions: (1) The dispersion contribution for a given chloride is equal to the energy of solution for the appropriate alkane. (2) The induction contribution is given by the difference between the enthalpies of solution of chloride and alkane in C_{20}. (3) The dispersion contribution is independent of the extent of polar interactions. (4) Induction and orientation effects are independent and separable. We have

$$\Delta E_{\text{soln}} = E_{\text{disp}} + x_1 E_1 + x_0 E_0 \qquad (1)$$

where ΔE_{soln} ($= \Delta H_{\text{soln}} + RT$) refers to DNK, x_1 and x_0 are the fractions of the solute molecules engaging in induction and orientation, respectively, and E_1 and E_0 are the associated energies per mole. In addition

$$\frac{x_1}{x_0} = \exp\left[\frac{S_1 - S_0}{R}\right] \exp\left[\frac{-(E_1 - E_0)}{RT}\right] \qquad (2)$$

and

$$x_1 + x_0 = 1 \qquad (3)$$

Our data allow estimation of all but four variables: x_1, x_0, E_0, and S_0, the latter being the entropy change associated with the dipole-dipole alignment of solute and solvent. The three equations therefore do not determine the values in question unequivocally; however, reasonable estimates can be made for S_0, and the resulting values examined. Tables III and IV contain experimental quantities and calculated estimates of the fraction of solute molecules involved in dipole-dipole interactions, and the contributions of orientation and induction

Table III. Experimental Energies (kcal/mol) Used in Calculation of Orientation Energy Contributions

	$-\Delta E_{\text{soln}}$	$-E_{\text{disp}}$	$-E_1$
1-Chloropentane	8.11	6.42	1.10
1,1-Dichlorobutane	8.59	6.00	1.60
1,4-Dichlorobutane	9.71	6.42	1.90

Table IV. Calculation of Orientation Energy (kcal/mol) Contribution to Enthalpy of Solution[a]

Solute	$\exp[(S_1 - S_o)/R]$	x_o	$-E_o$	$-E_{orient}$	$-E_{ind}$
1-Chloropentane	1	0.766	1.87	1.43	0.26
	2	0.656	2.00	1.31	0.38
	2.73	0.617	2.07	1.28	0.42
	4	0.554	2.16	1.20	0.49
1,1-Dichlorobutane	1	0.844	2.77	2.35	0.25
	1.83	0.785	2.86	2.25	0.34
	2	0.762	2.90	2.21	0.38
	4	0.671	3.07	2.06	0.53
1,4-Dichlorobutane	1	0.910	3.43	3.12	0.17
	2	0.854	3.53	3.02	0.28
	2.13	0.848	3.54	3.00	0.29
	4	0.784	3.67	2.88	0.41

[a] See Table III for input data.

to the energy of solution for 1-chloropentane, 1,1-dichlorobutane, and 1,4-dichlorobutane. These three solutes are considered representative of the three series under study.

In order to place an upper limit on the entropy difference between the orientation and induction interactions, we measured the transfer properties of chloroform, which was expected to hydrogen bond with the carbonyl oxygen of DNK, and carbon tetrachloride as a "nonpolar" solute of similar constitution. That significant hydrogen bonding does indeed occur is shown by a comparison of enthalpies and entropies of transfer (Table II) of dichloromethane and chloroform. The latter displays considerably more negative values for both, in spite of its lower dipole moment (1.0 D vs. 1.6 D for CH_2Cl_2).

To be conservative in placing an upper limit on the entropy change associated with the orientation interaction, we ignore any induction interaction between chloroform and eicosane, and assume the former's transfer properties reflect specific interaction between its hydrogen and the oxygen of the dinonyl ketone. It is thus expected that the quantity $(S_1 - S_o)$ in Table IV will be less than $(S_1 - (-3.1))$, where -3.1 is the entropy of transfer of chloroform. Figure 2 provides the following estimates of S_1: 1-chloropentane, -1.1; 1,1-dichlorobutane, -1.9; 1,4-dichlorobutane, -1.6 eu. Use of these values leads to the nonintegral entries in column two of Table IV. The associated values of E_o and x_o are lower limits, and to the extent that the present model is valid, it is safe to say that more than 60% of the 1-chloroalkanes, and 80–85% of the dichloroalkanes present at infinite dilution in DNK are associated with the latter's carbonyl dipole. Put another way, each molecule spends this percentage of its time in the immediate vicinity of a moiety which represents less than 6% of the total volume of the solvent. The contribution of induction to the energy of solution is relatively small.

The transfer entropies in Table II become increasingly negative from the 1-chloro series through the α,ω-dichloro series, average values being -0.9, -1.8, and -2.3 eu, respectively. This is in qualitative support of increased orientation interaction in that order.

We return to the question of the remarkable additional contribution of the ω-chlorine to solution energy in DNK. A close examination of the enthalpies of transfer reveals a certain amount of structure. Figure 5 shows that there is a falloff with chain length for the two series with dipoles at only one end, but not for the α,ω series. The former effect is quite consistent with experimental estimation of orientation interactions for pure monofunctional polar liquids.[6] In addition, Taft and Kamlet[9] have shown that CH_2Cl_2 hydrogen bonds to acceptors with a strength about 0.4 times that of $CHCl_3$. Our results for $CHCl_3$ and CCl_4 in DNK lead to estimates of 0.25 to 0.75 kcal/mol for the hydrogen bond contribution to the enthalpy of solution of CH_2Cl_2 in DNK. Subtraction of the average of these esti-
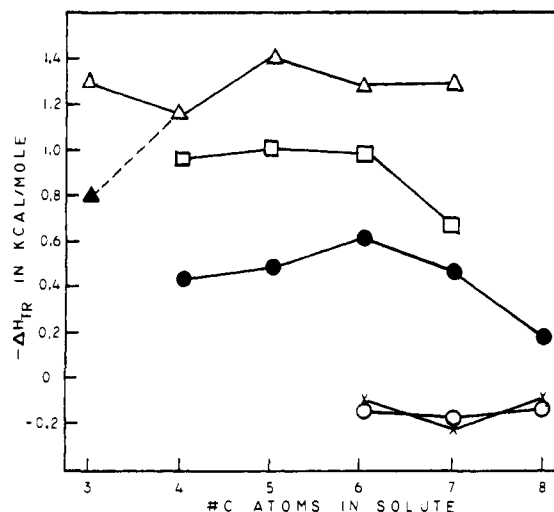
Figure 5. Enthalpy of transfer from n-eicosane to di-n-nonyl ketone at 60 °C (symbols have same meaning as in Figure 1).

mates from $\Delta H°_{tr}$ leads to the lower triangle for CH_2Cl_2 in Figure 5, which then provides evidence that a disadvantage is associated with the shorter chains in the α,ω series. At first thought, this may be considered evidence that a different solvent dipole is involved with each chlorine atom, and chains with less than three carbons cannot span the intercarbonyl distance. However, the possibility of simultaneous interaction of both chlorines with the same dipole cannot be ruled out. The chlorine atoms of the first and second members of the series are more severely restricted in their motion, and would not be expected to accommodate themselves to the field of the carbonyl group as efficiently as higher members of the series could.

Similar experiments using di-n-heptadecyl ketone and n-hexatriacontane would resolve the question of the number of solvent dipoles involved in the α,ω-dichloroalkane energies of solution.

References and Notes

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Conformational Analysis of Protected Norvaline Oligopeptides by High Resolution Proton Magnetic Resonance

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Abstract: Proton magnetic resonance spectra at 270 MHz are reported for Boc(L-Nva)$_n$OMe, n = 1–4, and for Ac-L-Nva-OMe, in CDCl$_3$ and CDCl$_3$/Me$_2$SO-d_6 mixtures. A method is reported for assigning the C$^\alpha$H resonance at the C-terminal residue of ester C-protected peptides, based on the downfield shift of that resonance in CDCl$_3$ with increasing temperature. No folded forms are found for the unaggregated dipeptide (0.009 M), but mixtures of several folded forms are found at low concentrations of the tripeptide (0.007 M) and tetrapeptide (0.005 M). At higher concentrations aggregates form, with increasing ease as the peptide chain lengthens. Whereas the dipeptide and tripeptide aggregates are best described as a network of extended "out-of-register" forms, the tetrapeptide associations are "in-register", i.e., primitive β sheets. These conclusions correlate with the results of previous circular dichroism and infrared studies.

Previous work[2-7] has shown that homo-oligoheptapeptides with alkyl, arylalkyl, and thioether-containing side chains take up the β conformation both in structure-supporting solvents and in the solid state. Of relevant interest has been the finding that the peptide chains generally align in an antiparallel fashion in forming the intermolecularly H-bonded β sheet when the amino acid side chains are small, but the presence of bulky, aromatic, or β-branched side chains leads to an increased tendency toward parallel alignment. In particular, in the case of the norvaline oligomers it was concluded that some of both the parallel and antiparallel arrangements are present in the β sheet which forms.[3-8] In solution, as the peptide concentration is lowered or the temperature is increased, nonaggregated forms become dominant.

High resolution ^{1}H NMR[9] has come to be a valuable and widely used technique in the area of conformational analysis of homo-oligopeptides in solution. Goodman and co-workers have studied by ^{1}H NMR several series of synthetic monodisperse protected peptides including those derived from γ-alkyl esters of glutamic acid,[10-12] alanine,[13-16] and isoleucine.[13,15] Bystrov et al.[17] examined in detail diastereomeric protected alanine dipeptides, mainly in CCl$_4$, and Dimicoli and Ptak[18] investigated a protected alanine dipeptide in CDCl$_3$.

This work is part of a study devoted to the investigation by high resolution ^{1}H NMR of the role of the side chains of saturated hydrocarbon amino acid residues on the formation of ordered secondary structures in protected homo-L-oligopeptides in solvents of low polarity. The number of carbon atoms, shape of the side chain (whether linear or branched), and position of branching will be considered. In this paper we wish to discuss the results obtained in the case of the synthetic monodisperse homologous series Boc(L-Nva)$_n$OMe where n = 1–4. The pentapeptide was not examined because its solubility in CDCl$_3$ is too low for a ^{1}H NMR study. Norvaline was investigated because it is the simplest amino acid residue having a δ carbon in the side chain. In this context, of particular interest is the question of the detailed structure of any nonas-

sociated intramolecularly H-bonded folded forms which occur, and also the nature of the aggregated forms which develop at higher peptide concentrations.

$$\begin{array}{c} CH_3 \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ -NH-CH-CO- \end{array}$$

norvaline
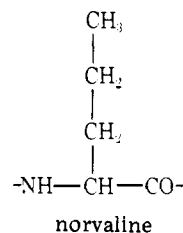
The CD of an internal Nva-Nva peptide chromophore within a randomly coiled chain in 1,1,1,3,3,3-hexafluoro-2-propanol has been determined by subtracting the total molar ellipticity values of the tripeptide from those of the tetrapeptide.[19] The CD properties of the dipeptide in aqueous solution[8] have represented the first experimental verification of Mattice's prediction[20] of the occurrence of a temperature and salt-sensitive dichroic band near 210–215 nm in aqueous solutions of linear randomly coiled peptides with saturated hydrocarbon side chains.

Experimental Section

The details of the synthesis and the chemical and optical characterizations of Boc(L-Nva)$_2$ $_4$OMe are reported in ref 21.

Boc-L-Nva-OMe. This compound was prepared from *tert*-butyloxycarbonyl azide and HCl·H-L-Nva-OMe[22] in anhydrous ethyl acetate using N-methylmorpholine to deprotonate the ammonium group: yield 75% oil; $[\alpha]^{23}_D$ = $-30.0°$ (c = 1; methanol).

Anal. for C$_{11}$H$_{21}$NO$_4$. Calcd: C, 57.1; H, 9.1; N, 6.1. Found: C, 56.5; H, 8.9; N, 6.0.

Ac-L-Nva-OMe.[23] This compound was prepared from acetyl chloride and HCl·H-L-Nva-OMe[22] in anhydrous chloroform using triethylamine to deprotonate the ammonium group: yield 82%; mp 53–54 °C (from ethyl acetate/petroleum ether); $[\alpha]^{23}_D$ = $-57.4°$ (c = 2; water).