Journal of the American Chemical Society / 102:12 / June 4, 1980

Solution Thermodynamic Studies. 5.[1a] A Thermodynamic Study of Solvent Effects on the Relative Stability of Diastereoisomers. The *trans*-1,2-Dibromo-4-*tert*-butylcyclohexane, *trans*-2,3-Dibromodecalin, and 1-Bromo-4-*tert*-butylcyclohexane Systems

J. J. Moura Ramos,[1b] L. Dumont,[1c] M. L. Stien,[1c] and J. Reisse*[1c]

Contribution from the Centro de Quimica-Fisica Molecular, Complexo Interdisciplinar, Lisboa, Portugal, and the Laboratoire de Chimie Organique E.P., Université Libre de Bruxelles, 1050 Bruxelles, Belgium.

Received November 5, 1979

Abstract: Calorimetric measurements of transfer enthalpies associated with activity-coefficient determinations lead us to a precise description of the solvent influence on the relative stability of the stereoisomers of the title compounds. This solvent influence is important since it is higher than 1 kcal/mol in solvents like C_6H_6 or acetone with respect to cyclohexane (in terms of enthalpy contribution). The antagonist entropy contribution does not cancel out the enthalpy contribution. The solvent effect, therefore, remains very effective at the ΔG° level.

Introduction

The study of the influence of solvents on the physical or chemical properties of a solute is still an important research area in physical organic chemistry. In particular, the so-called "solvent effect" on the relative stability of conformers has been studied by many authors. Generally, the systems which are chosen for these kinds of studies are conformers in conditions of fast equilibrium. In other words, there is always a state of equilibrium between the conformers, and solvent effects are measured by parameters like $\delta\Delta G^\circ$, $\delta\Delta H^\circ$, and $\delta\Delta S^\circ$ where δ is the solvent operator as introduced by Leffler and Grunwald[2] and defined by the following expressions:

$$[\delta\Delta G^\circ]_{S1\rightarrow S2} = (\Delta G^\circ)_{S2} - (\Delta G^\circ)_{S1} \qquad (1)$$

$$[\delta\Delta H^\circ]_{S1\rightarrow S2} = (\Delta H^\circ)_{S2} - (\Delta H^\circ)_{S1} \qquad (2)$$

$$[\delta\Delta S^\circ]_{S1\rightarrow S2} = (\Delta S^\circ)_{S2} - (\Delta S^\circ)_{S1} \qquad (3)$$

It is well known that ΔH° and ΔS° are much more difficult to measure with precision than ΔG°. In particular, the correlation between the errors on ΔH° and ΔS° as obtained by the van't Hoff relationship[3] casts doubt upon the significance of many of the ΔH° and ΔS° values published in the literature. We can consequently affirm that many of the $[\delta\Delta H^\circ]_{S1\rightarrow S2}$ and $[\delta\Delta S^\circ]_{S1\rightarrow S2}$ values are also unreliable. Starting from this conviction, we decided to determine $[\delta\Delta H^\circ]_{S1\rightarrow S2}$ and $[\delta\Delta S^\circ]_{S1\rightarrow S2}$ values by using a completely different and new approach which does not require the use of the van't Hoff relationship and which is therefore free of any risk of errors correlation.

Principles of the Method

As it was shown by Leffler and Grunwald,[2] the δ and Δ operators commute. In other words, if X° is a thermodynamic quantity like G°, H°, or S°, we have

$$[\delta\Delta X^\circ]_{S1\rightarrow S2} = [\Delta\delta X^\circ]_{S1\rightarrow S2} \qquad (4)$$

The solvent effect on an equilibrium can therefore be obtained by measuring X° for each component of the equilibrium in S1 and in S2. Taking into account the relation $G = H - TS$, the estimation of the terms $[\Delta\delta G^\circ]_{S1\rightarrow S2}$, $[\Delta\delta H^\circ]_{S1\rightarrow S2}$, and $[\Delta\delta S^\circ]_{S1\rightarrow S2}$ only requires the determination of the transfer enthalpy $[\delta H^\circ]_{S1\rightarrow S2}$ and the transfer free energy $[\delta G^\circ]_{S1\rightarrow S2}$ for the various components of the equilibrium. In the case of a simple isomerization $A \rightleftharpoons B$, in two solvents, the number of independent transfer measurements is therefore equal to 4, i.e., $[\delta H^\circ]_{S1\rightarrow S2}$ for A and B and $[\delta G^\circ]_{S1\rightarrow S2}$ for A and B.

The measurement of transfer quantities requires that A and B should be isolated in a pure form at the temperature of the experiment. This fact leads to the choice of isomers which are not in fast equilibrium at normal temperature. It could therefore be argued that the two terms of the identity (4) cannot be measured at the same temperature for the same system. This remark is valid if we except equilibria for which the rate constants can be increased by the addition of a catalyst. Nevertheless, this fact does not constitute a limitation on the method we propose. We can illustrate this affirmation by the following examples which are the same as those (see Figure 1) studied in this work.

trans-1,2-Dibromocyclohexane (I) exists as a mixture of two conformations in fast equilibrium at normal temperature. Furthermore, the 4-*tert*-butyl (II) and the *trans*-decalin (III) systems are characterized by equilibria which can be considered to be infinitely slow at normal temperature in all solvents (in absence of catalyst). I_{aa} and I_{ee} are two diastereoisomers like II_{aa} and II_{ee} or III_{aa} and III_{ee}.

Moreover, as we shall see later, the structural similarities which exist between these various systems lead to similar behaviors with respect to the solvent.

Determination of $[\Delta\delta H^\circ]_{S1\rightarrow S2}$ by Calorimetric Measurements

If we consider a particular molecule, let us say II_{ee}, the heat of transfer (or enthalpy of transfer) from solvent S1 to solvent S2 is obtained by measuring in a calorimeter the heat of solutions of II_{ee} in S1 and in S2, respectively, at constant pressure. By definition, the difference between these two quantities is the enthalpy of transfer of II_{ee} from S1 to S2, i.e., $[\delta H^\circ]_{S1\rightarrow S2}$. The accuracy (and precision) of the calorimetric method permits determinations of $[\delta H^\circ]_{S1\rightarrow S2}$ with an error of ±0.03 kcal/mol. It follows that $[\Delta\delta H^\circ]_{S1\rightarrow S2}$, which is the difference between two heats of transfer (as measured for II_{ee} and II_{aa}, for example), can be obtained with a precision of ±0.06 kcal/mol.

Table I gives the heat of solution of II_{ee}, II_{aa}, III_{ee}, and III_{aa} in various solvents, as well as the heat of solution of the parent compounds IV and V in the same solvents. By convention, a positive value in Table I corresponds to an endothermic solution process while a negative value corresponds to an exothermic process.

0002-7863/80/1502-4150$01.00/0

Table I. Heats of Solution (kcal/mol) at Infinite Dilution and at 25 °C

deriv	solvent				
	C_6H_{12}	CCl_4	C_6H_6	CS_2	$(CH_3)_2CO$
II_{ee}	1.27	0.38	−0.08	0.69	0.83
II_{aa}	0.53	−0.19	0.52	0.40	1.46
III_{ee}	5.16	4.30	3.62	4.45	4.67
III_{aa}	5.29	4.51	5.23	4.88	6.28
IV	0.03	0.24	1.15	0.74	2.08
V	−0.03	0.14	0.99	0.37	2.10

Table II. Solvent Effect $[\Delta\delta H°]_{S1\to S2}$ on the Relative Stability of II_{ee}/II_{aa} and III_{ee}/III_{aa} (kcal/mol)

deriv	solvent				
	C_6H_{12}	CCl_4	C_6H_6	CS_2	$(CH_3)_2CO$
II_{ee}/II_{aa}	0.00	−0.17	−1.34	−0.45	−1.37
III_{ee}/III_{aa}	0.00	−0.08	−1.48	−0.30	−1.48

The heat of transfer from cyclohexane to another solvent is obtained by simple subtraction from values given in Table I. Table II gives $[\Delta\delta H°]_{S1\to S2}$ values for the two series of dibromo derivatives: II_{ee} and II_{aa} on the one hand, and III_{ee} and III_{aa} on the other. The $[\Delta\delta H°]_{S1\to S2}$ values are defined by the following equation:

$$[\Delta\delta H°]_{S1\to S2} = [(H°)_{S2} - (H°)_{S1}]_{ee} - [(H°)_{S2} - (H°)_{S1}]_{aa}$$

As we have previously said (cf. relationship 4) the $[\Delta\delta H°]_{S1\to S2}$ values are the exact equals of the $[\delta\Delta H°]_{S1\to S2}$ values and must therefore be considered to be direct estimations of the solvent effect on the relative stability (on an enthalpy scale) of the stereoisomers under study. We would like to emphasize the fact that the direct measurement of $[\delta\Delta H°]_{S1\to S2}$ relative to the systems II_{ee}/II_{aa} or III_{ee}/III_{aa} would be very difficult and would require isomerization catalysts. These molecules can, of course, be looked upon as model compounds of the two conformations of *trans*-1,2-dibromocyclohexane. These conformations being in fast equilibrium, it is possible to imagine the measurement of $[\delta\Delta H°]_{S1\to S2}$ on this system. As far as we know, this has never been done, even at a low level of precision (cf. previous discussion on the van't Hoff data treatment).

A negative sign in Table II implies that, with respect to the diaxial stereoisomer, the diequatorial stereoisomer is more stable in solvent S_2 than in the reference solvent (C_6H_{12}). The examination of Table II leads us to some very important conclusions. The first concerns the similarities between the two systems II_{ee}/II_{aa} and III_{ee}/III_{aa}. With respect to the diaxial isomer, the stabilization of the diequatorial isomer is similar in all solvents for systems II and III. This fact is remarkable if we take into account the great differences which exist between the heats of solution of diequatorial or diaxial derivatives depending on the series to which they belong (cf. Table I). This observation can be emphasized by comparing the differences between the heat of transfer of the various dibromo derivatives to the heat of transfer of their parent hydrocarbons. Table III gives the differences, *D*, which are defined in the following way:

$$DII_{ee}/IV = [\delta H°]_{S1\to S2} \text{ for } II_{ee} - [\delta H°]_{S1\to S2} \text{ for IV}$$

$$DII_{aa}/IV = [\delta H°]_{S1\to S2} \text{ for } II_{aa} - [\delta H°]_{S1\to S2} \text{ for IV}$$

$$DIII_{ee}/V = [\delta H°]_{S1\to S2} \text{ for } III_{ee} - [\delta H°]_{S1\to S2} \text{ for V}$$

$$DIII_{aa}/V = [\delta H°]_{S1\to S2} \text{ for } III_{aa} - [\delta H°]_{S1\to S2} \text{ for V}$$

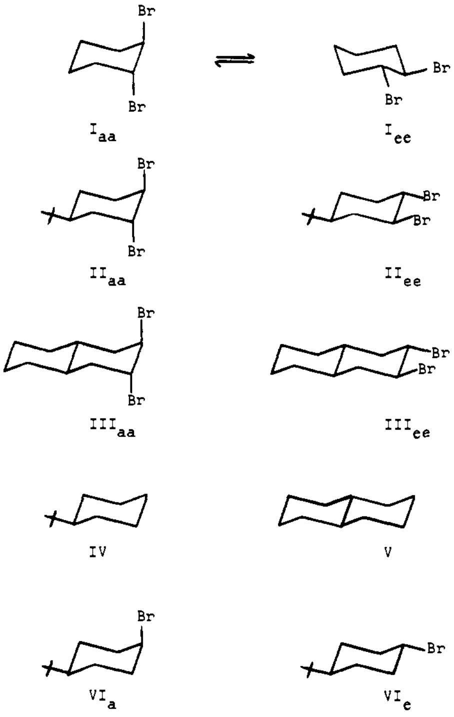

Figure 1. Molecules under study in this work.

Table III. Values of the Difference, *D* (kcal/mol), between the Heats of Transfer of the Dibromo Derivatives and Their Parent Hydrocarbons in Various Solvents at 25 °C

D	solvent				
	C_6H_{12}	CCl_4	C_6H_6	CS_2	$(CH_3)_2CO$
DII_{ee}/IV	0	−1.10	−2.47	−1.29	−2.49
DII_{aa}/IV	0	−0.93	−1.13	−0.84	−1.12
$DIII_{ee}/V$	0	−1.03	−2.56	−1.11	−2.62
$DIII_{aa}/V$	0	−0.95	−1.08	−0.81	−1.14

By using an additivity rule in which we neglect the influence of the two CH bonds, we can consider the values of *D* to be a direct measure of the heat of transfer of the two vicinal C–Br bonds, in gauche (ee) and anti (aa) orientations, respectively. Once again, the similarity in behavior of II_{ee} and III_{ee} on the one hand and of II_{aa} and III_{aa} on the other hand is notable. We can safely assume that the solvent effect $[\Delta\delta H°]_{S1\to S2}$ on the relative stability of II_{ee} compared to II_{aa} or of III_{ee} compared to III_{aa} (Table II) is very similar to the solvent effect $[\delta\Delta H°]_{S1\to S2}$ which characterizes the conformation equilibrium $I_{aa} \rightleftharpoons I_{ee}$, and which was unknown before the present work was completed.

With respect to solvent C_6H_{12}, the $[\Delta\delta H°]_{S1\to S2}$ values of Table II confirm that all solvents have a stabilizing effect on the diequatorial compared to the diaxial isomer. While this stabilizing effect is far from negligible even in the apolar CS_2 solvent, it is considerably greater (more than 1 kcal/mol) in benzene and acetone. At this point it is interesting to point to a sentence taken from a paper by Allinger and Wuesthoff[4] on the calculation of dipole moment and energy of dihalides. "Thus it would seem that the electrostatic calculations described in this paper are probably adequate, but solvation is going to have to be explicitly taken into account."

Our results show that the phenomenon of solvation is at least as great as the intramolecular factors which govern the enthalpy difference or the free-energy difference between the diaxial and diequatorial dibromo derivatives under study.[5]

In this paper we would like to place special emphasis on the quantitative determination of solvent effect on the thermodynamic parameters which characterizes an equilibrium between stereoisomers. The detailed interpretation of the results will be given in a following paper. We would, nevertheless, like to take the opportunity to point out the particular behavior of

Table IV. Heat of Solution of VI_a and VI_e and the Solvent Effect $(\Delta\delta H°)_{S1\rightarrow S2}$ on the Relative Stability of the VI_e/VI_a System (kcal/mol) at 25 °C

	solvent				
deriv	C_6H_{12}	CCl_4	C_6H_6	CS_2	$(CH_3)_2CO$
VI_a	0.41	−0.06	0.43	0.53	1.38
VI_e	0.46	−0.04	0.24	0.44	1.23
VI_e/VI_a	0	−0.03	−0.24	−0.14	−0.20

benzene as a solvent. This behavior has already been observed by many authors:[6] benzene gives strong interactions with polar solutes and these interactions cannot be explained without taking into account the formation of complexes involving benzene and the polar solute (here the diequatorial isomer). The dipole-induced dipole interaction as it is included in the reaction field model[7,8] makes it impossible to interpret the "benzene effect" correctly. The solvent effect of acetone is normal in the sense that the polar solvent stabilizes the polar isomer[5,9,10] ($\mu(II_{ee}) = 3.3$, $\mu(III_{ee}) = 3.3$ D) with respect to the less polar isomer ($\mu(II_{aa}) = 1.2$, $\mu(III_{aa}) = 1.15$ D).

From a quantitative point of view, the reaction field model as used by Abraham and Sieverns[7] and more recently by Allinger[8] does not give theoretical results in agreement with the experimental results. Nevertheless, it is necessary to take into consideration that these theoretical treatments give an estimation of the free energy of solvation[11] and not of the energy of solvation as claimed by Abraham et al. in their original paper.[12] Therefore, the comparison between experimental and theoretical results has to be carried out at the level of $[\Delta\delta G°]_{S1\rightarrow S2}$ and not at the level of $[\Delta\delta H°]_{S1\rightarrow S2}$ (see Table VI).

In order to extend the discussion of the $[\Delta\delta H°]_{S1\rightarrow S2}$ contributions, we have performed similar measurements on the cis and trans diastereoisomers of 1-bromo-4-*tert*butylcyclohexane (Table IV). Once again, as in Table II, a negative sign for the $[\Delta\delta H°]_{S1\rightarrow S2}$ values corresponding to the VI_e/VI_a system implies that, with respect to the axial stereoisomer, the equatorial one is more stable in the solvents S2 than in the reference solvent ($S1 = C_6H_{12}$). It is easy to observe that, even in the case of the monosubstituted cyclohexane, the solvent effect is far from negligible: it is of the same order of magnitude as the enthalpy difference between the two diastereoisomers.[13] Once again, the more polar stereoisomer ($\mu(VI_e) = 2.25$,[14] $\mu(VI_a) = 2.15$ D[14]) is stabilized relative to the axial stereoisomer in all solvents with respect to cyclohexane.

Determination of $[\Delta\delta G°]_{S1\rightarrow S2}$ by Activity Coefficient Measurements

The determination of the free energy of transfer from S2 to S1, $[\delta G°]_{S1\rightarrow S2}$ of a solute, implies the measurement of the activity coefficient of the solute in S2 and S1. This kind of measurement is well described in the literature[15] but requires the development of an apparatus which permits very precise vapor-pressure determinations. If we consider a solute A which is dissolved in a solvent S, the variation of the excess free energy of A (G^E) with respect to the mole fraction of A (x_A) is given by

$$(\partial G^E/\partial x_A)^S{}_{P,T} = RT[\ln \gamma_A - \ln \gamma_S + x_A\,(\partial \ln \gamma_A/\partial x_A) - x_S(\partial \ln \gamma_S/\partial x_S)] \quad (5)$$

If the Gibbs-Duhem relationship is applied, (5) gives

$$(\partial G^E/\partial x_A)^S{}_{P,T} = RT[(\ln \gamma_A - \ln \gamma_S) \quad (6)$$

The limit of $(\partial G^E/\partial x_A)^S{}_{P,T}$ for $x_A \rightarrow 0$ is equal to the free energy of solution. Therefore

$$\lim_{x_A\rightarrow 0}\,(\partial G^E/\partial x_A)^{S_2}{}_{P,T} - \lim_{x_A\rightarrow 0}\,(\partial G^E/\partial x_A)^{S_1}{}_{P,T} = [\delta G°]_{S1\rightarrow S2} \quad (7)$$

The method we have used consists of determining the value of $\lim_{x_A\rightarrow 0}\,(\partial G^E/\partial x_A)^S{}_{P,T}$ for II_{ee} and II_{aa} in various solvents S, i.e., C_6H_{12}, C_6H_6, and $(CH_3)_2CO$. The difficulty and the slowness of the measurement process have prevented the carrying out of similar measurements on the other solvents and the other solutes mentioned. The experimental method we applied to determine

$$\lim_{x_A\rightarrow 0}\,(\partial G^E/\partial x_A)^S{}_{P,T} = RT(\lim_{x_A\rightarrow 0}\,\ln \gamma_A) = RT(\ln \gamma^\infty{}_A) \quad (8)$$

was described by Prigogine and Defay.[15]

Because solutes II_{ee} and II_{aa} were characterized by a very low volatility ($p°_A \sim 0.1$ mmHg), we were obliged to apply an indirect method. Starting from the equation

$$\ln \gamma_S = \sum_k a_k x_A{}^{b_k} \quad (9)$$

where a_k is a coefficient and b_k is an exponent superior to 1 but not necessarily an integer, it is possible to derive an expression for $\ln \gamma_A$ on the basis of the Gibbs-Duhem equation:

$$\ln \gamma_A = \sum_k a_k x_A{}^{b_k} - \sum_k a_k(b_k x_A{}^{b_k-1} - 1)/(b_k - 1) \quad (10)$$

Therefore

$$RT(\ln \gamma^\infty{}_A) = RT\sum_k a_k/(b_k - 1) \quad (11)$$

Equation 11 can also be derived in another way following the Van Ness treatment.[16] The determination of $\ln \gamma_S$ therefore appears as the crucial problem in our approach. For a system composed of two constituents and two phases (liquid and vapor) the variables are p, T, x, and y_A (mole fraction of A in the gas phase).[17] The variance of this system is equal to 2. We have, therefore, decided to keep T and x_A constant and to determine p and y_A. In fact, as has been shown by McKay and Salvador,[18] the determination of y_A is unnecessary when A is poorly volatile, which is the case here. In these conditions, we have

$$\ln \gamma_S = (\ln P_S/P°_S x_S) + [(B_{11} - V°_S)(P - P°_S)/RT] \quad (12)$$

where P_S is the partial pressure of the solvent (estimated via the relation $P_S = P - x_A P°_A$), P is the total pressure, $P°_A$ and $P°_S$ are the vapor pressures of pure solute and solvent, respectively, B_{11} is the second virial coefficient of the solvent, and $V°_S$ is the molar volume of the pure solvent.

The determination of the composition of the liquid phase was made by gravimetry (taking into account the buoyancy correction and the vaporization of A and S). We presupposed an ideal behavior for A (very slightly volatile) and a nonideal behavior for S. The number of moles $n^g{}_A$ and $n^g{}_S$ of A and S going in the vapor phase are, therefore, given by

$$n^g{}_A = P_A V^G/RT \text{ with } P_A = P°_A x_A \quad (13)$$

$$n^g{}_S = (P - P_A)V^G/[RT + B_{11}\,(P - P_A)] \quad (14)$$

Eight to nine experiments were performed in the range of concentrations $x_A = 0.5$–0.02 in order to be able to make a precise extrapolation. Relationship 9 assumes the form

$$\ln \gamma_S = a_1 x_A{}^2 + a_2 x_A{}^{2.5} + a_3 x_A{}^3 \quad (15)$$

and (11) becomes

$$RT(\ln \gamma^\infty{}_A) = RT(a_1 + 2a_2/3 + a_3/2) \quad (16)$$

Table V. Free Energy of Solution at Infinite Dilution of II_{ee} and II_{aa} in Various Solvents at 25 °C (kcal/mol)

deriv	solvent C_6H_{12}	C_6H_6	$(CH_3)_2CO$
II_{aa}	0.19	0.06	0.87
II_{ee}	0.69	−0.16	0.55

Table VI. $[\Delta\delta H^\circ]_{S1\rightarrow S2}$, $[\Delta\delta G^\circ]_{S1\rightarrow S2}$, and $T[\Delta\delta S^\circ]_{S1\rightarrow S2}$ Values (kcal/mol) for the II_{ee}/II_{aa} System

	C_6H_{12}	C_6H_6	$(CH_3)_2CO$
$[\Delta\delta H^\circ]_{S1\rightarrow S2}$	0	−1.34[a]	−1.37[a]
$[\Delta\delta G^\circ]_{S1\rightarrow S2}$	0	−0.72[b]	−0.82[b]
$T[\Delta\delta S^\circ]_{S1\rightarrow S2}$	0	−0.62[c]	−0.55[c]

[a] Absolute error ±0.04 kcal/mol. [b] Absolute error ±0.16 kcal/mol. [c] Absolute error ±0.20 kcal/mol.

Table V gives $RT(\ln \gamma^\infty{}_A)$ for the three solvents, A being respectively II_{ee} and II_{aa}. $RT(\ln \gamma^\infty{}_A)$ is equivalent to the free energy of solution of the pure liquid A, $(G^\circ)^S$, at infinite dilution. It is therefore the exact quantity we needed for our treatment of the solvent effect on the free-energy difference between II_{ee} and II_{aa}. The estimated errors involved in measuring the free energy of solution (Table V) are ±0.03 kcal/mol when the solvents are benzene or acetone and ±0.05 kcal in cyclohexane. In Table VI, we have collected the solvent effects $[\Delta\delta H^\circ]_{S1\rightarrow S2}$ $[\Delta\delta G^\circ]_{S1\rightarrow S2}$, and $T[\Delta\delta S^\circ]_{S1\rightarrow S2}$ as determined for the II_{ee}/II_{aa} system.

The importance of the results given in Table VI springs from the fact that they constitute an accurate estimate of a solvent effect on the relative stability of stereoisomers, the stability being measured not only in terms of free enthalpy but also of entropy and enthalpy. The accuracy is due to the fact that the $[\Delta\delta H^\circ]_{S1\rightarrow S2}$ and $[\Delta\delta S^\circ]_{S1\rightarrow S2}$ terms are obtained independently without any risk of errors correlation relative to these two quantities. The results given in Table VI confirm the existence of a true correlation between the enthalpy and entropy contribution to the solvent effects. This result is in complete agreement with the conclusion we presented in the preliminary note we published on the subject.[19] Nevertheless, the two contributions do not cancel each other out.

The $[\Delta\delta G^\circ]_{S1\rightarrow S2}$ term remains important in benzene and in acetone. It is very interesting to compare these $[\Delta\delta G^\circ]_{S1\rightarrow S2}$ values with the $[\delta\Delta G^\circ]_{S1\rightarrow S2}$ values obtained directly by the study of the $I_{aa} \rightleftharpoons I_{ee}$ equilibrium[7,20] (−0.75 kcal/mol in C_6H_6 and −0.95 kcal/mol in acetone). The agreement is excellent and this fact provides further proof that the solvation phenomena on systems I, II, and III are very similar.

As we pointed out previously, the theoretical results obtained by Abraham and Sievens[7] are in disagreement with the $[\Delta\delta H^\circ]_{S1\rightarrow S2}$ values we have obtained in this work. On the other hand, their theoretical results are in agreement with the $[\Delta\delta G^\circ]_{S1\rightarrow S2}$ values we obtained. This agreement is probably not fortuitous. As we said, the reaction field theory used by Abraham and Sievens and more recently by Dosen-Micovic and Allinger[8] leads to the free energy of solvation and not to the enthalpy of solvation. The comparison between what, on the one hand, the authors call a calculated energy of solvation and, on the other, an experimental value of free energy of solvation (considered by them to be a good measure of the enthalpy of solvation) leads to a satisfactory concordance not because $[\Delta\delta S^\circ]_{S1\rightarrow S2}$ is negligible but, simply, because their calculated values are, in fact, free energies of solvation! This comment is valid only with acetone as a solvent. The reaction field cannot be used for benzene if, as is probably the case, a complex exists between benzene and the more polar solutes I_{ee}, II_{ee}, or III_{ee}. The $[\Delta\delta S^\circ]_{S1\rightarrow S2}$ value obtained in benzene reflects an organization of the solvent around the more polar solute or, at least, a preferential orientation of the solvent molecules with respect to the solute II_{ee} compared to II_{aa}.

General Conclusions

As we pointed out many years ago[21] it is hopeless to try to interpret an equilibrium between isomers in a solvent S without having the various thermodynamic parameters in hand, i.e., ΔH° and ΔS° obtained in various solvents including an "inert" one (or, better, the gas phase) and the transfer enthalpies and entropies from the "inert" solvent (or the gas phase) to the solvent S. When the two isomers have similar molecular volumes (as is the case for the derivatives studied here[22]), the enthalpy associated with the cavity formation in the solvent[23] is very similar for the two isomers. In these conditions, the difference between ΔH° measured in an "inert" solvent and in the gas phase can be considered to be essentially due to the solvent-solute interactions (and not to solvent-solvent interactions). The fact remains that, when the two isomers have different dipole moments, cyclohexane itself cannot be looked upon as a truly inert solvent. This fact can be easily verified by using the reaction field theory.[7,8] Therefore, at least in the case of the dibromo derivatives, our reference solvent has certainly some influence on the relative stability of the stereoisomers. In the absence of a knowledge of the enthalpy of vaporization or the sublimation of the derivatives under study we remain unable to refer to the gas phase. Even in the absence of these thermodynamic parameters, we were, nevertheless, able to prove that the intermolecular contribution to the equilibrium, i.e., the solvent effect on the equilibrium, is more important in some solvents (C_6H_6 and acetone) than the intramolecular contributions to the equilibrium as estimated by Zefirov et al.[24] At the enthalpy level we were also able to show that CS_2 and even CCl_4 are not "inert" solvents compared to cyclohexane. These observations show the importance of the quantitative study of solvent effects in organic chemistry. This quantitative study requires at least calorimetric measurements (and better calorimetric measurements and activity-coefficient measurements) in order to prevent the risk of errors compensation when ΔH° (and ΔS°) are obtained via van't Hoff's law. For ΔH° of the order of 0.0–1 kcal/mol, which frequently characterizes the enthalpy difference between stereoisomers, it is no longer a question of a "risk" but a "certainty." This is the fundamental reason why, in spite of the great number of studies of solvent effects on the equilibrium between stereoisomers, this very important problem remains more or less open.

Experimental Section

Preparation of the Derivatives. *cis*- and *trans*-1-bromo-4-*tert*-butylcyclohexane (VI_a and VI_e). The mixture of the two derivatives was obtained by following the procedure laid down by Eliel and Martin.[25] The separation of the two isomers was based on the possibility of forming a crystalline clathrate between the trans isomer and thiourea. The purification of the two isomers was carried out first by recrystallization in pentane and then by distillation under reduced pressure. The purity of the two derivatives was determined by NMR (purity higher than 99%).

***tert*-Butylcyclohexane (IV).** This reagent substance was obtained by the hydrogenation at normal pressure of 4-*tert*-butylcyclohexene which had been prepared by following the procedure described by Sicher et al.[26] Purification was performed by distillation at normal pressure on a Nester-Faust Corp. distillation apparatus (T_E 168 °C). Purity (higher than 99%) was determined by VPC.

***trans*-Decalin (V).** The purity of this substance, which was taken from laboratory stocks, was tested by VPC (purity higher than 99%).

***trans,trans*- and *trans,cis*-1,2-Dibromo-4-*tert*-butylcyclohexane (II_{aa} and II_{ee}).** The addition of bromine to 4-*tert*-butylcyclohexene was carried out as described by Eliel and Raber.[27] The reaction mixture contained essentially the trans,trans isomer. By heating at 120 °C in a nitrogen atmosphere for 24 h, the mixture was enriched in the trans,cis isomer (thermal isomerization).[28] The separation of the two

Table VII. Experimental Results for the Estimation of ln γ_S Values (II_{aa} in C_6H_{12} as Solvent), Pressures in mmHg at 25 °C, $p°_a{}^a = 0.13$, $B_{11}{}^c = -1.555$ cm^3/mol, $p°_S{}^b = 97.87$

$x_S{}^d$	$x_A{}^e$	p^f	$p_S{}^g$	$p - p°_S$	ln γ_S
0.5852	0.4148	62.63	62.58	−35.24	0.0918
0.6378	0.3622	66.55	66.50	−31.32	0.0661
0.7644	0.2356	77.16	77.13	−20.71	0.0324
0.8516	0.1484	84.57	84.55	−13.30	0.0155
0.8980	0.1020	88.63	88.62	−9.24	0.0091
0.9495	0.0505	93.98	93.97	−3.89	0.0115
0.9623	0.0377	95.00	95.00	−2.87	0.0089

[a] Vapor pressure of pure II_{aa}. [b] Vapor pressure of pure solvent (C_6H_{12}). [c] Second virial coefficient of the solvent. [d] Mole fraction of the solvent (C_6H_{12}). [e] Mole fraction of the solute (II_{aa}). [f] Total pressure of the solution. [g] Partial pressure of the solvent (C_6H_{12}).

isomers was then performed by chromatography on silica gel. The ultimate purification of the two separated isomers was performed by distillation under reduced pressure. Purity (higher than 99%) was determined by NMR and IR spectroscopy.[27]

2,3-Dibromodecalin (III_{aa} and III_{ee}). *cis*- and *trans*-dibromo-*trans*-decalin were obtained by following the procedure described by Johnson.[29] The first step was the diene condensation of *p*-benzoquinone and butadiene. This 1:1 adduct was then reduced selectively with zinc dust to give the *cis*-2,3,5,8,9,10-hexahydro-1,4-naphthoquinone. The crude cis dione was treated under Huang-Minlon reduction conditions to produce a mixture of *cis*- and *trans*-Δ^2-octalin. The dibromides were obtained by the bromination of this Δ^2-octalin mixture. Pure 2(a), 3(a)-dibromo-*trans*-decalin (III_a) was obtained by repeated recrystallizations from absolute ethanol. The 2(e), 3(e)-dibromo-*trans*-decalin (III_{ee}) was obtained by the thermal equilibration of the diaxial isomer,[28] the two isomers being then separated by chromatography on silica gel: mp III_{aa} 85 °C;[31,32] mp III_{ee} 89 °C.[30,32]

Calorimetric Measurements. The heats of solution were measured on a LKB 8700-1 calorimeter. The data treatment was performed as described in Wadso's original paper.[33] The accuracy of the apparatus was tested by performing the reference solution reaction of Tris in an aqueous solution of HCl (0.1 mol/L).[34]

Vapor Pressure Measurements. The apparatus which was constructed to perform the measurements was similar to that described by McGlashan and Williamson[35] and modified by Gomez-Ibanez and Shieh.[36] The modifications we made were only of a minor nature. The procedure itself was identical with that used by McGlashan and Williamson.[35] The mole fraction of the solute was approximately between 0.4 and 0.05. Table VII gives an example of the data collected in order to determine the ln γ_S values in the case of II_{aa} with C_6H_{12} used as a solvent.

References and Notes

(1) (a) J. J. Moura Ramos, J. Reisse, and M. H. Abraham, *Can. J. Chem.*, **57**, 500 (1979); (b) Centro Quimica Fisica Molecular; (c) Chimie Organique E.P.
(2) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, 1963.
(3) (a) R. C. Peterson, J. H. Markgraf, and S. D. Ross, *J. Am. Chem. Soc.*, **83**, 3819 (1961); (b) R. R. Krug, W. G. Hunter, and R. A. Grieger, *J. Phys. Chem.*, **80**, 2335 (1976); (c) N. M. Sergeyev, *Org. Magn. Reson.*, **11**, 127 (1978); (d) N. M. Sergeyev and O. A. Subbotin, *Russ. Chem. Rev. (Engl. Transl.)*, **47**, 265 (1978).
(4) N. L. Allinger and M. T. Wuesthoff, *Tetrahedron*, **33**, 3 (1977).
(5) A. Y. Meyer and N. L. Allinger, *Tetrahedron*, **31**, 1971 (1975).
(6) (a) W. G. Schneider, *J. Chem. Phys.*, **88**, 2653 (1962); (b) N. Oi and J. F. Coetzee, *J. Am. Chem. Soc.*, **91**, 2478 (1969); (c) H. J. Hageman and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **88**, 97 (1969).
(7) R. J. Abraham and T. M. Sieverns, *J. Chem. Soc., Perkin Trans. 2*, 1587 (1972).
(8) L. Dosen-Micovic and N. L. Allinger, *Tetrahedron*, **34**, 3385 (1978).
(9) C. Altona, H. R. Buys, H. J. Hageman, and E. Havinga, *Tetrahedron*, **23**, 2265 (1967).
(10) H. J. Hageman and E. Havinga, *Tetrahedron*, **22**, 2271 (1966).
(11) C. J. F. Bottcher, "The Theory of Electric Polarization", Vol. 1, Elsevier, Amsterdam, 1973.
(12) In a subsequent paper devoted to a different problem, R. J. Abraham et al., *J. Chem. Soc., Perkin Trans. 2*, 1677 (1975), have admitted this point of view.
(13) (a) J. A. Hirsch, *Top. Stereochem.* **1**, 199 (1967); (b) F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.*, **3**, 139 (1971); (c) O. A. Subbotin and N. M. Sergeyev, *J. Am. Chem. Soc.*, **97**, 1080 (1975); (d) H. J. Schneider and V. Hoppen, *Tetrahedron Lett.*, 579 (1974); (e) D. Höfner, S. A. Lesko, and G. Binsch, *Org. Magn. Reson.*, **11**, 179 (1978).
(14) H. G. Geise, A. Tieleman, and E. Havinga, *Tetrahedron*, **22**, 183 (1966).
(15) I. Prigogine and R. Defay, "Chemical Thermodynamics", Longman, London, 1973, p 101.
(16) H. C. Van Ness and R. V. Mrazek, *Am. Inst. Chem. Eng. J.*, **5**, 209 (1959).
(17) V. Mathot, *Bull. Soc. Chim. Belg.*, **59**, 111 (1950).
(18) D. McKay and R. J. Salvador, *Ind. Eng. Chem., Fundam.*, **10**, 167 (1971).
(19) L. Dumont, J. J. Moura Ramos, D. Zimmermann, and J. Reisse, *Tetrahedron Lett.*, 355 (1974).
(20) J. Reisse, J. C. Celotti, and R. Ottinger, *Tetrahedron Lett.*, 2167 (1966).
(21) J. Reisse in "Conformational Analysis", G. Chiurdoglu, Ed., Academic Press, New York, 1971, p 219.
(22) K. R. Crook, E. Wyn-Jones, and W. J. Orville-Thomas, *Trans. Faraday Soc.*, 1597 (1970).
(23) J. J. Moura Ramos, M. Lemmers, R. Ottinger, M. L. Stien, and J. Reisse, *J. Chem. Res. (S)*, 56 (1977); *J. Chem. Res. (M)*, 0658 (1977).
(24) N. S. Zefirov, V. V. Samoshin, O. A. Subbotin, V. I. Baranenkov, and S. Wolfe, *Tetrahedron*, **34**, 2953 (1978).
(25) E. L. Eliel and R. J. L. Martin, *J. Am. Chem. Soc.*, **90**, 689 (1968).
(26) J. Sicher, F. Sipos, and M. Tichy, *Collect. Czech. Chem. Commun.*, **26**, 847 (1961).
(27) E. L. Eliel and R. G. Raber, *J. Org. Chem.*, **24**, 143 (1959).
(28) P. L. Barili, G. Bellucci, G. Berti, F. Marioni, A. Marsili, and I. Morelli, *Chem. Commun.*, 1437 (1970).
(29) W. Johnson, V. Bauer, J. Margrave, L. Dreger, and W. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).
(30) W. Hückel, H. Waiblinger, and H. Feltkamp, *Justus Liebigs Ann. Chem.*, **678**, 24 (1974).
(31) W. Hückel, R. Daneel, A. Schwarz, and A. Gercke, *Justus Liebigs Ann. Chem.*, **474**, 121 (1929).
(32) W. Hückel and H. Waiblinger, *Justus Liebigs Ann. Chem.*, **888**, 17 (1963).
(33) I. Wadso, *Sci. Tools*, **13**, 33 (1966).
(34) J. O. Hill, G. Ojelund, and I. Wadso, *J. Chem. Thermodyn.*, **1**, 111 (1969).
(35) M. L. McGlashan and A. G. Williamson, *Trans. Faraday Soc.*, **57**, 588 (1961).
(36) J. D. Gomez-Ibanez and J. J. C. Shieh, *J. Phys. Chem.*, **89**, 1660 (1965).