### Solution Thermodynamic Studies. 5.<sup>1a</sup> 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,<sup>1b</sup> L. Dumont,<sup>1c</sup> M. L. Stien,<sup>1c</sup> and J. Reisse\*<sup>1c</sup>

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  $\Delta G^{\circ}$  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  $\delta$  is the solvent operator as introduced by Leffler and Grunwald<sup>2</sup> and defined by the following expressions:

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

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

$$[\delta \Delta S^{\circ}]_{S_1 \to S_2} = (\Delta S^{\circ})_{S_2} - (\Delta S^{\circ})_{S_1}$$
(3)

It is well known that  $\Delta H^{\circ}$  and  $\Delta S^{\circ}$  are much more difficult to measure with precision than  $\Delta G^{\circ}$ . In particular, the correlation between the errors on  $\Delta H^{\circ}$  and  $\Delta S^{\circ}$  as obtained by the van't Hoff relationship<sup>3</sup> casts doubt upon the significance of many of the  $\Delta H^{\circ}$  and  $\Delta S^{\circ}$  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,<sup>2</sup> the  $\delta$  and  $\Delta$  operators commute. In other words, if X° is a thermodynamic quantity like G°, H°, or S°, we have

$$[\delta \Delta X^{\circ}]_{S1 \to S2} = [\Delta \delta X^{\circ}]_{S1 \to S2}$$
(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  $[\Delta\delta G^{\circ}]_{S1\to S2}$ ,  $[\Delta\delta H^{\circ}]_{S1\to S2}$ , and  $[\Delta\delta S^{\circ}]_{S1\to S2}$  only requires the determination of the transfer enthalpy  $[\delta H^{\circ}]_{S1\to S2}$  and the transfer free energy  $[\delta G^{\circ}]_{S1\to S2}$ 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<sub>ee</sub>, 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<sub>ee</sub> in S1 and in S2, respectively, at constant pressure. By definition, the difference between these two quantities is the enthalpy of transfer of II<sub>ee</sub> 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  $\pm 0.03$ 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<sub>ee</sub> and II<sub>aa</sub>, for example), can be obtained with a precision of  $\pm 0.06$ 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.

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

deriv	$\overline{C_6H_{12}}$	CCl4	solvent C <sub>6</sub> H <sub>6</sub>	CS <sub>2</sub>	(CH <sub>3</sub> ) <sub>2</sub> CO
	1.27	0.29	0.09	0.60	0.92
II ee	1.27	0.38	-0.08	0.09	0.83
IIaa	0.53	-0.19	0.52	0.40	1.46
III <sub>ee</sub>	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  $[\Delta \delta H^{\circ}]_{S1 \rightarrow S2}$  on the Relative Stability of  $II_{ee}/II_{aa}$  and  $III_{ee}/III_{aa}$  (kcal/mol)

			solvent		
deriv	C <sub>6</sub> H <sub>12</sub>	CCl <sub>4</sub>	C <sub>6</sub> H <sub>6</sub>	$CS_2$	$(CH_3)_2CO$
$\frac{II_{ee}/II_{aa}}{III_{ee}/III_{aa}}$	0.00 0.00	-0.17 -0.08	-1.34 -1.48	-0.45 -0.30	-1.37 -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  $[\Delta \delta H^{\circ}]_{S1 \rightarrow S2}$  values for the two series of dibromo derivatives: II<sub>ee</sub> and II<sub>aa</sub> on the one hand, and III<sub>ee</sub> and III<sub>aa</sub> on the other. The  $[\Delta \delta H^{\circ}]_{S1 \rightarrow S2}$  values are defined by the following equation:

$$[\Delta \delta H^{\circ}]_{S_1 \to S_2} = [(H^{\circ})_{S_2} - (H^{\circ})_{S_1}]_{ee} - [(H^{\circ})_{S_2} - (H^{\circ})_{S_1}]_{aa}$$

As we have previously said (cf. relationship 4) the  $[\Delta\delta H^{\circ}]_{S1\to S2}$  values are the exact equals of the  $[\delta\Delta H^{\circ}]_{S1\to S2}$  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  $[\delta\Delta H^{\circ}]_{S1\to S2}$  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  $[\delta\Delta H^{\circ}]_{S1\to S2}$  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:

$$\begin{split} DII_{ee}/IV &= [\delta H^\circ]_{S1 \to S2} \text{ for } II_{ee} - [\delta H^\circ]_{S1 \to S2} \text{ for } IV \\ DII_{aa}/IV &= [\delta H^\circ]_{S1 \to S2} \text{ for } II_{aa} - [\delta H^\circ]_{S1 \to S2} \text{ for } IV \\ DIII_{ee}/V &= [\delta H^\circ]_{S1 \to S2} \text{ for } III_{ee} - [\delta H^\circ]_{S1 \to S2} \text{ for } V \\ DIII_{aa}/V &= [\delta H^\circ]_{S1 \to S2} \text{ for } III_{aa} - [\delta H^\circ]_{S1 \to S2} \text{ for } V \end{split}$$

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



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

			solvent		
D	C <sub>6</sub> H <sub>12</sub>	CCl <sub>4</sub>	C <sub>6</sub> H <sub>6</sub>	CS <sub>2</sub>	(CH <sub>3</sub> ) <sub>2</sub> CO
$DII_{ee}/IV$	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

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<sub>ee</sub> and III<sub>ee</sub> on the one hand and of II<sub>aa</sub> and III<sub>aa</sub> on the other hand is notable. We can safely assume that the solvent effect  $[\Delta \delta H^{\circ}]_{S1 \rightarrow S2}$  on the relative stability of II<sub>ee</sub> compared to II<sub>aa</sub> or of III<sub>ee</sub> compared to III<sub>aa</sub> (Table II) is very similar to the solvent effect  $[\delta \Delta H^{\circ}]_{S1 \rightarrow S2}$  which characterizes the conformation equilibrium I<sub>aa</sub>  $\rightleftharpoons$  I<sub>ee</sub>, and which was unknown before the present work was completed.

With respect to solvent  $C_6H_{12}$ , the  $[\Delta\delta H^\circ]_{S1\to S2}$  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<sup>4</sup> 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.<sup>5</sup>

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  $(\Delta \delta H^\circ)_{S1\to S2}$  on the Relative Stability of the  $VI_e/VI_a$  System (kcal/mol) at 25 °C

	solvent						
deriv	C <sub>6</sub> H <sub>12</sub>	CCl <sub>4</sub>	C <sub>6</sub> H <sub>6</sub>	$CS_2$	(CH <sub>3</sub> ) <sub>2</sub> CO		
VIa	0.41	-0.06	0.43	0.53	1.38		
VIe	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:<sup>6</sup> 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<sup>7,8</sup> 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<sup>5,9,10</sup> ( $\mu$ (II<sub>ee</sub>) = 3.3,  $\mu$ (III<sub>ee</sub>) = 3.3 D) with respect to the less polar isomer ( $\mu$ (II<sub>aa</sub>) = 1.2,  $\mu$ (III<sub>aa</sub>) = 1.15 D).

From a quantitative point of view, the reaction field model as used by Abraham and Sieverns<sup>7</sup> and more recently by Allinger<sup>8</sup> 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<sup>11</sup> and not of the energy of solvation as claimed by Abraham et al. in their original paper.<sup>12</sup> Therefore, the comparison between experimental and theoretical results has to be carried out at the level of  $[\Delta\delta G^{\circ}]_{S1 \rightarrow S2}$  and not at the level of  $[\Delta\delta H^{\circ}]_{S1 \rightarrow S2}$  (see Table VI).

In order to extend the discussion of the  $[\Delta \delta H^{\circ}]_{S1 \rightarrow S2}$  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  $[\Delta \delta H^{\circ}]_{S1 \rightarrow S2}$  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<sub>6</sub>H<sub>12</sub>). 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.<sup>13</sup> Once again, the more polar stereoisomer ( $\mu(VI_e) = 2.25$ ,<sup>14</sup>  $\mu(VI_a) = 2.15 D^{14}$ ) is stabilized relative to the axial stereoisomer in all solvents with respect to cyclohexane.

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

The determination of the free energy of transfer from S2 to S1,  $[\delta G^{\circ}]_{S1\to S2}$  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<sup>15</sup> 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

$$(\partial G^{\rm E}/\partial x_{\rm A})^{\rm S}{}_{P,T} = RT[\ln \gamma_{\rm A} - \ln \gamma_{\rm S} + x_{\rm A} (\partial \ln \gamma_{\rm A}/\partial x_{\rm A}) - x_{\rm S}(\partial \ln \gamma_{\rm S}/\partial x_{\rm S})] \quad (5)$$

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

$$(\partial G^{\rm E}/\partial x_{\rm A})^{\rm S}_{P,T} = RT[(\ln \gamma_{\rm A} - \ln \gamma_{\rm S}) \tag{6}$$

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

$$\lim_{x_A \to 0} (\partial G^{\mathsf{E}} / \partial x_A)^{\mathsf{S}_{2_{P,T}}} - \lim_{x_A \to 0} (\partial G^{\mathsf{E}} / \partial x_A)^{\mathsf{S}_{1_{P,T}}} = [\delta G^{\circ}]_{\mathsf{S}_1 \to \mathsf{S}_2}$$
(7)

The method we have used consists of determining the value of  $\lim_{x_A \to 0} (\partial G^E / \partial x_A)^S_{P,T}$  for  $\Pi_{ee}$  and  $\Pi_{aa}$  in various solvents S, i.e.,  $C_6 H_{12}$ ,  $C_6 H_6$ , and  $(CH_3)_2 CO$ . 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

$$\lim_{x_A \to 0} \left( \partial G^E / \partial x_A \right)^{S_{P,T}} = RT(\lim_{x_A \to 0} \ln \gamma_A) = RT(\ln \gamma^{\infty}_A)$$
(8)

was described by Prigogine and Defay.15

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

$$\ln \gamma_{\rm S} = \sum_{k} a_k x_{\rm A} b_k \tag{9}$$

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:

$$\ln \gamma_{\rm A} = \sum_{k} a_k x_{\rm A}^{b_k} - \sum_{k} a_k (b_k x_{\rm A}^{b_k - 1} - 1) / (b_k - 1) \quad (10)$$

Therefore

$$RT(\ln \gamma^{\infty}_{A}) = RT \sum_{k} a_{k}/(b_{k} - 1)$$
(11)

Equation 11 can also be derived in another way following the Van Ness treatment.<sup>16</sup> 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).<sup>17</sup> 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,<sup>18</sup> the determination of  $y_A$  is unnecessary when A is poorly volatile, which is the case here. In these conditions, we have

$$\ln \gamma_{\rm S} = (\ln P_{\rm S}/P^{\circ}_{\rm S}x_{\rm S}) + [(B_{11} - V^{\circ}_{\rm S})(P - P^{\circ}_{\rm S})/RT]$$
(12)

where  $P_S$  is the partial pressure of the solvent (estimated via the relation  $P_S = P - x_A P^\circ_A$ ), P is the total pressure,  $P^\circ_A$  and  $P^\circ_S$  are the vapor pressures of pure solute and solvent, respectively,  $B_{11}$  is the second virial coefficient of the solvent, and  $V^\circ_S$  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  $n_A^g$  and  $n_S^g$  of A and S going in the vapor phase are, therefore, given by

$$n_{\rm A}^{\rm g} = P_{\rm A} V^{\rm G} / RT$$
 with  $P_{\rm A} = P_{\rm A}^{\circ} x_{\rm A}$  (13)

$$n^{g}_{S} = (P - P_{A})V^{G} / [RT + B_{11} (P - P_{A})]$$
(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

$$\ln \gamma_{\rm S} = a_1 x_{\rm A}^2 + a_2 x_{\rm A}^{2.5} + a_3 x_{\rm A}^3 \tag{15}$$

and (11) becomes

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

**Table V.** Free Energy of Solution at Infinite Dilution of IIee andIIaa in Various Solvents at 25 °C (kcal/mol)

	solvent					
deriv	$\overline{C_6H_{12}}$	C <sub>6</sub> H <sub>6</sub>	(CH <sub>3</sub> ) <sub>2</sub> CO			
IIaa	0.19	0.06	0.87			
II <sub>ce</sub>	0.69	-0.16	0.55			

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  $\pm 0.03$  kcal/mol when the solvents are benzene or acetone and  $\pm 0.05$  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.<sup>19</sup> Nevertheless, the two contributions do not cancel each other out.

The  $[\Delta\delta G^{\circ}]_{S1\to S2}$  term remains important in benzene and in acetone. It is very interesting to compare these  $[\Delta\delta G^{\circ}]_{S1\to S2}$ values with the  $[\delta\Delta G^{\circ}]_{S1\to S2}$  values obtained directly by the study of the  $I_{aa} \rightleftharpoons I_{ee}$  equilibrium<sup>7,20</sup> (-0.75 kcal/mol in C<sub>6</sub>H<sub>6</sub> 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 Sieverns<sup>7</sup> are in disagreement with the  $[\Delta \delta H^{\circ}]_{S_1 \rightarrow S_2}$  values we have obtained in this work. On the other hand, their theoretical results are in agreement with the  $[\Delta \delta G^{\circ}]_{S_1 \to S_2}$  values we obtained. This agreement is probably not fortuitous. As we said, the reaction field theory used by Abraham and Sieverns and more recently by Dosen-Micovic and Allinger<sup>8</sup> 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  $[\Delta \delta S^{\circ}]_{S_1 \to S_2}$  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 Iee, II<sub>ee</sub>, or III<sub>ee</sub>. 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 IIee compared to IIaa.

### **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.,  $\Delta H^{\circ}$  and  $\Delta S^{\circ}$  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

**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<sub>ee</sub>/II<sub>aa</sub> System

	C <sub>6</sub> H <sub>12</sub>	C <sub>6</sub> H <sub>6</sub>	(CH <sub>3</sub> ) <sub>2</sub> CO	
$\begin{bmatrix} \Delta \delta H^{\circ} ]_{S1 \to S2} \\ [\Delta \delta G^{\circ} ]_{S1 \to S2} \\ T [\Delta \delta S^{\circ} ]_{S1 \to S2} \end{bmatrix}$	0 0 0	$-1.34^{a}$ $-0.72^{b}$ $-0.62^{c}$	$-1.37^{a}$ $-0.82^{b}$ $-0.55^{c}$	

<sup>*a*</sup> Absolute error  $\pm 0.04$  kcal/mol. <sup>*b*</sup> Absolute error  $\pm 0.16$  kcal/mol. <sup>*c*</sup> Absolute error  $\pm 0.20$  kcal/mol.

solvent S. When the two isomers have similar molecular volumes (as is the case for the derivatives studied here<sup>22</sup>), the enthalpy associated with the cavity formation in the solvent<sup>23</sup> is very similar for the two isomers. In these conditions, the difference between  $\Delta H^{\circ}$  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.<sup>7,8</sup> 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.<sup>24</sup> At the enthalpy level we were also able to show that  $CS_2$  and even CCl<sub>4</sub> 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  $\Delta H^{\circ}$  (and  $\Delta S^{\circ}$ ) are obtained via van't Hoff's law. For  $\Delta H^{\circ}$  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-tertbutylcyclohexane (VI<sub>a</sub> and VI<sub>e</sub>). The mixture of the two derivatives was obtained by following the procedure laid down by Eliel and Martin.<sup>25</sup> 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.<sup>26</sup> 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<sub>aa</sub> and II<sub>ee</sub>). The addition of bromine to 4-tert-butylcyclohexene was carried out as described by Eliel and Raber.<sup>27</sup> 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).<sup>28</sup> The separation of the two

**Table VII.** Experimental Results for the Estimation of  $\ln \gamma_{\rm S}$ Values (II<sub>aa</sub> in C<sub>6</sub>H<sub>12</sub> as Solvent), Pressures in mmHg at 25 °C,  $p_{a}^{\circ} = 0.13, B_{11}^{\circ} = -1.555 \text{ cm}^3/\text{mol}, p_{S}^{\circ} = 97.87$ 

-						
$x_S^d$	$x_A^e$	$p^f$	ps <sup>g</sup>	$p - p^{\circ}s$	$\ln \gamma_{ m S}$	
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	

<sup>a</sup> Vapor pressure of pure II<sub>aa</sub>. <sup>b</sup> Vapor pressure of pure solvent  $(C_6H_{12})$ . <sup>c</sup> Second virial coefficient of the solvent. <sup>d</sup> Mole fraction of the solvent ( $C_6H_{12}$ ). <sup>e</sup> Mole fraction of the solute (II<sub>aa</sub>). <sup>f</sup> 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<sub>aa</sub> and III<sub>ee</sub>). cis- and trans-dibromotrans-decalin were obtained by following the procedure described by Johnson.<sup>29</sup> 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*- $\Delta^2$ -octalin. The dibromides were obtained by the bromination of this  $\Delta^2$ -octalin mixture. Pure 2(a), 3(a)-dibromo-trans-decalin (III<sub>a</sub>) was obtained by repeated recrystallizations from absolute ethanol. The 2(e), 3(e)-dibromo-*trans*-decalin (III<sub>ee</sub>) was obtained by the thermal equilibration of the diaxial isomer,<sup>28</sup> the two isomers being then separated by chromatography on silica gel: mp III<sub>aa</sub> 85 °C;<sup>31,32</sup> mp III<sub>ee</sub> 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.<sup>33</sup> 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 Williamson35 and modified by Gomez-Ibanez and Shieh.<sup>36</sup> The modifications we made were only of a minor nature. The procedure itself was identical with that used by McGlashan and Williamson.<sup>35</sup> 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  $\gamma_{\rm S}$  values in the case of II<sub>aa</sub> with C<sub>6</sub>H<sub>12</sub> 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 Química Física Molecular; (c) Chimie Organique E.P.

- (2) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions",
- (2) S. L. Leffler and E. Gruinwald, Pates 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 47. 265 (1978).
- A. Y. Allinger and M. T. Wuesthoff, *Tetrahedron*, **33**, 3 (1977).
   A. Y. Meyer and N. L. Allinger, *Tetrahedron*, **31**, 1971 (1975).
- (6) (a) W. G. Schneider, J. Chem. Phys., 66, 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
- (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., 666, 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. Shleh, J. Phys. Chem., 69, 1660 (1965)