The solvent contribution to the activation free energy for chair–boat isomerization of cyclohexane is estimated. The rate of isomerization has been measured as a function of temperature and pressure in a variety of solvents by Hasha, Eguchi, and Jonas. Interpretation of the experimental data hinges on the behavior of the free energy. Our calculations indicate that the free energy barrier increases with increasing pressure or density of the solvent. Yet according to experiment, the isomerization rate increases with increasing pressure. These two results imply that the transmission coefficient for the isomerization of solvated cyclohexane is an increasing function of pressure, and this implication is in contradiction with recent theoretical estimates of the transmission coefficient by Zawadowski and Hynes.

I. Introduction

Transition-state theory estimates rate constants in terms of static properties of the reactive system.\(^1\) For a unimolecular activated process such as the chair–boat isomerization of cyclohexane, the effect of solvation is described by

\[
(k/k_0)_{\text{ST}} = \exp(-\beta \Delta u^*)
\]

(1)

where \(k\) and \(k_0\) denote rate constants in the presence and absence of solvent, respectively, \(\beta = k_B T\) is Boltzmann's constant times temperature, and \(\Delta u^*\) is the solvation contribution to the free energy of activation. That is, \(\Delta u^*\) is the solvent contribution to the change in chemical potential or reversible work performed on the solvent in changing the \(\text{C}_6\text{H}_{12}\) molecule from one of its chair conformers to the transition state between a chair and boat conformer:

\[
\Delta u^* = \mu_{\text{trans}} - \mu_{\text{solv}}
\]

(2)

In reality, the rate constants for isomerization differ from those estimated by transition-state theory. The differences are due to dynamical effects described by the transmission coefficient, \(k = k_{\text{STST}}\).

\[
k = k_{\text{STST}}
\]

(3)

Roughly speaking, \(k\) is the fraction of successful trajectories, and its precise value can, in principle, be determined from the computation of certain well-defined time correlation functions.\(^2\)

Several years ago, Montgomery et al.\(^3\) suggested that for some isomerization processes in liquids, the transmission coefficient should be an increasing function of solvent density. The high-pressure NMR experiments of isomerization of cyclohexane by Hasha et al.\(^4\) seem to verify this theoretical prediction. More recent theoretical work, however, calls into question the earlier prediction and the validity of the interpretation of the NMR experiments. In particular, Hynes and co-workers\(^5\) suggest that high dimensionality and vibrational energy transfer between modes of polyatomic molecules will suppress the so-called inertial or Lindemann regime of unimolecular kinetics\(^6\) and due to that suppression, they suggest that, for cyclohexane, one will observe in a liquid only the diffusive regime first elucidated by Kramers.\(^7\) The implication of this suggestion is that \(k\) is a decreasing function of solvent density. Yet, the experimental rate for cyclohexane isomerization is an increasing function of density. Therefore, if the suggestion of Hynes and co-workers is to agree with experiment, it must mean the \(k_{\text{STST}}\) is an increasing function of solvent density, and increasing at a rate much greater than imagined possible by Hasha et al.\(^4\)

To address the issue of whether the experimental measurements of \(k\) indicate an increase or decrease in \(k\) as a function of solvent density, we have performed RISM calculations of the chemical potential surface for cyclohexane in liquid CS\(_2\) for various liquid densities and for various conformational arrangements of the cyclohexane solute. Liquid carbon disulfide is one of the solvents investigated by Hasha et al.\(^4\) According to our calculations, the free energy of activation increases with increasing solvent density. Thus, eq 1 and 3 together with the experimentally observed rate imply that \(k\) increases with increasing solvent density.

In the next section, we describe the required theory, and the results of our calculation are presented in section III.

II. Calculation of \(\Delta u^*\)

Our starting point in calculating \(\Delta u^*\) is the specification of the intermolecular interactions. We adopt the standard interaction site potential form between solvent and solute assuming a picture of the cyclohexane molecule in which the six CH\(_2\) groups are spherical extended atoms with their centers located at the carbon nuclei. A pair potential between a cyclohexane molecule and one of the solvent molecules is therefore

\[
\Delta u^* = \sum_{\mu = 1}^{6} \sum_{\nu = 1}^{n} \mu_{\mu}(r_{\mu\nu} - r_{\mu\nu})
\]

(4)

Here \(r_{\mu\nu}\) denotes the position of the \(\mu\)th carbon nucleus in the cyclohexane molecule, and \(r_{\mu\nu}\) denotes the position of the \(\nu\)th interaction site of the solvent molecule. There are \(n\) interaction sites in a solvent molecule. With this form of interaction, the reference interaction site methodology, RISM,\(^8\) is immediately applicable. The pertinent equations for the pair correlation functions are

\[
\rho_{\mu\nu}(r) = \sum_{\tau} \omega_{\mu\nu}(c_{\tau}\rho_{\tau}(r))
\]

(5)

\[
c_{\mu\nu}(r) = -\beta u_{\mu\nu}(r) + h_{\mu\nu}(r) - \ln [1 + h_{\mu\nu}(r)]
\]

The symbols all have their usual meaning;\(^4\) for example, \(\chi_{\tau}(r)\) is the pure solvent site density pair correlation function. Equation 4 is the infinite dilution limit of the Ornstein–Zernike-like equation introduced by Chandler and Andersen,\(^2\) and eq 5 the hypernetted-chain closure of the Chandler–Andersen equation. The
combination of eq 4 and 5 are the infinite dilution form of the extended RISM equation.10

The chemical potential for the solute conformer can be obtained from the solute–solvent pair correlation functions by the standard coupling parameter integration.8 The result of this integration on using eq 4 and 5 is11

$$-\beta \mu_{\text{sub}}(r) = \rho \sum_{\alpha, \beta} \int \text{d}r \left[ c_{\alpha \beta}(r) - \frac{1}{2} h_{\alpha \beta}(r) \right] + \frac{1}{2} \sum_{\alpha, \beta, \gamma} c_{\alpha \beta} c_{\beta \gamma} c_{\gamma \alpha} \left( \text{r}^{\alpha \beta \gamma} - r^2 \right)$$

(6)

where we have emphasized that $\mu_{\text{sub}}$ is a function of the solute conformation as specified by the coordinates $[r^{\alpha \beta \gamma}]$. Note that this dependence is found both in the explicit coordinate dependence on the right-hand side of eq 6 and also the implicit dependence due to the fact that $c_{\alpha \beta}(r)$ and $h_{\alpha \beta}(r)$ are nonlinear functionals of $\gamma$ the intramolecular pair correlation functions, $\omega_{\alpha \beta}(r)$. An alternative expression for $\mu_{\text{sub}}$ is obtained from a Gaussian field theory of solution.12 The result from that theory is

$$-\beta \mu_{\text{sub}}(r) = \frac{1}{2} \sum_{\alpha, \beta} \int \text{d}r c_{\alpha \beta}(r) + \sum_{\alpha, \beta, \gamma} c_{\alpha \beta} c_{\beta \gamma} c_{\gamma \alpha} \left( \text{r}^{\alpha \beta \gamma} - r^2 \right)$$

(7)

Since both eq 6 and 7 are approximate, and since it is uncertain which of the two are more accurate, we present calculations using both formulas. It will be seen that the same conclusions are drawn from either expression.

The solvent-induced activation free energy $\Delta_{\text{act}}^*$ is obtained by subtracting $\mu_{\text{sub}}(r)$ calculated for the carbon positions $[r^c]$ of the chair from $\mu_{\text{sub}}(r)$ of the transition state. Carbon–carbon distances in the two conformers are determined from the molecular potential energy surface. We adopt the empirical force field of Pickett and Strauss11 for the six torsional and bending degrees of freedom of the carbon ring, and treat the much higher frequency carbon–carbon stretches as frozen. The Pickett and Strauss force field has an energy barrier of roughly 14 kcal/mol going from chair to boat which is about 3 or 4 kcal/mol higher than experimental estimates or more elaborate force fields which treat hydrogen atoms explicitly.14 However, the conformation of transition-state cyclohexane from the Pickett and Strauss force field has not been questioned in later treatments, and we stress that our calculations only use carbon–carbon distances derived from the force field.

The Pickett and Strauss reaction surface for the isomerization can be mapped onto a set of fictitious spherical angles $\theta$ and $\phi$.11 The reaction path for our work is determined by adjusting the torsion and bending coordinates to minimize the molecular force field energy while holding $\theta$ and $\phi$ fixed. This path is almost pure $\theta$ motion, with the chair at $\theta = 0$, the boat at $\theta = \pi/2$, and another chair at $\theta = \pi$. The transition states occur at $\theta = 50^\circ$ and $130^\circ$, the precise value depending slightly on $\phi$.

Besides the simplified model potentials and the use of pair correlation functions from extended RISM theory to evaluate $\Delta_{\text{act}}^*$, there is another approximation implicit in our procedure. Properly, changes in high vibrational frequencies upon solution should be accounted for. The changes are neglected, however, in our analyses of $\Delta_{\text{act}}^*$ because reasonable estimates of their contribution to the free energy are no larger than a few hundredths of $\beta$. It may be that the total changes in $\Delta_{\text{act}}^*$ are also this small, but free energetics of this size cannot effect the interpretation of the experiments reported by Hasha et al.4

III. Results

As stated above, the solvent we consider is carbon disulfide. The experimental equation of state10 is used to relate the experimental pressure, $p$, to the bulk density, $\rho$, employed in our calculations. We determine the pure solvent site density correlation function, $\omega_{\alpha \beta}(r)$, from the extended RISM equation, employing the site-site potentials $u_{\alpha \beta}(r)$ given by Tilley and Madden.10 In this model each C2S molecule contains three interaction sites (of two different types) located on the respective nuclei. Tilley and Madden's simulation studies demonstrated that their potentials satisfactorily reproduce thermodynamic and structural data of the liquid. We have compared the extended RISM calculations of the pair structure with those of Tilley and Madden's simulation with the same potential and verified that the extended RISM correlation functions are in reasonable accord with those of simulation.

For the $u_{\alpha \beta}(r)$ potentials coupling the cyclohexane solute to the solvent, we use the Lennard-Jones potential with the usual combining rules

$$\sigma_{\alpha \beta} = \sqrt{\sigma_{\alpha} \sigma_{\beta}}$$

(8)

$$\epsilon_{\alpha \beta} = \frac{\epsilon_{\alpha \alpha} \epsilon_{\beta \beta}}{\epsilon_{\alpha \beta}}$$

(9)

Here, the $\sigma$ and $\epsilon$ are the energy and length parameters in the Lennard-Jones potential. The $\sigma_{\alpha}$ and $\epsilon_{\alpha}$ for the extended CH2 groups on cyclohexane are taken as $\sigma_{CH2}/k_B = 57.47$ K and $\epsilon = 3.98$ A, respectively. These are the values adopted from studies of alkanes liquids.12 The $\sigma$ and $\epsilon$ for carbon disulfide were taken from Tilley and Madden.10

In addition to performing calculations with these potentials, we have also examined the case in which all the Lennard-Jones site-site potentials are replaced by the corresponding WCA repulsive site-site potential.12 We call the interaction model with the full Lennard-Jones potentials model A, and we use model B to denote the case with the WCA repulsive potentials.

Our results for $\Delta_{\text{act}}^*$ are plotted in Figure 1. As mentioned in the Introduction, we find that $\Delta_{\text{act}}^*$ is an increasing function of pressure for both interaction models whether the free energy is estimated from eq 6 or from eq 7.

Among the earlier studies of activation free energies and conformational equilibria in solution, Rossky and co-workers12 have also employed the extended RISM theory and eq 6. Their results compared with simulation in a variety of circumstances have always indicated that this theory correctly predicts all qualitative trends. Further, their examination of isomerization, in particular, shows that the errors that do exist in the RISM


Figure 1. The solvent contribution to the activation free energy for cyclohexane isomerization in liquid C2S as a function of pressure. The four lines are computed as described in the text for two different models, A and B, and with two different equations for the free energy, (6) and (7).
theory are always in the direction of overestimating magnitudes of solvation effects. In each case examined herein, the theory predicts a small solvation effect and one that increases slightly with pressure. Therefore, in light of these observations, it seems safe to conclude that the activation barrier for cyclohexane isomerization in liquid CS₂ is an increasing function of solvent pressure or density, and the corresponding transition-state theory rate constant is a decreasing function of pressure. And thus, for this unimolecular reaction must increase with increasing pressure.

We remark that we have also examined several other simple solvents including argon modeled as a Lennard-Jones fluid. In every case

$$
(\partial \Delta \mu^*/\partial p)_p > 0
$$

(10)

In light of our results, the study of cyclohexane in gaseous SF₆ by Ross and True²⁰ should be mentioned. This work is cited in ref 5 as experimental evidence that the Lindemann regime of the cyclohexane isomerization does not extend beyond 2–5 atm pressures, and that the increasing rate at several kilobars measured in the liquid phase by Hasha et al.⁴ is due to static effects. This apparent contradiction to our findings should be questioned for two reasons: First, it is not obvious that Ross and True's data depict the functional form assumed in ref 5—a linearly increasing rate at low pressures crossing over to a region of zero slope; other monotonically increasing functions of pressure could fit the data, and, in fact, the smallest values of d ln k/ dp that can be confidently extracted from the gas-phase work are all positive and at least 10² times larger than those observed by Hasha et al.⁴ for the liquid. Second, Borkovec et al.²¹ have recently suggested that the Lindemann regime is not characterized by a simple linear increase of rate with pressure but displays more complicated behavior reflecting competition between time scales for energy transfer from solute to solvent and intramolecular vibrational energy relaxation within the solute.

In all experiments to date,⁴,²⁰ the cyclohexane isomerization rate is observed to increase with pressure. As a result of our findings for the equilibrium contribution to the rate, the experimental observation seems best explained as a dynamical effect requiring time correlation function calculations of the transmission coefficient.

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