Acknowledgment. This work was supported by National Science Foundation Grant CHE 77-01585. We thank Mr. Don Schifferl for invaluable assistance with NMR studies.

References and Notes

(1) G. C. Demitras and E. L. Muetterties, *J. Am. Chem. Soc.*, **99**, 2796 (1977).

(2) E. L. Muetterties, *Bull. Soc. Chim. Belg.*, **84**, 959 (1975), and references therein.

(3) C. P. Casey and S. M. Neumann, *J. Am. Chem. Soc.*, **98**, 3595 (1976).

(4) A. N. Nesmeyanov, K. N. Anisimov, N. E. Kolobova, and L. L. Krasnoslobodskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 860 (1970).

(5) R. P. Stewart, N. Okamoto, and W. A. G. Graham, *J. Organomet. Chem.*, **42**, C32 (1972).

(6) P. M. Treichel and R. L. Shubkin, *Inorg. Chem.*, **6**, 1329 (1967).

(7) L. J. Guggenberger and F. N. Tebbe, *J. Am. Chem. Soc.*, **98**, 4137 (1976).

(8) P. C. Wailes and H. Weigold, *J. Organomet. Chem.*, **24**, 413 (1970).

(9) J. Schwartz and J. A. Labinger, *Angew. Chem., Int. Ed. Engl.*, **15**, 333 (1976).

(10) J. C. Huffman, J. G. Stone, W. C. Krusell, and K. G. Caulton, *J. Am. Chem. Soc.*, **99**, 5829 (1977).

(11) J. M. Manriquez, D. R. McAlister, R. D. Sanner, and J. E. Bercaw, *J. Am. Chem. Soc.*, **98**, 6733 (1976).

(12) L. I. Shoer and J. Schwartz, *J. Am. Chem. Soc.*, **99**, 5831 (1977).

(13) J. A. Labinger, *Adv. Chem. Ser.*, in press.

(14) Because of its extreme air sensitivity (pyrophoric) and solubility properties (insoluble in all organic solvents; soluble in strong aqueous acid) this precipitate has not been fully characterized but appears to be some sort of polymeric niobium oxide species.

(15) Gas mixtures were analyzed qualitatively by mass spectrometry and gas chromatography (Porapak column) and estimated quantitatively from gas chromatographic peak intensities.

(16) A similar degradation of Cp rings to smaller hydrocarbons has been reported in the thermal decomposition of $Cp_2Ti(CD_3)_2$ at temperatures comparable with those employed here: H. G. Alt, F. P. Di Sanzo, M. D. Rausch, and R. C. Uden, *J. Organomet. Chem.*, **107**, 257 (1976).

(17) Reaction followed in benzene at 20 °C, using a kinetics program for a Varian XL-100 spectrometer. Under these conditions the peak assigned to the formyl intermediate reached a maximum (~20% of total Nb concentration from peak intensity) after ~4 min and then began to decrease; the reaction was ~90% complete after 10 min.

(18) Crystal data and refinement results: monoclinic; $a = 7.819$ (3), $b = 13.481$ (2), $c = 15.135$ (2) Å; $\beta = 97.05$ (2)°; space group $P2_1/c$; $Z = 4$; $R_1 = 0.033$, $R_2 = 0.042$; 3063 unique observed data. All atoms including hydrogen were located.

(19) Key structural parameters: Nb–Fe, 3.318 (1), Nb–H, 1.91 (3), H–Fe, 1.61 (3) Å; Nb–H–Fe, 141 (2)°. Details of the structure will be discussed in a subsequent publication.

Jay A. Labinger,* Kwai Sam Wong, W. Robert Scheidt
Department of Chemistry, University of Notre Dame
Notre Dame, Indiana 46556

Received February 2, 1978

Ab Initio Calculation of the Free Energy of Liquid Water

Sir:

We report herein the first fully ab initio calculation of the free energy of a molecular liquid. The system is liquid water at 25 °C and a density of 1 g/cm^3. The computational method employed is statistical thermodynamic Monte Carlo computer simulation based on an intermolecular potential function representative of quantum mechanical calculations on the water dimer.

Ab initio theoretical calculations of the thermodynamic internal energy and average quantities such as radial distribution functions have been reported for liquid water from several laboratories. Computer simulations based on the analytical potential function developed by Matsuoka, Clementi, and Yoshimine[1] and representative of moderately large ab initio intermolecular configuration interaction calculations are found to produce oxygen-oxygen radial distribution functions in close accord with experiment at 25 °C.[2,3] The calculated internal energy, -8.58 ± 0.06 kcal/mol, may be compared with the corresponding observed value of -9.9 kcal/mol.[4] The discrepancy of 1.3_2 kcal/mol is ascribed to the assumption of pairwise additivity in the configurational energy calculations and limitations in the intermolecular potential function due to truncation errors in the configuration interaction basis set and truncation errors in the orbital basis set expansion in the quantum mechanical data base of pairwise interaction energies. A detailed theoretical analysis of the structure of liquid water using Monte Carlo computer simulation based on this function has been contributed previously from this laboratory.[3]

The ensemble average expression for free energy is not convenient for computational procedures owing to the ill-conditioned nature of the integrand and concommitant convergence problems.[5] The various possible computational approaches to free energy considered to date have been recently reviewed by Valleau and Torrie,[6] who have discussed the theoretical or computational limitations of each method. The procedure used herein follows Kirkwood,[7,8] wherein the Helmholz configurational free energy A is given by

$$A = \int_0^1 U(\xi)\mathrm{d}\xi \qquad (1)$$

Here the integrand $U(\xi)$ can be expressed as an ensemble average,

$$U(\xi) = \int \cdots \int E(\mathbf{X}^N)P(\mathbf{X}^N/\xi)\mathrm{d}\mathbf{X}^N \qquad (2)$$

where $E(\mathbf{X}^N)$ is the configurational energy and $P(\mathbf{X}^N, \xi)$ is the probability of observing the system in configuration $\mathbf{X}^N$, conditional upon the auxiliary parameter ξ,

$$P(\mathbf{X}^N/\xi) = \frac{\exp[-\beta E(\mathbf{X}^N, \xi)]}{\int \cdots \int \exp[-\beta E(\mathbf{X}^N, \xi)]\mathrm{d}\mathbf{X}^N} \qquad (3)$$

with β representing $(kT)^{-1}$. When the auxiliary parameter serves to couple the system according to the expression

$$E(\mathbf{X}^N, \xi) = \xi E(\mathbf{X}^N) \qquad (4)$$

the free energy is defined with respect to an ideal gas reference state of liquid density and is equivalent to the general class of "thermodynamic integrations" for free energy,[6] the main disadvantages of which stem from problems in the integration over ξ. The simple extra computational effort required may be complicated by convergence problems for small ξ and possible discontinuities in $U(\xi)$.

In view of the central importance of liquid water in the chemistry and physics of liquids we have proceeded with Monte Carlo calculations of the free energy of liquid water based on eq 1–4 despite the problems outlined above. The computational labor may be kept down by keeping the number of particles explicitly considered to a minimum and effecting the integration over ξ by a low order numerical quadrature.

The $U(\xi)$ in this calculation were determined by canonical ensemble Monte Carlo Metropolis[10] computer simulation on 64 molecules treated under periodic boundary conditions in the minimum image convention.[11] A spherical cutoff at half the cell edge was applied to the potential function. In previous studies it has been found that simulations based on 64 particles give essentially the same results for internal energy as those with 0(125) particles,[2,3] the number used when further detail is required on structure. Convergence criteria and statistical error bounds were established using control functions.[12] Convergence to the correct result was established for $N = 125$ by carrying out two independent calculations on the worst case ($\xi = 1$), one beginning from an initial configuration near the minimum of energy for the ensemble and one beginning at a very high energy configuration. The calculation converged to the same result well within the quoted error bounds, and agreed with the results of Clementi et al. obtained from an independent computer program and different initial guess. Thus we feel we have not encountered any practical nonergodicities.

The Monte Carlo calculations of $U(\xi)$ involved surprisingly few difficulties. The $U(\xi)$ for each of the 8 points converged

0002-7863/78/1500-3255$01.00/0

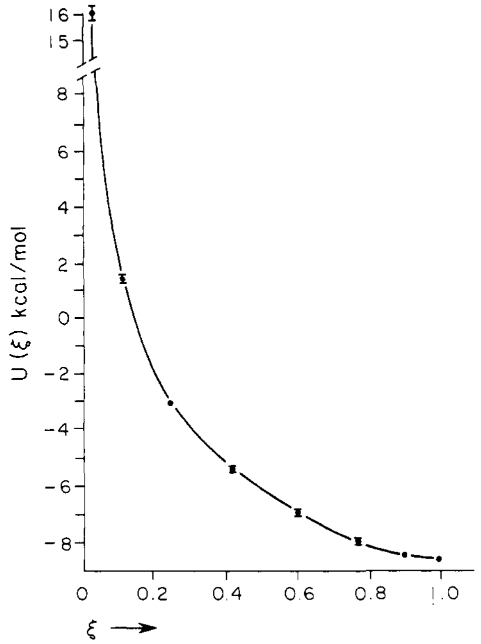


Figure 1. Calculated $U(\xi)$ vs. ξ for liquid water.

to ∼1% within 500 K Metropolis steps. Each point required 100 K bytes of core and 4 h of computer time on the IBM 370/168 machine. A plot of $U(\xi)$ vs. ξ, including error bounds on each calculated point, is shown in Figure 1. The observed smoothness of the function can be understood by considering ξ as a temperature weighting factor and the ξ coordinate as a transcritical tieline. The integration over ξ was carried out by means of an 8-point Gaussian integration.[13]

The free energy was calculated directly from the integration over ξ and the entropy of the system was calculated using the free energy and the previously determined internal energy of the system. The results were found to be the following. Free energy: calculated, -4.31 ± 0.07; observed,[4] -5.74 kcal/mol. Entropy: calculated, -14.33 ± 0.09; observed[4] -13.96 cal/deg mol.

A comparison of the calculated and observed values shows the discrepancy between the calculated and observed free energy to be closer to that found for internal energy alone, and is thus ascribed to same reasons as enumerated above. The close accord between calculated and observed values of entropy indicates the statistical part of the problem to be well described under the assumption of pairwise additivity for this particular system, but further study on this point is required before any generalizations may be set forth.

Acknowledgment. This research was supported by NIH Grant 1-R01-NS12149 and Research Career Development Award (D.L.B.) 6T-K04-GM21281.

References and Notes

(1) O. Matsuoka, E. Clementi, and M. Yoshimine, *J. Chem. Phys.*, **64**, 1351 (1976). The MCY-CI potential function as used herein was augmented with an r^{-12} term joined smoothly to the short range region so that the function was defined on all intermolecular separations.
(2) G. C. Lie, E. Clementi, and M. Yoshimine, *J. Chem. Phys.*, **64**, 2314 (1976).
(3) S. Swaminathan and D. L. Beveridge, *J. Am. Chem. Soc.*, **99**, 8392 (1977). The calculated and observed values for *U* quoted in this reference differ by a factor of 3*RT* from those reported herein.
(4) G. N. Sarkisov, V. G. Dashevsky, and G. G. Malenkov, *Mol. Phys.*, **27**, 1271 (1974).
(5) J. C. Owicki and H. A. Scheraga, *J. Am. Chem. Soc.*, **99**, 7403 (1977).
(6) J. P. Valleau and G. M. Torrie in "Modern Theoretical Chemistry: Statistical Mechanics", Part A, B. J. Berne, Ed., Plenum Press, New York, N.Y., 1977. See also J. C. Owicki and H. A. Scheraga, *J. Phys. Chem.*, in press.
(7) J. G. Kirkwood, in "Theory of Liquids", B. J. Alder, Ed., Gordon and Preach, New York, N.Y., 1968.
(8) D. A. McQuarrie, "Statistical Mechanics", Harper and Row, New York, N.Y., 1976.
(9) For a related work on ion–water clusters, see M. R. Mruzik, F. F. Abraham, D. E. Schreiber, and G. M. Pound, *J. Chem. Phys.*, **64**, 481 (1976).
(10) N. Metropolis, A. W. Rosenbluth, M. N. Rosenbluth, A. H. Teller, and E. Teller, *J. Chem. Phys.*, **21**, 1087 (1953).
(11) F. Kohler, "The Liquid State", Crane Russack, 1972, Chapter 3.
(12) W. W. Wood in "Physics of Simple Liquids", H. N. V. Temperley, F. S. Rowlinson, and G. S. Rushbrooke, Ed., North-Holland Publishing Co., Amsterdam, 1968, pp 116–230.
(13) K. J. Nielsen, "Methods in Numerical Analysis", MacMillan, New York, N.Y., 1964.

Mihaly Mezei, S. Swaminathan, David L. Beveridge*
Chemistry Department
Hunter College of the City University of New York
New York, New York 10021
Received November 8, 1977

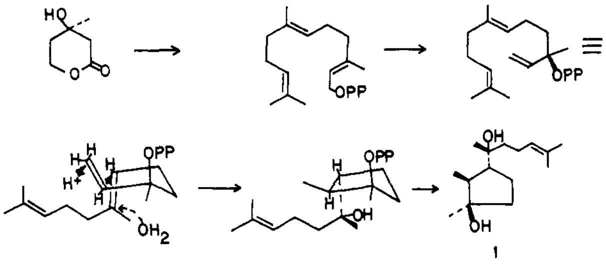
Conversion of Farnesyl and Nerolidyl Pyrophosphate to Cyclonerodiol by a Cell-Free Extract from *Gibberella fujikuroi*

Sir:

Biosynthetic incorporation experiments carried out in our laboratory[1] and that of Hanson[2] have established the mevalonoid origin of the fungal metabolite cyclonerodiol (**1**)[3] and suggested a biosynthetic pathway in which a molecule of water adds across the central double bond and the vinyl group of nerolidyl pyrophosphate, formed by the isomerization of farnesyl pyrophosphate. The proposed scheme (Scheme I) is further corroborated by the apparent conversion of farnesyl pyrophosphate to **1** by cultures of *Trichothecium roseum.*[2] On the other hand the failure of *T. roseum* to incorporate nerolidol itself has led the Sussex group to postulate an alternative cyclization mechanism involving the intermediacy of a cyclopropyl cation. We have independently observed that neither nerolidol, when fed to cultures of *Gibberella fujikuroi,* nor nerolidyl pyrophosphate, when administered to *T. roseum,* is incorporated into cyclonerodiol. On the assumption that the above negative results might be due in part to permeability problems with the intact organism, we have turned our attention to developing a suitable cell-free system. We report below the successful conversion of both nerolidyl and farnesyl pyrophosphates to cyclonerodiol by cell-free extracts of *G. fujikuroi.*[4]

The mycelium from a four-day-old culture of *G. fujikuroi,* ATCC 12616 (1 L), grown in the usual manner,[1,3] was harvested by filtration and washed with several volumes of cold distilled water, followed by 0.1 M sodium phosphate buffer, pH 7.6. The wet mycelium (52–57 g), suspended in 15 mL of phosphate buffer containing 2 mM DTE, was then passed through a precooled French Press under 10 000–15 000-psi pressure. After addition of 5 mL of phosphate/DTE buffer to the crushed cell mass, the suspension was centrifuged for 20 min at 15 000 g to remove cell debris. The supernatant fraction (S_{15}) was recentrifuged at 27 000 g for 60 min, the resulting cloudy S_{27} being filtered through a plug of glass wool to remove floating lipid. All centrifugations were carried out at 0–4 °C

Scheme I



1