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Conformational Preferences of Phosphodiester Torsion Angles in Dimethylphosphate Anion in Free Space and Water: Quasi-Harmonic Monte Carlo and Hydration Shell Calculations

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Monte Carlo determinations of the intramolecular thermodynamics of dimethylphosphate anion in free space, with the phosphodiester torsion angles in the gauche–gauche, gauche–trans, and trans–trans conformations, are reported. The configurational entropies are estimated in the quasi-harmonic approximation. The free energies of hydration are evaluated through the solvation shell model. The net relative conformational free energies indicate that the phosphodiester torsion angles favor the gauche–gauche conformation, with the extended forms and, in particular, the gauche–trans form possibly thermally accessible at ambient temperature. The results are generally in accord with experimental data on this system.

I. Introduction

Phosphodiester torsion angles (α, ζ)[1] comprise an important set of conformational coordinates of the nucleotide backbone of nucleic acids. Three conformations, gauche–gauche (gg), gauche–trans (gt), and trans–trans (tt), are found to be significant for the phosphodiester torsions from both experimental and theoretical studies (ref 2 and references therein). Dimethylphosphate anion (DMP⁻), shown in Figure 1 in the gg, gt, and tt conformations, is one of the simplest model compounds exhibiting the α, ζ torsional degrees of freedom. The background literature on the structural chemistry of DMP⁻ is reviewed extensively in a previous publication.[2] The present study is aimed at determining the conformational preferences of DMP⁻ in free space and in aqueous solutions.

The statistical mechanical treatment of conformational analysis of macromolecules is traditionally based on the idea that conformational transitions are largely governed by the torsional degrees of freedom and vibrational modes around the torsional minima on the potential energy surface. Attempts were made in the past,[3] with various constraints on the solute geometry, to estimate the contribution of the vibrational partition function to intramolecular thermodynamics of conformational changes. A method to estimate the configurational entropies through computer simulations was proposed by Karplus and Kushick[4] and this was further extended to compute the vibrational frequencies in the quasi-harmonic approximation by Levy et al.[5] The methodology for determining the intramolecular thermodynamics by Monte Carlo methods in the quasi-harmonic approximation was illustrated by Ravishanker et al.[6] in an application to the conformational problem in alanine dipeptide.[6,7] The solvation shell model originally proposed by Scheraga and co-workers[8-10] and further elucidated by Hopfinger[11,12] is an empirical scheme to evaluate solvation free energies and is particularly suited for studying the relative conformational free energies of hydration. We report herein studies on the conformational preferences of phosphodiester torsion angles in dimethylphosphate anion in free space and water.

II. Theory and Methodology

Intramolecular Thermodynamics. The intramolecular thermodynamics of the dimethylphosphate anion were determined by

a Monte Carlo calculation on the intramolecular degrees of freedom with entropies evaluated in the quasi-harmonic approximation. The configurational internal energy for the intramolecular modes of motion in the vicinity of a local minimum is computed by numerical integration as the average value

$$U_i^{\text{intra}} = \langle E(\mathbf{q})\rangle \qquad \mathbf{q} \in i$$

where $E(\mathbf{q})$ is the intramolecular potential energy as a function of the $\mathbf{q}$ internal degrees of freedom and the brackets denote a Boltzmann configurational average in $\mathbf{q}$ space. The energy function $E(\mathbf{q})$ is evaluated from an analytical force field. For entropies the procedure[4] is based on an effective potential of the form

$$V(\mathbf{q}) = (1/2)\mathbf{q}\cdot\mathbf{F}^{\text{QH}}\cdot\mathbf{q}$$

with the elements of the force constant matrix F^{QH} given by the expression

$$F_{kl} = k_{BT}[\sigma^{-1}]_{kl}$$

where σ is the covariance matrix of the internal coordinate fluctuations

$$\sigma_{kl} = \langle(q_k - \langle q_k\rangle)(q_l - \langle q_l\rangle)\rangle$$

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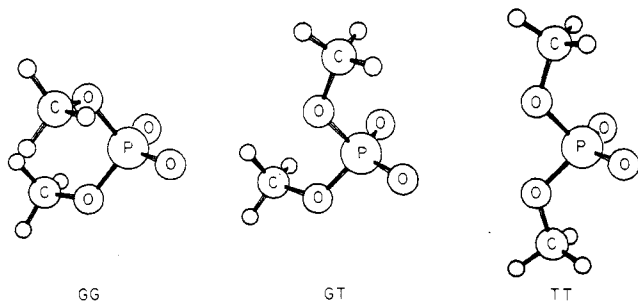
Figure 1. Molecular structure of dimethylphosphate anion in gauche-gauche (GG), gauche–trans (GT), and trans–trans (TT) conformations.

TABLE I: Calculated Vibrational Frequencies of DMP⁻ (in cm⁻¹)

	tt	gt	gg	from ref 17
>PO₂⁻ asym str	1213	1220	1232	1225
>PO₂⁻ sym str	1062	1082	1074	1086
C–O asym str	1043	1057	1041	1055
C–O sym str	1032	1022	1014	1040
>PO₂ asym str	747	827	876	813
>PO₂ sym str	772	738	707	750
bends & torsions	631	599	597	564
	554	560	551	523
	486	475	428	487
	438	410	408	390
	335	360	388	
	324	326	311	260
	174	217	234	222
	122	122	162	
	87	103	102	

Assuming that the differences in the Jacobian evaluated at the two equilibrium conformations i and j are negligible, the quasi-harmonic conformational entropy difference is given by

$$\Delta S^{\text{int}} = (1/2)k_{\text{B}} \ln (\sigma_i / \sigma_j)$$

where

$$\sigma_i = \det (\sigma) \qquad \sigma \in i$$

for displacements in the vicinity of the ith conformation. The relative internal energies and free energies follow straightforwardly from

$$\Delta U_{ij}^{\text{int}} = J_j^{\text{int}} - U_i^{\text{int}}$$

and

$$\Delta A_{ij}^{\text{int}} = \Delta U_{ij}^{\text{int}} - T\Delta S_{ij}^{\text{int}}$$

Full details of the calculations as carried out here are described in ref 6. The initial geometries for dimethylphosphate anion are similar to those of Alagona et al.[13,14] and identical with the values adopted by Newton[15] and are based on UpA crystal studies. The potential energy function used in the present calculations is that of Kollman and co-workers.[14] The intramolecular internal energies for the starting configurations of gg and gt conformations of DMP⁻ are seen to agree with the values reported in Table IV of ref 14. In a quasi-harmonic molecular simulation, the force constant matrix can be used in a Wilson FG procedure for normal mode analysis. A check on the force field employed is performed by calculating the quasi-harmonic force constant

$$F^{\text{QH}} = k_{\text{B}}T[\sigma]^{-1}$$

and solving the secular equation

$$|\mathbf{GF}^{\text{QH}} - \lambda\mathbf{I}| = 0$$

for the vibrational frequencies ($\lambda = 4\pi\nu^2$). The calculated and the experimental[16,17] vibrational frequencies are collected in Table

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TABLE II: Calculated Thermodynamic Quantities for the gg, gt, and tt Conformations of DMP⁻ Relative to tt[a]

	tt	gt	gg
Intramolecular			
ΔU^{int}	0.0	−0.98 ± 0.07	−1.88 ± 0.13
$-T\Delta S^{\text{int}}$	0.0	0.11 ± 0.04	0.28 ± 0.28
ΔA^{int}	0.0	−0.87 ± 0.08	−1.60 ± 0.31
Intermolecular[b]			
ΔA^{hyd} (>PO₂⁻)	0.0	−1.40	−1.77
ΔA^{hyd} 2(−O−)	0.0	0.84	1.01
ΔA^{hyd} 2(−CH₃)	0.0	−0.17	−0.31
ΔA^{hyd} (DMP⁻)	0.0	−0.73	−1.07
Total: Intramolecular + Intermolecular			
ΔA	0.0	−1.60	−2.67

[a] All entries are in kcal/mol. Error bounds are reported as ±2σ as determined by the method of batch means. *[b]* Error estimates in the solvation shell model are not known.

I. Results indicate reasonable agreement between the theoretical predictions and experiment.

Hydration Free Energies. The hydration free energy estimates are based on the superposition approximation

$$\Delta A^{\text{hyd}} = \sum_i \Delta A_i^{\text{hyd}}$$

where ΔA_i^{hyd} is the Helmholtz free energy of hydration of atom/functional group i and the summation over i extends over all solute atoms/functional groups

$$\Delta A_i^{\text{hyd}} = -(n_i f_i / V_i)\Delta V_i$$

Here ΔV_i is identified with the volume of exclusion due to nonbonded neighbors. The above equation in terms of the local solvent densities d_i can be expressed as

$$\Delta A_i = -f_i d_i \Delta V_i$$

The hydration free energies are computed as

$$\Delta A^{\text{hyd}} = -\sum_i f_i(n_i / V_i^{\text{hyd}})\Delta V_i^{\text{ex}}$$

with f_i values calibrated against experiment.[8] The n_i values are evaluated from energy minimization studies[9] or preferably through computer experiments conducted at appropriate density and temperature. V_i^{hyd} and ΔV_i^{ex} are computed analytically.[10,11] Hydration shell model calculations are performed on the gg, gt, and tt conformations of DMP⁻. The excluded volumes are calculated as prescribed by Hodes et al.[10] and Hopfinger.[11] Contributions from specific hydration[10] are equal for all the three conformations and do not contribute to the conformational free energy differences. Coordination numbers and radial cutoffs obtained from our previous Monte Carlo simulations (Table VIII of ref 2) on [DMP⁻]ₐq were utilized along with the free energy parameters of Hopfinger.[12] In the following we describe in sequence the results on intramolecular thermodynamics and the hydration free energy estimates.

III. Results

The calculated thermodynamic quantities for the gg, gt, and tt conformations of DMP⁻ are collected in Table II. The intramolecular free energies (ΔA^{int}) are observed to favor the gg conformation relative to gt and tt forms for the phosphodiester torsions in DMP⁻. The internal energies (ΔU^{int}) are seen to dictate the trends. The temperature-weighted entropy contributions ($T\Delta S^{\text{int}}$) are small and counter the above trends. The intramolecular free energy differences are within $3k_{\text{B}}T$. The hydration free energy (ΔA^{hyd}) results parallel the trends in ΔA^{int}. An analysis of ΔA^{hyd} in terms of functional group contributions suggests that ionic hydration plays a major role in the destabilization of the extended tt form of DMP⁻. The total relative conformational free

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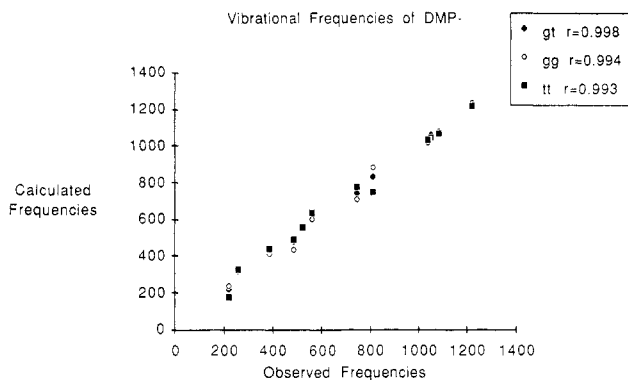(17) Garrigou-Lagrange, C.; Bouloussa, O.; Clement, C. *Can. J. Spectrosc.* **1976**, *21*, 75.

Figure 2. Linear plots of calculated vibrational frequencies of gg, gt, and tt conformations of dimethylphosphate anion shown against observed frequencies.

energies indicate a trend of gg > gt > tt for the stabilities of phosphodiester conformations. These results are consistent with conclusions based on IR and Raman studies of Shimanouchi et al.[16] and the ^{31}P NMR investigations of Gorenstein and co-workers.[18,19]

IV. Discussion

The performance of the potential function employed in the present study appears to be satisfactory particularly in the high-frequency region (Table I). The linear plots between calculated and observed vibrational frequencies, shown in Figure 2, indicate that an unambiguous identification of the solution conformation is not feasible from the calculated vibrational spectrum. The conformational analysis of DMP⁻ based on depolarized Rayleigh scattering and IR and Raman spectra by Garrigou-Lagrange et al.[17] suggested that extended rotational isomeric states (tt and gt) of DMP⁻ in water were highly populated. Shimanouchi et al.[16] through their normal mode analysis established the asymmetric stretch of the phosphodiester group (>PO$_2$) as a fingerprint zone for identifying the phosphodiester conformations. The gg conformation with C_2 symmetry was predicted to have a higher frequency for the asymmetric stretch (>PO$_2$ asymmetric stretch) relative to the symmetric stretch while the tt conformation with C_{2v} symmetry was predicted to give a higher frequency for the symmetric stretch (>PO$_2$ symmetric stretch). On the basis of this and the Raman spectrum, they concluded that the solution conformation was predominantly the gg form. The calculated frequencies here support their conclusions.

The intramolecular free energies of DMP⁻ are dominated by the internal energy contributions wherein the gg form emerges as the most stable conformation. The stability of the gg conformer in free space is generally attributed to anomeric effects,[1] and this bias is already built into the force field through the dihedral term. The configurational averaging performed here in the vicinity of

the local minima has not altered the trends in internal energies. The calculated entropies make no significant contribution to the conformational trends. It may be recalled that similar observations were made on configurational entropy contributions in the quasi-harmonic approximation for both alanine dipeptide and butane.[6,20]

The hydration shell model assumes a linear relationship between free energy changes due to hydration and changes in accessible volumes due to the encroachment of nonbonded neighbors into the hydration shell. Conformational trends in the hydration free energies as evaluated through this model are sensitive to the coordination numbers. For instance the coordination number for ester oxygens is assigned as 2 (ref 12) while in nucleic acids the hydrophilic hydration of ester oxygens seldom exceeds one water per ester oxygen. Thus if the parameter set given in ref 11 is used entirely, the hydration free energies relative to tt are 0.29 kcal/mol for gt and 0.59 kcal/mol for gg conformation. This trend is due to an unrealistically large emphasis given to the hydration of ester oxygens which stabilizes to a minor extent the fully extended tt form, the contribution from ionic hydration being equal for all the three conformations. Computer simulations within the hydration shell model come into play in handling the coordination numbers and in defining the first shell radii more accurately. Similar in spirit to the solvation shell model to incorporate solvent effects is the Gurney parameter approach of Ramanathan and Friedman.[21] Ben-Naim following a different theoretical route in the context of hydrophobic interactions finds the $P\Delta V$ approximation for solvation free energies of macromolecules justified.[22] A recalibration of the parameters for nucleic acid constituents should improve the reliability of the hydration shell model conclusions.

The hydration free energies of DMP⁻ favor the gg conformation relative to gt and tt. The conformational differences are however small. Interestingly the trends in hydration free energies arrived at through the hydration shell model here are consistent with the independent predictions of concentric dielectric continuum calculations[23] and free energy simulations[24] on [DMP⁻]$_{aq}$ from this laboratory.

The net relative conformational free energies are evaluated under the assumption of separability of intra- and intermolecular contributions. The gg conformation of DMP⁻ is predicted to be the most stable conformer for the phosphodiester torsion angles in both free space and water. The magnitude of the free energy differences however suggests that the extended forms and in particular the gt form may be thermally accessible to some extent at ambient temperatures.

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