Ab Initio Studies of the Exocyclic Hydroxymethyl Rotational Surface in α-D-Glucopyranose

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Received August 15, 1995[⊗]

Abstract: The potential energy surface for rotation of the exocyclic hydroxymethyl group of α-D-glucopyranose has been studied using *ab initio* quantum mechanical methods. Relevant stationary points, including for the first time rotational transition states, have been characterized by full geometry optimization using basis sets ranging in quality from 6-31G(d) to 6-311(2d,1p). Effects of dynamical electron correlation on both the geometric structures and the energy surface are also investigated using second-order Møller−Plesset perturbation theory (MP2) and density functional methods (BLYP). A total of six stationary points along the hydroxymethyl rotational surface, including three minima and three transition states, were identified. The effects of basis set augmentation and electron correlation on the relative energies are small; the relative energies for each stationary point vary by less than 5 kJ mol^{-1} for all levels of theory considered. Final energetic barriers to hydroxymethyl rotation ranged from 15 to 29 kJ mol^{-1}. Differences between these barriers and previously reported *ab initio* results on a carbohydrate model compound, 2-(hydroxymethyl)tetrahydropyran, as well as energies calculated using force field methods, are discussed.

Introduction

Carbohydrates are ubiquitous in biological systems and play an important role in many biochemical processes. Aside from their critical role in energy metabolism pathways, carbohydrates are also important in recognition processes as components of glycopeptides and glycolipids. Understanding these recognition processes through a characterization of the interactions between carbohydrates and other biological molecules has become an area of intense research interest, especially for computational biochemists. The size of most biologically relevant carbohydrate systems precludes the use of rigorous quantum mechanical methods; consequently, most computational studies to date aimed at exploring carbohydrate−protein interactions have relied on classical mechanics. An important requirement of such force field based methods is that the computed energies of various conformers accurately reproduce the true conformational energy surface for molecules of interest. Accurate description of the complete conformational surface for even the simplest of monosaccharides, including the quintessential monosaccharide glucopyranose (glucose), is, however, a formidable task given the size of the system and the large number of conformational degrees of freedom. A nearly complete description of glucose has been reported using force field techniques;[1] however, only select features of the complete surface have been characterized using more accurate *ab initio* methods. Despite the complexity of the problem, conformational analysis of prototype carbohydrates has been an active area of theoretical[2−9] and experimental[10,11] research for many years. Quantitative characterization of the conformational surface of simple monosaccharides like glucopyranose is a necessary first step to quantitatively model complex biological systems containing carbohydrates.

A particularly critical region of the glucopyranose conformational surface relates to rotation of the exocyclic hydroxymethyl group. This region of the conformational hypersurface has been studied both experimentally and theoretically for related model systems[12] and for glucopyranose itself.[1−5,9−11] Polavarapu and Ewig[5] reported the first *ab initio* study of the various minimum energy exocyclic hydroxymethyl conformers for isolated molecules of D-glucopyranose. Cramer and Truhlar[4] later performed a thorough study of D-glucopyranose comformers using semiempirical methods with solvation and found that the energetics for the minimum conformations of the hydroxymethyl rotational surface are not significantly perturbed by solvation. Salzner and Schleyer[3] reported the conformation of the exocyclic hydroxymethyl group had no effect on the relative energies of the α- and β- anomers at the HF/6-31G(d) level of theory, in agreement with the earlier work by Polavarapu and Ewig[5] at the HF/4-31G level. Glennon *et al.*[2] performed the most extensive computational study of mono- and disaccharides to date, focusing on conformers of α-D-glucopyranose. Three minimum conformations were found along the exocyclic hydroxymethyl rotational surface designated GG, GT, and TG, each separated by approximately 120° dihedral rotation. The relative energy differences between conformers was found to

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⊗ Abstract published in *Advance ACS Abstracts,* January 15, 1996.

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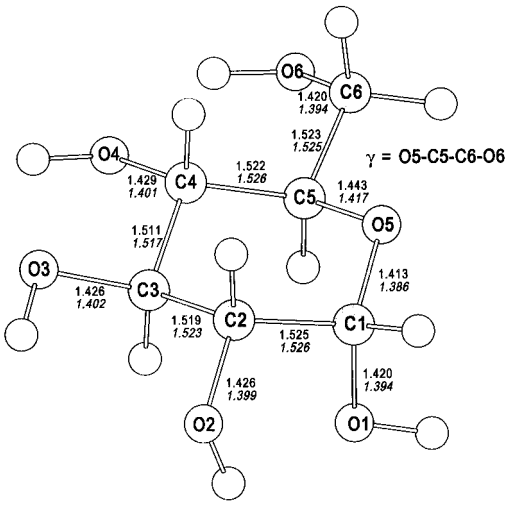

Figure 1. TG conformation of α-D-glucopyranose with appropriate atom labels. Bond distances (Å) are those obtained at the MP2 6-31G(d) and RHF 6-31G(d) (italics) levels of theory.

be small (<4 kJ mol^{-1}) and somewhat basis set dependent.[2] Although the work by Glennon *et al.* represents an excellent first step toward the complete characterization of the various glucopyranose conformers, their computational results are limited to the Hartree−Fock level with modest size basis sets (6-31G(d)). Recently, Barrows *et al*. have reported the most extensive *ab initio* study of any glucopyranose, employing basis sets exceeding the cc-pVTZ level of theory to study the TG and GT conformations of the two chair forms of *β*-D-glucopyranose.[9]

Although the minima of the exocyclic hydroxymethyl rotational surface have been studied extensively, no previous theoretical work has addressed any aspect of the rotational transition states connecting these minima. The energetics of rotation in simple monosaccharides is not only an interesting physical chemical problem but also has implications for understanding the conformational equilibria and solvation of carbohydrates, as well as for force field parametrization. Aside from issues related specifically to carbohydrates, these systems also represent an interesting example of molecules with strong intramolecular interactions. The magnitude of intramolecular effects and the way in which they perturb rotational energy hypersurfaces is important when considering the structure and energetics of such molecules. In this article we report *ab initio* quantum chemical results on various rotational conformers of α-D-glucopyranose (Figure 1) to characterize quantitatively, for the first time, the complete intrinsic gas-phase exocyclic hydroxymethyl rotational surface.

Computational Model

Structures, relative energies, and vibrational frequencies of the salient stationary points, including stable minima and the transition states connecting them, associated with rotation about the exocyclic C5−C6 bond have been determined at the restricted Hartree−Fock (RHF) and at correlated levels using basis sets ranging in quality from 6-31G(d) to 6-311G(2d,1p).[13] Effects of dynamical electron correlation on the structure and the relative energies were estimated using second-order Møller−Plesset perturbation theory (MP2)[14] and density functional methods, employing the Becke exchange functionals and Lee−Yang−Par correlation functionals (BLYP).[15] The most stable overall rotational conformation of α-D-glucopyranose, in which the hydroxyl groups at C1 through C4 are in a counterclockwise arrangement, was chosen as the reference state[16] (Figure 1), consistent with Polavarpu and Ewig[5] and Glennon *et al*.[2] Although various secondary hydroxyl substates, which will certainly be populated in solution and quite possibly could be populated in the gas phase, may perturb the relative energies of the primary alcohol conformations, only the lowest energy arrangement (determined by Polavarapu and Ewig[5]) of the C1 through C4 hydroxyls was chosen for analysis of the hydroxymethyl rotational surface. The various stationary points associated with exocyclic hydroxymethyl rotation were located by displacement of the O5−C5−C6−O6 dihedral angle in 60° increments, followed by reoptimization. Each stationary point was verified as a minimum or a transition state via analytic second derivative calculations. To ensure that each stationary point located along the C5−C6 rotational surface represents the most stable structure within the counterclockwise arrangement, the exocyclic hydroxyl rotational surface was also explored by rotation about the C6−O6 bond. Completely optimized structures were obtained for each stationary point at the RHF level using the 6-31G(d), 6-31G(2d,1p), and 6-311G(2d,-1p) basis sets and at the MP2 and BLYP level using the 6-31G(d) basis set. All calculations were performed using the Gaussian 94 electronic structure package[17] on either a Cray Y-MP4E/464 or an IBM RS 6000/590.

Results and Discussion

Figure 1 shows a three-dimensional representation of the most stable conformer of α-D-glucopyranose in the counterclockwise arrangement, designated TG (trans gauche) along with important bond distances obtained at the MP2 6-31G(d) level. Basis set expansion and electron correlation through 6-311(1d,2p) and MP2 were found to only moderately affect these structural parameters. For most bonds, including the C−O bonds and O−H bonds, basis set expansion causes a contraction (ca. 0.007 Å) while electron correlation causes bond elongation (ca. 0.02 Å), as expected. Interestingly, this trend does not hold for the C−C bonds (Figure 1). Inclusion of electron correlation through MP2 causes a slight contraction of the bonds. The reason for this is not clear, but could be a result of incorporation of charge transfer type configurations into the wave function, giving rise to an electron deficient ring at the MP2 level, or it could be a result of the limited flexibility of the 6-31G(d) basis set.

Figure 2 shows a graphical representation of the hydroxymethyl rotational energy surface at both the RHF 6-31G(d) and MP2 6-31G(d) levels. The rotational surface consists of three stable minima and three connecting transition states. Starting from the most stable rotational conformer at the RHF 6-31G(d) level, TG, in which the hydroxymethyl group is approximately parallel to the ring with a O5−C5−C6−O6 dihedral angle (γ) of 167.7, rotation about γ leads initially to structure TS1 ($\gamma = -138.1$), then to a second minimum structure GG ($\gamma = -57.8$), in which the hydroxymethyl group is roughly perpendicular to the glucopyranose ring. Continued rotation about γ leads to a second transition state, TS2 ($\gamma = -0.6$),

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(16) We refer to these orientations of the C−C−O−H torsional angles as counterclockwise (the appearance of the hydroxyl orientation when viewed from above the ring with O5 in the upper right) to be consistent with the description of α- and *β*-D-glucopyranose in previous work.

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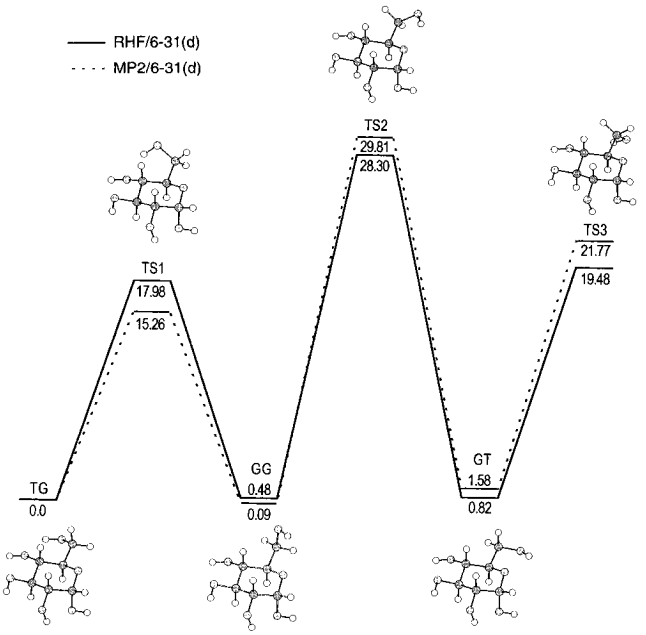

Figure 2. Relative energy diagram (kJ mol^{-1}) at the RHF 6-31G(d) (solid line) and MP2 6-31G(d) (dashed line) levels of theory for the stationary points along the exocyclic hydroxymethyl rotational surface of α-D-glucopyranose. The internal coordinate γ is defined as the O6−C6−C5−O5 dihedral angle.

Table 1. Relative Energies, ΔE, for Conformations of α-D-Glucopyranose (kJ mol^{-1})

conformer[a]	6-31G (d) RHF	6-31G (2d,1p) RHF	6-311G (2d,1p) RHF	6-31G(d) RB-LYP	6-31G(d) MP2
TG (167.7)	0.0[b]	0.0[b]	0.0[b]	0.0[b]	0.0[b]
TS1 (−138.1)	17.98	17.51	17.50	13.33	15.65
GG (−57.8)	0.48	−0.13	−0.68	2.04	0.09
TS2 (−0.6)	28.30	27.49	27.74	26.90	29.81
GT (58.7)	0.82	0.25	−0.16	3.40	2.36
TS3 (108.2)	19.48	18.35	17.26	20.75	21.77

[a] Values in parentheses are the O5−C5−C6−O6 dihedral angles of the MP2 optimized geometries. [b] Absolute energies for the TG conformation, in hartrees, are −683.334048, −683.400878, −683.559810, −686.944381, and −685.180845 for RHF 6-31G(d), RHF 6-31G(2d,1p), RHF 6-311G(2d,1p), RB-LYP 6-31G(d), and MP2 6-31G(d) calculations, respectively. The TG conformer was defined as zero by convention.

followed by a third minimum, GT ($\gamma = 58.7$). Further rotation about γ leads back to the initial structure TG through a third transition state, TS3 ($\gamma = 108.2$). Aside from slight variation in the C5−C6 bond distance between each minimum and their associated rotational transition states due to electron−electron repulsion, the overall structures of the various rotational conformers are very similar, with the orientation of the primary hydroxyl group as the only exception.

Tables 1 and 2 list the relative energetic data for each stationary point on the rotational surface at various *ab initio* computational levels along with relative strain energies calculated using Glennon *et al.*[2] and Homans[18] parametrizations of the AMBER force field, as implemented in the Discover software package (Biosym Technologies, San Diego, CA). The relative energetic data for each stationary point are only modestly influenced by basis set augmentation over the range 6-31G(d), 6-31G(2d,1p), to 6-311G(2d,1p), with shifts of less than 3 kJ mol^{-1} overall. The effect of electron correlation on the relative energetics is slightly larger, with shifts of up to 6 kJ mol^{-1} between the RHF and MP2 or BLYP results using the same basis set. Despite these modest shifts in the relative

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Table 2. Corrected Energies and Force Field Strain Energies for Conformations of α-D-Glucopyranose (kJ mol^{-1})

				AMBER	
conformer	$\Delta(E +$ ZPVE)[a]	$\Delta H°_g$[b]	$\Delta G°_g$[b]	Homans[c]	Glennon et al.[c]
TG	0.0	0.0	0.0	0.0 (0.0)	0.0 (0.0)
TS1	15.21	13.40	17.36	15.98	12.05
GG	−0.59	−0.25	−1.01	−10.46 (−12.64)	−4.23 (−4.89)
TS2	27.71	26.99	28.44	−1.76	3.26
GT	1.48	1.91	0.94	−14.69 (−15.27)	−4.35 (−4.94)
TS3	20.05	18.63	17.36	7.66	21.71

[a] Corrections are added to the 6-31G(d) MP2 energy. Zero-point vibrational energy (ZPVE) corrections were calculated from harmonic vibrational frequencies determined at the RHF 6-31G(d) level and scaled by a factor of 0.89 in accord with known overestimates at this level. [b] $\Delta H°_g = \Delta(E + \text{ZPVE}) + \Delta C_pT$ and $\Delta G°_g = \Delta H°_g + T\Delta S°_g$ are the relative gas-phase enthalpy and free energy, respectively. [c] Relative energies based on strain energies determined from single-point calculations using the indicated force field parametrization using MP2 6-31G(d) geometries. Values in parentheses are the relative energies of the force field minimized structures. Results reported here differ somewhat from those calculated by Glennon et al., where the conformers were ranked in the order TG (0.0) < GG (0.4) < GT (0.8). These differences could be due to slightly different geometries or differences in the computer programs (AMBER versus Discover).

energetics, the three minimum conformations (TG, GG, and GT) are found to be very close in energy. The relative energy difference between minimum conformers is less than 1 kJ mol^{-1} at the RHF level, with the GG conformer being slightly more stable at the RHF 6-311G(2d,1p) level. The relative ordering of the conformers differs slightly when comparing RHF results with those from BLYP or MP2, mainly due to the destabilization of the GT conformer. The final ordering, obtained at the MP2/6-31G(d) level with corrections for free energies, is GG (−1.01) > TG (0.0) > GT (0.94). Based on the shifts of MP2 energies relative to RHF and BLYP, as well as basis set shifts, it is unlikely that higher order correlation terms or basis set expansion would alter these results outside chemical accuracy. This conclusion is supported by the results of Barrows *et al.*, who reported basis set and electron-correlation dependent variations of less than 0.5 kJ mol^{-1} for the calculated energies of the GT and TG conformers of β-D-glucopyranose.[8]

All the stationary points identified on the hydroxymethyl rotational surface consist of conformations that are influenced by intramolecular interactions between the C6 hydroxyl and nearby oxygens. In the TG conformer the C6 hydroxyl forms an intramolecular hydrogen bond[19] with O4 (O6H−O4 distance 2.006 Å, O6−O6H−O4 angle 136.4°), and in the TS1 transition state this hydrogen bond is maintained (O6H−O4 distance 1.949 Å, O6−O6H−O4 angle 134.1°). Instead of orienting toward O4, O6H orients toward O5 in the GG conformer, but does not form a true hydrogen bond (O6H−O5 distance 2.268 Å, O6−O6H−O5 angle 108.6°). In the TS2 transition state O6H does form a hydrogen bond with O5 (O6H−O5 distance 1.892 Å, O6−O6H−O5 angle 122.9°), but the GT conformer, although still oriented toward O5, does not (O6H−O5 distance 2.271 Å, O6−O6H−O5 angle 108.7°). There is no apparent relation between those interactions that are within the specific hydrogen-bonding threshold and the stability of the conformers, suggesting that the somewhat arbitrary definition of hydrogen bonding loses its meaning when referring to intramolecular interactions in carbohydrates. Glennon *et al.* also found this to be true based on their analysis of intramolecular hydrogen bonds from dynamics simulations of α-D-glucopyranose.[2] They observed "'non-standard' (in the sense of the preferred angle between

(19) A hydrogen bond is defined by an O−H distance of less than 2.6 Å and a O−H−O angle of greater than 120°, consistent with the definition of Glennon *et al.*[1]

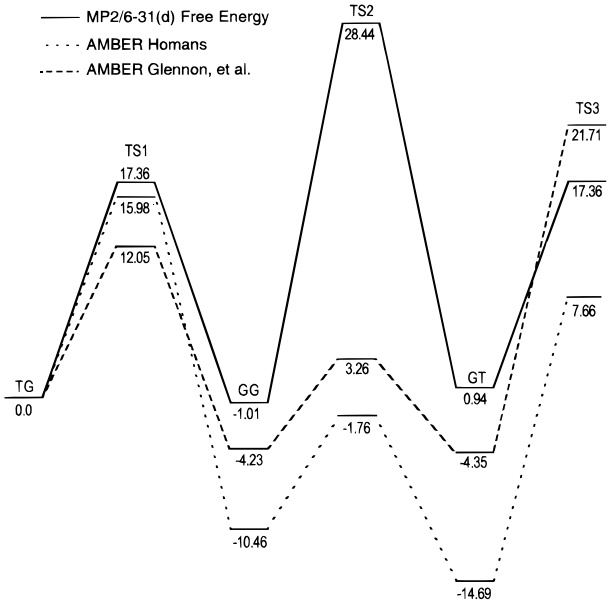

Figure 3. Relative energy diagram (kJ mol^{-1}) for free energies at the MP2/6-31G(d) level (solid line), the AMBER force field of Homans (shorter dashed line), and the AMBER force field of Glennon *et al.* (longer dashed line) for the stationary points along the exocyclic hydroxymethyl rotational surface of α-D-glucopyranose. The internal coordinate γ is defined as the O6−C6−C5−O5 dihedral angle.

the hydrogen bond donor and acceptor)" intramolecular hydrogen bonds, and a distance-only hydrogen bond showed a better correlation with the relative C−C−O−H dihedral angle flexibility.

Interestingly, the relative stabilities of the three rotational conformers of α-D-glucopyranose determined here are in sharp contrast with the relative populations for these conformations found in solution. Using NMR data Nishida *et al.*[11] found that the GG and GT conformers were nearly equally populated while TG was not populated at all, independent of the solvent used. Nishida *et al.* rationalized their observations by arguing that the TG conformation is destabilized by an unfavorable *syn*-diaxial interaction. Based on the results reported here, there is no intrinsic electronic destabilization of the TG conformer and, therefore, the population distribution found in solution must be due, at least in part, to solvation effects from specific interactions or through electrostatic fields. Comparison of the relative strain energies calculated for the three minimum conformations using the Homans[18] and Glennon *et al.*[2] modified AMBER force field also reveals striking dissimilarities with the final *ab initio* results. The Glennon results are somewhat closer, with both force fields giving a relative ordering of GT ≈ GG > TG. This comparison (Figure 3) highlights the need for improved force fields describing intramolecular interactions within simple monosaccharides.

The intrinsic exocyclic hydroxymethyl rotational barriers in glucopyranose are substantial, ranging from 12 kJ mol^{-1} for TS1 to 30 kJ mol^{-1} for TS2, depending on the level of theory. Similar to the minima, basis set augmentation has little affect on the structures or the relative energies of the rotational transition states. Electron correlation also has a small effect on transition state energies, with shifts relative to RHF of only 3 kJ mol^{-1}. Again, the results based on force field strain energy calculations using both the Glennon *et al.*[2] and Homans[18] AMBER parametrizations are only qualitatively consistent with the *ab initio* values, with the best agreement for TS1; differences between the methods of up to 10 kJ mol^{-1} are observed. Molecular dynamics simulations by Glennon *et al.*[2] of α-D-glucopyranose in water showed several interconversions between the GG and GT conformers and no interconversion from GG to TG over 150 ps. This result, although consistent with the force field energetic results, is inconsistent with the transition state energies presented here, which suggest that, in the absence of large solvation effects, little interconversion between any conformers over such a short time scale is likely. Moreover, based on the final *ab initio* results, the relative transition state energies are in the order TS2 > TS3 > TS1, indicating that the most facile interconversion in the gas phase is between TG and GG.

Previously, Zheng *et al.*[12] mapped the exocyclic hydroxymethyl rotational surface for a related molecule, 2-(hydroxymethyl)tetrahydropyran (2-HMTHP), through a series of single-point calculations at the 6-31G(d)//3-21G(d) level, but did not explicitly identify rotational transition states. Based on estimates from the single-point calculations, the rotational barriers of α-D-glucopyranose determined here are significantly higher, up to 11 kJ mol^{-1}, compared with those reported for 2-HMTHP. Stabilization of the minima on the glucopyranose rotational surface by nearby hydroxy groups effectively raises the energetic barrier to the transition states compared with the same transitions on the 2-HMTHP surface. These differences stress the caution that should be exercised when extrapolating results from model systems to a system of interest. Although one might expect that sufficient parametrization of a force field to reproduce the *ab initio* rotational surface for 2-HMTHP indicates transferability to glucose, since any interaction of the primary hydroxyl with the O4 hydroxyl will be contained in the electrostatic terms, the results reported here show that this is not necessarily the case.

Differences between the AMBER energies and quantum mechanical results are likely due to overestimation of intramolecular electrostatic interactions, as opposed to incorrect parametriztion of the O5−C5−C6−O6 dihedral angle force constant. Zheng *et al.* reported this conclusion when comparing quantum mechanical results with force field calculations for 2-HMTHP.[12] The force field results using the Glennon parameters are in better agreement with the *ab initio* results for the transitions states in which the polar hydroxyl groups are furthest apart and the electrostatic contribution to the energy is lower. Appropriate scaling of intramolecular electrostatic interactions beyond traditional 1−4 scaling could improve force field predictions of the exocyclic hydroxymethyl rotational surface of α-D-glucopyranose.

Conclusion

We have described the rotational energy surface for the exocyclic hydroxymethyl group of α-D-glucopyranose using the high-level *ab initio* methods including electron correlation. These data definitively establish the potential energy surface along this coordinate in the gas phase. Comparison with previous studies on model compounds indicates that the rotational barriers are increased due to stabilization of the minima via intramolecular interactions. Current force fields for carbohydrates are in good agreement with portions of the energy surface, but further refinement is necessary to accurately model overall carbohydrate rotational surfaces and structure.

Studies that focus on the anomeric effect and solvation effects and their impact on the hydroxymethyl rotational surface in glucopyranoses are currently underway.

Acknowledgment. The authors would like to thank the National Research Council (NRC) postdoctoral fellowship program for support. We are also grateful to Dr. Frederick Schwarz and Dr. Walter Stevens (Center for Advanced Research in Biotechnology, National Institute of Standards and Technology) for helpful discussion.

JA952804Y