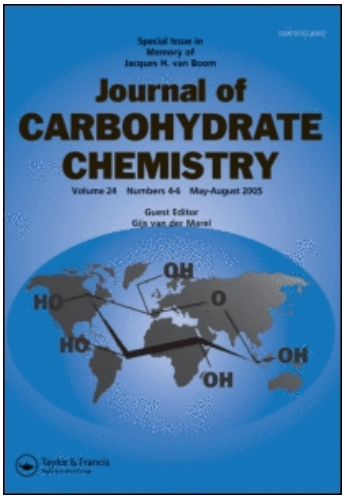

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MM3(96) CONFORMATIONAL ANALYSIS OF d-GLUCARAMIDE AND X-RAY CRYSTAL STRUCTURES OF THREE d-GLUCARIC ACID DERIVATIVES—MODELS FOR SYNTHETIC POLY(ALKYLENE d-GLUCARAMIDES)

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ABSTRACT

An exhaustive conformational analysis of D-glucaramide was carried out using MM3(96) [MM3(96). *Molecular Mechanics Software* used with permission from N.L. Allinger; University of Georgia]. Nine torsion angles were each driven in increments of 120°, generating 19,683 starting conformations. Each conformation was then fully energy-minimized using MM3's block diagonal/full matrix optimization option at dielectric constants of both 3.5 and 6.5. Conformer populations were calculated based on the modeling results and calculated theoretical average ^{1}H vicinal coupling constants were compared to experimental values obtained in D_2O solution. Crystal structures

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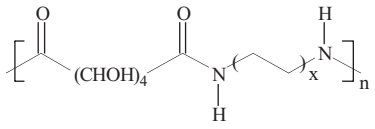
of three acyclic D-glucaric acid derivatives (*N*,*N*′-dimethyl-D-glucaramide, dipotassium D-glucarate, and sodium potassium D-glucarate) are reported. These structures and that of previously reported monopotassium glucarate correspond closely with model conformations that were within one kcal/mol of the global minimum.

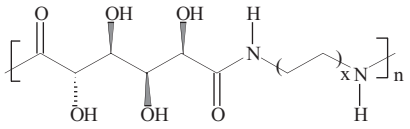
INTRODUCTION

Previously we used D-glucaric acid as an available chiral diacid monomer in polycondensation reactions with primary alkylenediamines to make so-called ''hydroxylated nylons'', or poly(alkylene D-glucaramides).[2–5] D-Glucaric acid [(2*R*,3*S*,4*S*,5*S*)-tetrahydroxyhexanedioic acid] introduces four chiral centers into each diacid residue incorporated into a polyamide chain. We have taken advantage of the asymmetry of this monomer to synthesize examples of three classes of poly(alkylene D-glucaramides): ''randomly aligned'' polyamides[2,3] and two classes of stereoregular polymers, repeating *head*, *tail*–polyamides[4] and alternating *head*, *tail*–*tail*, *head*–polyamides[6] (Figure 1). Our interest in studying the conformational characteristics of the glucaric acid component of these polymers stems from an effort to better understand the properties and potential applications of the resultant polyamides. To this end, we report here an exhaustive molecular mechanics investigation of D-glucaramide and x-ray crystal structures of various D-glucaric acid derivatives as model compounds for the repeating glucaryl acid unit of these polymers.

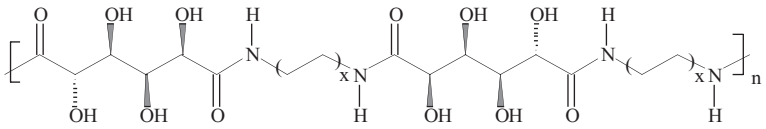
D-Glucaramide is a good model compound because it incorporates both the chiral glucaryl moiety of the polymer as well as the characteristic amide bonds, and its relatively small size allows for computation of the important conformational attributes of the polymers within a reasonable amount of computer time. The alkylene portion of the diamine component was not included in the calculations, as these aliphatic diamine units



"Random" poly(alkylene D-glucaramides)



Stereoregular repeating *Head, tail* - poly(alkylene D-glucaramides)



Stereoregular alternating *Head, tail* - *tail, head* - poly(alkylene D-glucaramides)

x = 1,2,3,4,5, or 6

Figure 1. Three classes of poly(alkylene D-glucaramides).

should adopt a conformation similar to polyethylene, with an extended or ''zig-zag'' conformation being dominant.[7]

Literature data suggest that an unfavorable steric interaction results from hydroxyl groups that are in a 1,3-parallel arrangement in acyclic carbohydrates, and that such compounds typically undergo a 120° rotation about an appropriate C—C bond to alleviate this interaction, producing bent or ''sickle'' conformations.[8] These interactions are similar to the destabilizing *syn*-diaxial interactions (1.9 kcal/mol) between 1,3-diaxial hydroxyl groups in chair conformations of substituted cyclohexanes.[9] This phenomenon accounted for results obtained previously in this laboratory from the molecular modeling of *N,N′*-dimethylxylaramide and *N,N′*-dihexylxylaramide using MacroModel V2.0.[10–12] For both compounds, it was found that two sickle conformations were lower in steric energy than the extended conformation. Presumably, the reduction in steric energy observed for the two sickle conformations with respect to the extended conformation is in part due to the alleviation of the 1,3-interaction between the hydroxyls at C2 and C4 in the sickle conformations. Other studies on acetylated carbohydrate derivatives also point to the importance of 1,3-interactions in determining preferred conformations. Sweeting et al.[13] utilized ^{1}H NMR vicinal coupling constant data as a means of studying the conformational characteristics of six peracetylated hexononitriles. They showed that an extended conformation predominated for their hexononitriles unless there was a 1,3-parallel interaction present. For penta-*O*-acetyl-D-gluconononitrile, in which the acetyl groups on C2 and C4 are eclipsed in the extended conformation, it was found that a sickle conformation was adopted preferentially. Angyal and co-workers[8,14] also conducted ^{1}H NMR conformational studies on various derivatives of glucose. In particular, they found that hexa-*O*-acetyl-D-glucitol prefers a sickle conformation over an extended conformation. Several other reports[15,16] also highlighted the role of 1,3-interactions in determining acyclic carbohydrate conformations, and it was expected that this phenomenon might contribute to the distribution of conformations observed in the present modeling study.

These molecules are fairly complex subjects for conformational analysis. Furthermore, the particular atomic sequences are not widely studied. It seemed reasonable to use an empirical force field (molecular mechanics) method because of the sheer number of conformations that must be considered. Because of the functional groups present and the absence of ring forms, we chose to use MM3(96) which has been seen to work well for mono- and disaccharide molecules.[17] This choice has some consequences. For example, hydrogen bonding in general purpose force fields has some limitations. Even MM3, which uses a complex, angle-dependent Buckingham potential plus dipole–dipole interactions, does not incorporate a dependence of the energy on the orientation of the acceptor hydroxyl group. Nor are the geometric consequences of donor-acceptor-donor-acceptor chains included.

Although MM3 does not provide methods for dealing with solvent, either explicitly in a molecular dynamics sense or implicitly with a continuum method, it does allow changing the dielectric constant and thus altering the strength of hydrogen bonds. For comparison of observed and calculated results for condensed phase systems, it is necessary to use an increased dielectric constant compared to the value deemed appropriate for an isolated molecule. This necessity can be explained in several ways, including the bulk dielectric of the phase. Importantly, the fact that hydrogen bonds can (and often do) form with solvent molecules reduces the influence of intramolecular

hydrogen bonds on the experimental conformations. This effect can be partly mimicked by reducing the strength of intramolecular hydrogen bonds. Another reason is that the formation of a hydrogen bond involves a loss of entropy. The experimental structures result from their free energies, including entropy, but energy minimization studies based on steric energy do not. MM3 was able to calculate total zero point vibrational energies that were similar to HF/6-31G* values for glucose, but it is unknown how comparable these values are to solution values.

Recently[18] it was shown that the observed crystal structures are well predicted at dielectric constants of either 3.5 or 7.5. A value of 1.5 was clearly inferior, while the population vs. energy lines for the 3.5 and 7.5 calculations approximated a Boltzmann distribution. The similarity of these two results suggested that a higher dielectric constant would not help to explain the distribution of crystal structures. Values of 3.5 and 6.5 were chosen in the present work.

Other limitations include the lack of provision for specific solvent effects during conformational analysis in the MM3 code. These limitations of MM3 were accepted because of the positive experiences with carbohydrates and because of the large number of structures that required examination.

There are several ways that the conformations of these compounds might be explored. There are nine torsional angles that allow rotation including five in the backbone and four for the hydroxyl groups. In isolation, these torsion angles would be expected to each take one of the three staggered conformations, resulting in 3^9 distinct conformations. Energy minimization of this number (19,683) of structures is within the capabilities of even a (now obsolete) personal computer. We preferred the exhaustive examination of conformations, since it was reasonably inexpensive, to the use of more sophisticated routines that randomly search for stable conformers until no new low-energy forms are found.[19] Such routines, or a molecular dynamics simulation, would become a practical necessity for molecules that are just a little larger.

An obstacle that was encountered at the beginning of the study was the absence of MM3(96) torsional parameters for the N—C—C—O sequence in the α-hydroxyamide functionality (connectivity of N—C(=O)—C—OH). We undertook ab initio calculations on a simpler α-hydroxyamide, glycolic amide, in order to obtain a reasonable estimate of the needed torsional constants, and applied ab initio results from HF/6-31G* level calculations to generate the needed torsional parameters[20] that were subsequently used throughout this study.

RESULTS AND DISCUSSION

Ab Initio Calculations on Glycolic Amide

Energies for glycolic amide were calculated at 20° increments of rotation about the C—C bond at the HF6-31G* level of ab initio theory (GAUSSIAN94[21]), along with comparable MM3 calculations with values of V1 = V2 = V3 = 0 for the torsion angle in question. These data were then sent to N. L. Allinger's group at the Computational Center for Molecular Structure and Design at the University of Georgia, where the following parameters were estimated using their TorsFind program: $V_1 = -2.157$, $V_2 = -0.592$, and $V_3 = 0.466$.

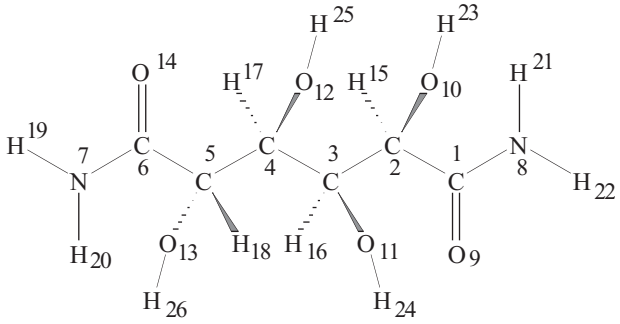


Figure 2. Numbering scheme for model compound.

Conformational Analysis of D-Glucaramide

Nine torsion angles of D-glucaramide were varied in the conformational analysis. Five of the angles correspond to rotation about the glucaramide backbone, while the other four account for hydroxyl rotamers. The numbering scheme for the model compound is shown in Figure 2, and the varied torsion angles are listed in Table 1. Torsion angles were varied in increments of 120°, starting with −180°, to give the three staggered orientations for each angle. Varying these nine angles between three values resulted in 3^9 (19,683) starting conformations. Eighty-one separate input files with 243 conformations each were generated using the torsional driver routine of MM3(96)[1] (−3 option, no minimization). Using the separate input files kept the output files from becoming too large to process the resulting data under MS-DOS. Each of the 81 input files was next submitted to the block diagonal minimization/full matrix optimization routine of MM3(96) using the newly derived torsional parameters and a dielectric constant (ε) of 3.5. This value of ε is higher than MM3's default value of 1.5 (which estimates conformational behavior in a vacuum),[22] and was used in order to probe the condensed-phase conformational characteristics of the model compound.[17] The full matrix minimization method calculates both a steric energy term and a value for the free energy which takes molecular vibration into account.

The energies of the resulting 19,683 minimized conformations were extracted from the output files using a local QBASIC program. They were sorted in order of lowest final

Table 1. Torsion Angles Varied in MM3(96) Studies on D-glucaramide

Backbone	Hydroxyl Rotamers
O14−C6−C5−H18	H23−O10−C2−H15
H15−C2−C1−O9	H24−O11−C3−H16
H15−C2−C3−H16	H25−O12−C4−H17
H16−C3−C4−H17	H26−O13−C5−H18
H17−C4−C5−H18	

steric energy to highest. A histogram was generated showing the number of starting conformations (Nc) that minimized to each particular final energy. Conformations with energies varying by ±0.0001 kcal/mol were considered to be equivalent.

The lowest-energy structures (ranging from the minimum observed energy to the minimum +1 kcal) were then used to generate conformer populations for each, using the following equations (10):

$$\mathrm{N}a/\mathrm{N}o = \mathrm{e}^{-\Delta \mathrm{E}/\mathrm{RT}} \tag{1}$$

$$\mathrm{Pa} = [(\mathrm{N}a/\mathrm{N}o)/\Sigma(\mathrm{N}i/\mathrm{N}o)] \times 100 \tag{2}$$

N*a*/N*o* is the molar ratio of some rotamer *a* to the most stable rotamer *o*, and the energy difference between the two rotamers is ΔE. Pa is the population (in percent) of any rotamer *a* among a total of *i* rotamers. Two sets of populations were calculated and presented herein; one set is based on the relative final steric energies of the low-energy conformations, and the other is based on the relative free energies of the low-energy conformations.

The vicinal coupling constants for H15–H16, H16–H17, and H17–H18 were calculated for each low-energy conformation using the program ''Vicinal Coupling Constants for Microcomputers'' (Quantum Chemistry Program Exchange), which employs an empirical generalization of the Karplus equation.[23,24] It takes into account the electronegativities of substituents on each carbon, as well as the configuration of those substituents. Theoretical average coupling constants for $^3J_{15,16}$, $^3J_{16,17}$, and $^3J_{17,18}$ were calculated based on the equation:[10]

$$\mathrm{Jcalcd} = \Sigma Xi \times Ji$$

where *Xi* is the percent population (Pa) of each rotamer and *Ji* is the corresponding calculated coupling constant for that particular rotamer.

The entire conformational analysis experiment was repeated at a dielectric constant of 6.5 in order to emulate a more polar environment, and the data were worked up in the same manner as that employed for the calculations done at $\varepsilon = 3.5$. Results were compared between data sets at the two different dielectric constants as well as with data from ^{1}H NMR in D_2O and a number of crystal structures of acyclic D-glucaric acid derivatives.

Results from Conformational Analysis at Dielectric Constant of 3.5

Figure 3 summarizes the computational results. The number of initial structures that minimized to each observed final steric energy is depicted. A total of 2085 distinct energies resulted from minimization of the initial 19,683 starting conformations. The energies ranged from 3.89 kcal/mol for the global minimum to the highest minimum of 28.33 kcal/mol. Both the potential energy (final steric) and the free energy were retained for each structure. The free energy is based on both the potential energy and the vibrational entropy at room temperature.

Only ten different conformations were found within the range of the minimum energy and minimum energy + 1 kcal/mol. These ten conformations are shown in Figure 4

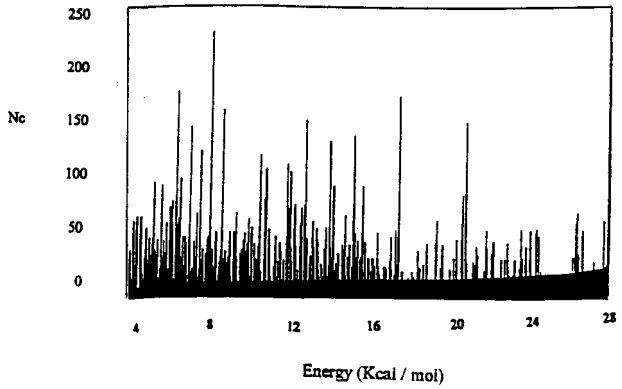


Figure 3. Histogram showing the number of initial structures (Nc) that minimized to each observed final steric energy at $\varepsilon = 3.5$.

with the appropriate rotational labels,[25] and their corresponding energies and percent of population for each are given in Table 2. While several of the low energy conformations are those in which one or more sets of hydroxyl groups are eclipsed in a 1,3-parallel interaction, 45–50% of the population as a whole (depending on whether ΔE or ΔG was used to calculate conformer populations) accounts for conformations in which this interaction is alleviated. The global minimum (labeled conformation **1a**) and the related conformation **3a** (which differs from **1a** only in the orientation of the hydroxyl group at C3) are indeed bent structures that have no 1,3-parallel interactions. However, conformation **2a** and related conformation **4a** (again, the

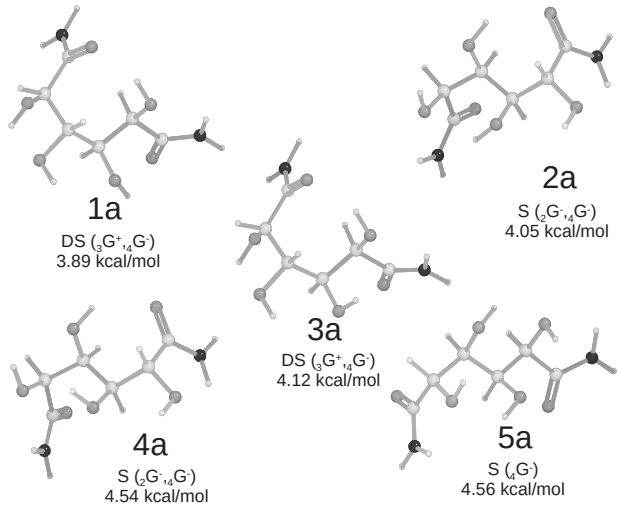


Figure 4. Ten lowest energy structures from molecular modeling at $\varepsilon = 3.5$.

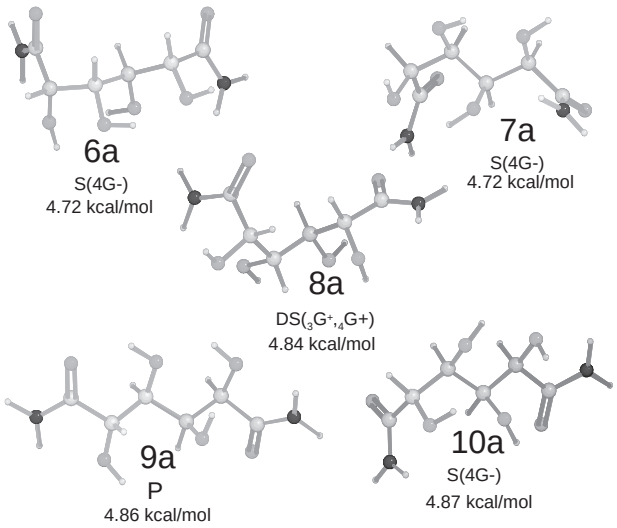


Figure 4. Continued.

two differ only in the orientation of the C-3 hydroxyl) have a 1,3-parallel interaction between the hydroxyl groups at C3 and C5. Even more interesting is the presence of two sets of hydroxyl groups in a 1,3-relationship in related conformations **5a** and **10a** (differing in the orientation of the hydroxyl groups at C4), and conformations **6a** and **7a**. Conformation **8a** is unique, with no 1,3-interactions. Conformation **9a** is fully extended and has the hydroxyl groups at C2 and C4 eclipsed. These calculations suggest that conformations having 1,3-interactions are stabilized to some extent by intramolecular hydrogen bonding between alternating hydroxyl groups.

Table 2. Calculated Energies and Percent Populations for Ten Lowest Energy Structures ($\varepsilon = 3.5$)

Conformation	Steric Energy (kcal/mol)	Free Energy (kcal/mol)	%[a]	%[b]
1a	3.8865	104.545	24.0	24.2
2a	4.0488	104.292	18.3	37.1
3a	4.1214	104.919	16.2	12.9
4a	4.5372	105.783	8.0	3.0
5a	4.5579	106.347	7.7	1.2
6a	4.7216	105.877	5.9	2.6
7a	4.7223	105.878	5.9	2.6
8a	4.8383	104.914	4.8	13.0
9a	4.8583	106.141	4.7	1.6
10a	4.8743	106.060	4.5	1.8

[a] Calculations based on relative steric energies.
[b] Calculations based on relative free energies.

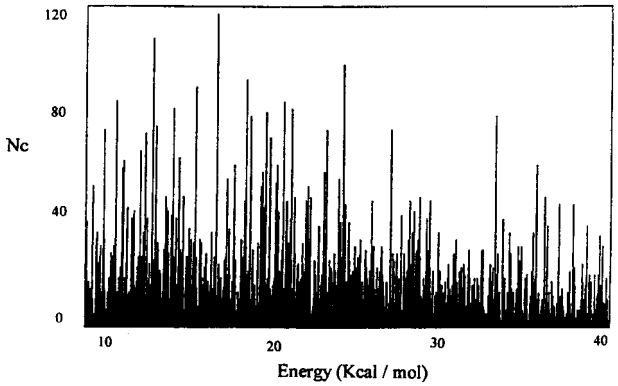


Figure 5. Histogram showing the number of initial structures (Nc) that minimized to each observed final steric energy at $\varepsilon = 6.5$.

Results from Conformational Analysis at Dielectric Constant of 6.5

Figure 5 shows the number of initial structures at $\varepsilon = 6.5$ that minimized to each observed final steric energy. A total of 3335 distinct energies were generated from the initial 19,683 starting conformations. The energies ranged from 8.91 kcal/mol for the global minimum to the highest minimum of 41.80 kcal/mol.

Thirty-five different conformations were found within the range of the minimum energy and minimum energy + 1 kcal/mol. Many of these conformations were very

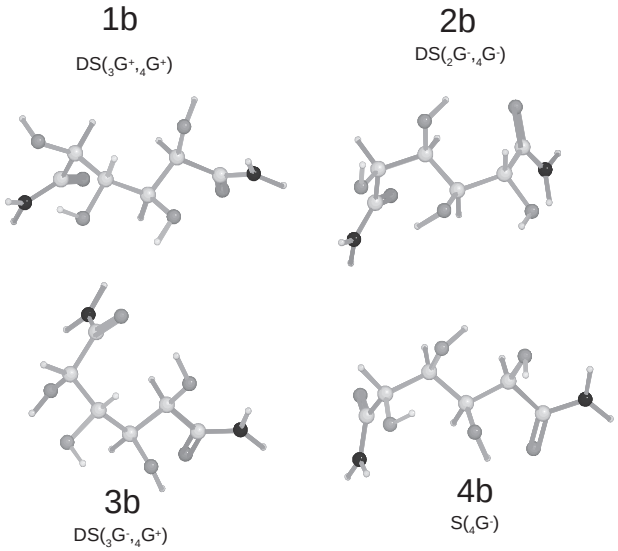


Figure 6. Four groupings of low-energy conformations from modeling at $\varepsilon = 6.5$.

Table 3. Percent of Population Occupied by Each Grouping of Conformations ($\varepsilon = 6.5$)

Grouping	Percent of Population[a]	Percent of Population[b]
1b	44.4	16.2
2b	27.9	43.9
3b	14.4	36.0
4b	13.3	3.9

[a] Calculations based on relative final steric energies.
[b] Calculations based on relative free energies.

similar, so for simplicity they were grouped together into four general conformational families. Variations within the families were primarily due to hydroxyl rotamers. General structures with appropriate rotational labels are shown for the four groupings in Figure 6, and the corresponding percent of population occupied by each family is given in Table 3. The global minimum fell into Group **1b**. Both groups **1b** and **3b** have no 1,3-parallel interactions, whereas group **2b** has one set of hydroxyl groups in a 1,3-relationship and group **4b** has both sets of hydroxyl groups eclipsed. Together groups **1b** and **3b** account for 52–59% of the population. It appears that at the higher dielectric constant, the 1,3-parallel interaction is slightly more destabilizing and therefore less favored. Thus, the intramolecular hydrogen bonding contribution between alternating hydroxyl groups is somewhat reduced but not eliminated in a simulated more polar environment.

Factors That Influence the Calculated Conformational Distribution of D-Glucaramide-Alleviation of 1,3-Parallel Dihydroxy Interactions and Stabilization by Intramolecular Hydrogen Bonding

As previously indicated, in the fully extended conformation of D-glucaramide, the hydroxyl groups at C2 and C4 are in a 1,3-parallel relationship. Five of the ten low-energy structures, including the global minimum from the modeling at $\varepsilon = 3.5$ (**1a–4a** and **8a**) correspond to conformations in which this parallel interaction has been avoided. In addition, groups **2b** and **3b** from the modeling at $\varepsilon = 6.5$ are also composed of conformations without 1,3-parallel interactions between the C2 and C4 hydroxyl groups. Interestingly, conformations **2a** and **4a**, as well as group **2b**, incorporate instead a new 1,3-parallel interaction between the hydroxyl groups at C3 and C5. Intramolecular hydrogen bonding between H—O···H of the two hydroxyl groups appears to stabilize these conformations. The approximate calculated O···H distance = 2.1 Å in all cases (calculated with Alchemy 2000[26] software).

Four other conformations resulting from calculations at $\varepsilon = 3.5$ (**5a**, **6a**, **7a**, and **10a**), as well as group **4b** from calculations at $\varepsilon = 6.5$, also benefit from hydrogen bonding between 1,3-parallel hydroxyl groups (again, calculated O···H distance = 2.1 Å).

An additional source of hydrogen bonding, that between a vicinal amide N—H and hydroxyl group, is encountered at both terminal amide bonds in all of the calculated

low-energy conformations. The calculated N—H···O—H distance is approximately 2.1 Å. This preference for hydrogen bonding accounts for the relatively small dihedral angles exhibited for N8—C1—C2—O10 and N7—C6—C5—O13 (generally less than ±30° in all low-energy conformations). This phenomena can be seen in the extended backbone crystal structures of **11** discussed below. This structure possessed torsion angles N9—C1—C2—O10 = 20.2^0 and N7—C6—C5—O13 = -23.7^0.

We have also observed some special cases of hydrogen bonding between the oxygen of a carbonyl group and the hydrogen of a hydroxyl group. One such case presents itself in conformations **1a** and **3a**, where an eight-membered ring is completed by hydrogen bonding between the carbonyl oxygen O14 and the hydrogen (H23) of the hydroxyl group at C2. This hydrogen bond may be a special stabilizing factor for these two conformations, compensating somewhat for the 1,3-parallel interaction introduced between C2 and C6 as a result of the alleviation of the original 1,3-parallel interaction between the C2 and C4 hydroxyl groups. A second case is encountered in the extended conformation **9a**, where a five-membered hydrogen bonding system is formed between the carbonyl oxygen O14 and the hydrogen (H25) of the hydroxyl group at C4. In both of these cases, the H—O···C—O distance was approximately 2.0 Å.

In effect, the two dominant considerations when evaluating the calculated low-energy conformations from the molecular modeling of D-glucaramide appear to be 1,3-parallel interactions and intramolecular hydrogen bonding. Many literature examples[8,10,13–16] provide evidence for the destabilizing effects of 1,3-parallel interactions, and we have indeed encountered several low-energy conformations that are stabilized by the alleviation of such interactions. However, many other calculated low-energy conformations for D-glucaramide have either the C3 and C5 hydroxyl groups in 1,3-parallel orientations, or have both sets of hydroxyl groups (C3 and C5 as well as C2 and C4) in a 1,3-relationship. In addition, acyclic glucaric acid derivatives **11** and **12** from this study have crystal structures with extended conformations with 1,3-parallel hydroxyl groups.

Comparison of Calculated and Experimentally Determined Coupling Constants

The theoretical average vicinal coupling constants based on the two data sets from the modeling studies are given in Table 4, along with experimentally determined coupling constants for D-glucaramide as well as a number of other amides derived from D-glucaric acid.

Calculated values for $^3J_{15,16}$ and $^3J_{16,17}$ at both dielectric constants (Table 4) agree fairly well with observed values for all of the listed glucaramides. However, both calculated values for $^3J_{17,18}$ are underestimated. The modeling approach therefore effectively simulates the average conformational characteristics about the C2—C3 and C3—C4 bonds, but is not as accurate at the C4—C5 junction.

In general, both theory and experiment confirm that the preferred conformational relationship between H15 and H16 is *gauche* with some contribution from *anti* conformations. When populations are calculated based on the final steric energies, the percentage of *gauche* conformations is approximately 75%, while the percentage of *anti* is

Table 4. Comparison of Calculated and Experimental Coupling Constants (Hz)

Compound	$^3J_{15,16}$	$^3J_{16,17}$	$^3J_{17,18}$
D-glucaramide (observed[a])	3.08	4.88	5.16
N,N′-dimethyl-D-glucaramide (observed[a])	2.98	4.83	5.16
Head, *tail*–poly(tetramethylene D-glucaramide) (observed[a])	2.87	4.53	5.23
D-glucaramide (theoretical;[b] $\varepsilon = 3.5$)	2.73	4.47	2.58
D-glucaramide (theoretical;[c] $\varepsilon = 6.5$)	3.01	5.56	2.16
D-glucaramide (theoretical;[d] $\varepsilon = 3.5$)	3.94	5.00	2.36
D-glucaramide (theoretical;[e] $\varepsilon = 6.5$)	4.37	5.08	2.07

[a] ^{1}H NMR, D_2O.
[b] Calculated using the set of 10 lowest energy conformations and their relative steric energies.
[c] Calculated using the set of 35 lowest energy conformations and their relative steric energies.
[d] Calculated using the set of 10 lowest energy conformations and their relative free energies.
[e] Calculated using the set of 35 lowest energy conformations and their relative free energies.

25%. Using populations calculated based on the free energies, the percentage of *gauche* conformations decreases to approximately 60%, with the *anti* conformation accounting for the remaining 40%. About the C3—C4 bond, however, approximately equal quantities of *gauche* and *anti* arrangements between H16 and H17 are predicted by theory (regardless of whether final steric or free energy is used to calculate the populations). Experimental data are well matched to the theoretical data. The $^3J_{16,17}$ value of approximately 5 Hz is intermediate between usual values observed for either all-*gauche* or all-*anti* conformations, indicating conformational averaging.[27]

Theoretical J values of approximately 2.0 for vicinal coupling between H17 and H18 support a largely *gauche* arrangement about the C4—C5 bond ($\geq 95\%$ *gauche*, with $\leq 5\%$ *anti*), a prediction which is not borne out by the experimentally observed coupling constants which are greater than 5.0 for all of the glucaramides listed. Thus, the experimental results show much more conformational averaging for the C4—C5 bond than predicted from the modeling study. The reasons for the discrepancy between theoretical and experimental coupling constants at the C4—C5 junction are not clear at this time. It is possible that

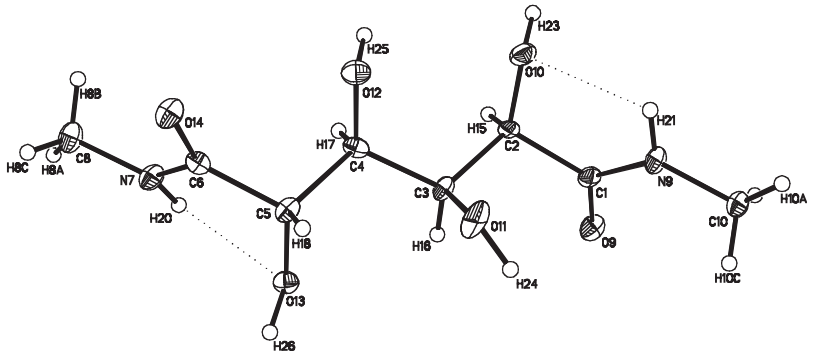


Figure 7. The labeling of the atoms in the crystal structure of *N,N′*-dimethyl-D-glucaramide (**11**).

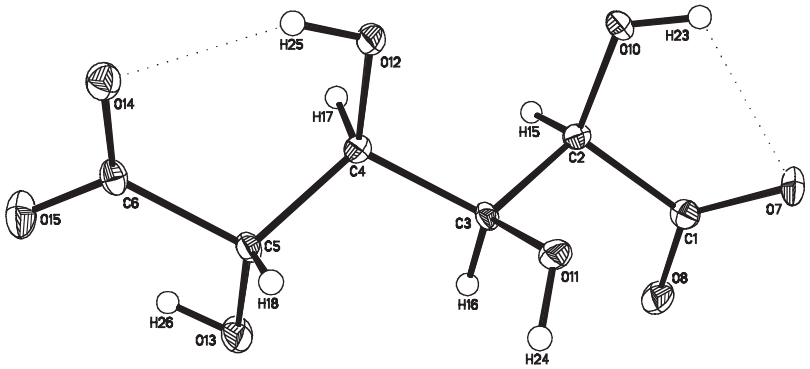


Figure 8. Labeling of the atoms of the crystal structure of dipotassium D-glucarate monohydrate (**12**). The potassium ions and water molecule are shown in the unit cell for **12**, Figure 12.

specific solvent (D_2O) effects account for some discrepancies between experiment and prediction, and since the relative energies of the various conformers are very close, small errors in the force field could account for some of the discrepancy.

In addition, it appears that the calculations carried out here employing MM3(96) at dielectric constants of 3.5 and 6.5 generate conformations that are overly favored by

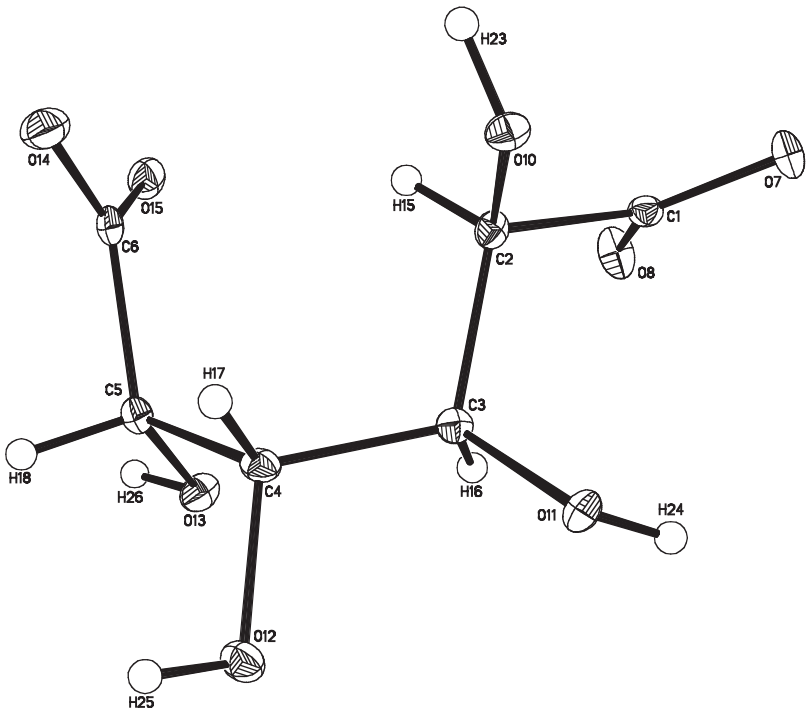


Figure 9. The labeling of the atoms of the crystal structure of sodium potassium D-glucarate dihydrate (**13**). The sodium and potassium ions are shown in the unit cell for **13**, Figure 13.

intramolecular hydrogen bonding. This is manifested by the relationship between dielectric constant used and calculated values for the dipole–dipole component of the final steric energies obtained in the conformational analysis. The dipole–dipole contribution to final steric energy varies greatly with dielectric constant. At a low dielectric constant of 1.0, the dipole–dipole contribution to final steric energy is very high, on the order of −31 kcal/mol. At higher dielectric constants (3.5 and 6.5), those used in the calculations described here, the stabilizing dipole–dipole contributions drop to about −8 kcal/mol and −4 kcal/mol, respectively. However, these contributions still contribute significantly to biasing structures with various stabilizing intermolecular hydrogen bonds at the expense of destabilizing steric interactions such as those associated with 1,3-parallel interactions. Thus in conformations **1a**–**10a**, only **9a** (the extended structure) has a large (*anti*) dihedral angle between H–17, H–18 about the C4—C5 bond, a result that is not consistent with the observed H17–H18 coupling of ca. 5.1 Hz for D-glucaramide. Consequently, based on the results presented here, it is suggested that care be exercised in

Table 5. Selected Bond Distances (Å) and Angles (°) for *N*,*N*′-Dimethyl-D-glucaramide (**11**), Dipotassium D-Glucarate Monohydrate (**12**) and Sodium Potassium D-Glucarate Dihydrate (**13**)

	11	**12**	**13**
Bond Distances	C1—C2 = 1.517 (9)	C1—C2 = 1.533 (3)	C1—C2 = 1.534 (3)
	C2—C3 = 1.541 (8)	C2—C3 = 1.533 (3)	C2—C3 = 1.526 (3)
	C3—C4 = 1.517 (9)	C3—C4 = 1.520 (3)	C3—C4 = 1.528 (3)
	C4—C5 = 1.526 (8)	C4—C5 = 1.548 (3)	C4—C5 = 1.535 (4)
	C5—C6 = 1.544 (9)	C5—C6 = 1.524 (3)	C5—C6 = 1.536 (4)
	C1—O9 = 1.255 (8)	C1—O7 = 1.240 (3)	C1—O7 = 1.252 (3)
	C1—N9 = 1.313 (9)	C1—O8 = 1.264 (3)	C1—O8 = 1.249 (3)
	C2—O10 = 1.422 (7)	C2—O10 = 1.418 (3)	C2—O10 = 1.427 (3)
	C3—O11 = 1.425 (10)	C3—O11 = 1.421 (3)	C3—O11 = 1.426 (3)
	C4—O12 = 1.415 (7)	C4—O12 = 1.426 (3)	C4—O12 = 1.440 (3)
	C5—O13 = 1.406 (7)	C5—O13 = 1.432 (3)	C5—O13 = 1.417 (3)
	C6—O14 = 1.224 (8)	C6—O14 = 1.243 (3)	C6—O14 = 1.255 (3)
	C6—N7 = 1.334 (9)	C6—O15 = 1.260 (3)	C6—O15 = 1.251 (3)
	N7—H20 = 0.98 (7)	O10—H23 = 1.10 (5)	O10—H23 = 0.87 (3)
	N9—H21 = 0.78 (8)	O11—H24 = 0.86 (3)	O11—H24 = 0.93 (3)
		O12—H25 = 0.89 (3)	O12—H25 = 0.76 (3)
		O13—H26 = 1.02 (4)	O13—H26 = 0.83 (3)
		C2—H15 = 0.90 (4)	C2—H15 = 0.92 (2)
		C3—H16 = 0.96 (4)	C3—H16 = 0.91 (2)
		C4—H17 = 0.98 (4)	C4—H17 = 0.93 (2)
		C5—H18 = 1.01 (5)	C5—H18 = 1.02 (2)
Bond Angles	C1—C2—C3 = 108.8 (5)	C1—C2—C3 = 109.9 (2)	C1—C2—C3 = 109.9 (2)
	C2—C3—C4 = 112.9 (5)	C2—C3—C4 = 113.4 (2)	C2—C3—C4 = 112.7 (2)
	C3—C4—C5 = 111.4 (5)	C3—C4—C5 = 111.6 (2)	C3—C4—C5 = 113.6 (2)
	C4—C5—C6 = 108.9 (5)	C4—C5—C6 = 112.0 (2)	C4—C5—C6 = 115.3 (2)
	H20—N7—C6 = 111 (4)	H23—O10—C2 = 113 (2)	H23—O10—C2 = 105 (2)
	H21—N9—C1 = 116 (6)	H24—O11—C3 = 103 (2)	H24—O11—C3 = 105 (2)
		H25—O12—C4 = 108 (2)	H25—O12—C4 = 102 (2)
		H26—O13—C5 = 105 (5)	H26—O13—C5 = 107 (2)

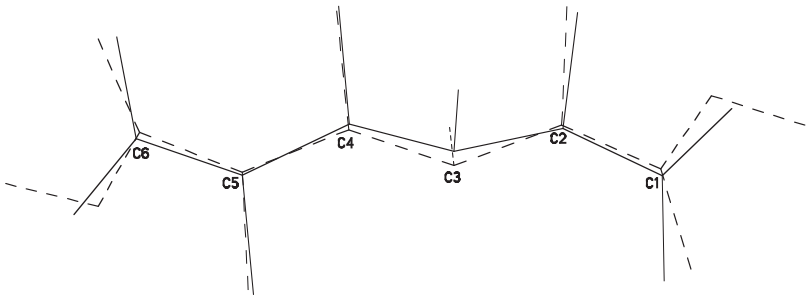


Figure 10. The superimposed structures of *N*,*N*′-dimethyl-D-glucaramide (line drawing, **11**) and dipotassium D-glucarate monohydrate (dashed drawing, **12**).

assigning relative importance to various conformations of acyclic carbohydrates, even at dielectric constants of 3.5 and higher, due to overemphasis of hydrogen bonding in structure stabilization.

Discussion of the X-ray Crystal Structures of Three Acyclic D-Glucaric Acid Derivatives 11, 12 and 13

X-ray diffraction studies were performed on one D-glucaric acid diamide, *N*,*N*′-dimethyl-D-glucaramide (**11**), and two disalts, dipotassium D-glucarate monohydrate (**12**), and sodium potassium D-glucarate dihydrate (**13**). The labeling of the atoms of (**11**), (**12**) and (**13**) is reported in Figures 7, 8, and 9, respectively. Selected bond distances and angles are reported in Table 5.

Table 6. Comparison of Selected Torsion Angles (°) for Compounds **11**, **12**, and Theoretical Conformation **9a**

Torsion Angle	**11**	**12**	Conformation **9a**
C1−C2−C3−C4	−177.9	−170.8	−170.8
O10−C2−C3−C4	59.7	66.5	67.1
C1−C2−C3−O11	60.4	65.0	66.3
O10−C2−C3−O11	−61.9	−57.7	−55.9
C2−C3−C4−C5	179.3	165.7	−177.7
C2−C3−C4−O12	−61.6	−70.4	−57.9
O11−C3−C4−C5	−58.1	−72.8	−54.9
O11−C3−C4−O12	61.0	51.1	64.9
C3−C4−C5−C6	−179.4	174.2	−175.8
O12−C4−C5−C6	57.8	50.9	64.5
C3−C4−C5−O13	−57.0	−63.4	−55.3
O12−C4−C5−O13	−179.8	173.3	−175.0
H15−C2−C3−H16	−60.4	70.8	67.5
H16−C3−C4−H17	−60.9	−79.1	−59.2
H17−C4−C5−H18	−177.4	−167.7	−173.8

Table 7. Comparison of Selected Torsion Angles (°) for Compound 13 Theoretical Conformation **1a**

Torsion angle	**13**	Conformation **1a**
C1—C2—C3—C4	−161.4	175.2
O10—C2—C3—C4	72.5	53.0
C1—C2—C3—O11	76.1	56.8
O10—C2—C3—O11	−50.0	−65.3
C2—C3—C4—C5	67.9	63.8
C2—C3—C4—O12	−173.0	−179.4
O11—C3—C4—C5	−168.9	−177.0
O11—C3—C4—O12	−49.8	−60.2
C3—C4—C5—C6	−73.0	−72.1
O12—C4—C5—C6	167.8	170.0
C3—C4—C5—O13	53.4	51.4
O12—C4—C5—O13	−65.8	−66.4
H15—C2—C3—H16	67.8	55.8
H16—C3—C4—H17	−168.4	175.7
H17—C4—C5—H18	−60.1	−64.7
H15—C2—O10—H23	−21.7	32.7
H16—C3—O11—H24	26.7	45.2
H17—C4—O12—H25	30.8	−61.6
H18—C5—O13—H26	57.6	−59.0

N,*N*′-Dimethyl-D-glucaramide (**11**) and dipotassium D-glucarate monohydrate (**12**) both adopt extended conformations with similar skeletal carbon backbones in the crystalline state. Both of these molecules possess intramolecular 1,3-parallel interactions. Figure 10 provides a superimposed image of both structures which shows the high degree of overlap. The structure of sodium potassium D-glucarate (**13**) is distinctly different. It adopts the double-sickle conformation in which there are no 1,3-parallel interactions. This bent structure is similar to that observed for crystalline monopotassium D-glucarate.[28]

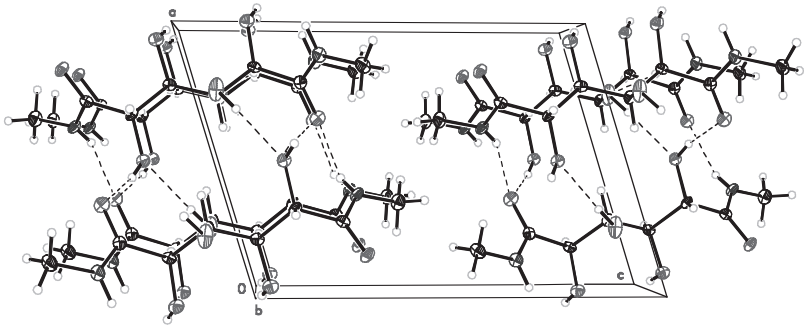


Figure 11. The unit cell of *N*,*N*′-dimethyl-D-glucaramide (**11**) as viewed perpendicular to the ac-plane showing the hydrogen bonding system associated with the crystal structure.

All three of the crystal structures correspond to populated conformations in the modeling study. Structures **11** and **12** are similar to the extended conformation **9a** from the modeling study at $\varepsilon = 3.5$. A comparison of selected torsion angles for **11** and **12** and the theoretical conformation **9a** are given in Table 6. Structure **13** with two sickle arrangements ($_3G^+$, $_4G^-$) is very similar to the global minimum (conformation **1a**) from the modeling done at $\varepsilon = 3.5$ as well as conformations in Group **3b** from the modeling done at $\varepsilon = 6.5$. Selected torsion angles for **13** are compared to the theoretical conformation **1a** in Table 7.

All three crystal structures have extensive hydrogen bonding systems, and all four hydroxyl hydrogen atoms are included in the hydrogen bonding system for each crystal structure. The hydroxyl hydrogen atoms were fixed in the crystal structure of *N*,*N*′-dimethyl-D-glucaramide (**11**) to maximize the intermolecular hydrogen bonding (Figure 11). This resulted in the strong intermolecular hydrogen bonding interactions d(H26···O9) = 1.898 Å, d(H25···O12) = 2.094 Å, d(H24···O13) = 2.144 Å and d(H23···O14) = 1.895 Å. The amide hydrogen atoms were refined and possessed strong intramolecular hydrogen bonds d(H21···O10) = 2.151 Å and d(H20···O13) = 2.233 Å with H21 also forming an intermolecular hydrogen bond d(H21···O9) = 2.298 Å.

In the extended dipotassium D-glucarate monohydrate stucture (**12**) (Figure 12), the atoms H23, H24 and H26 form strong intermolecular hydrogen bonds with adja-

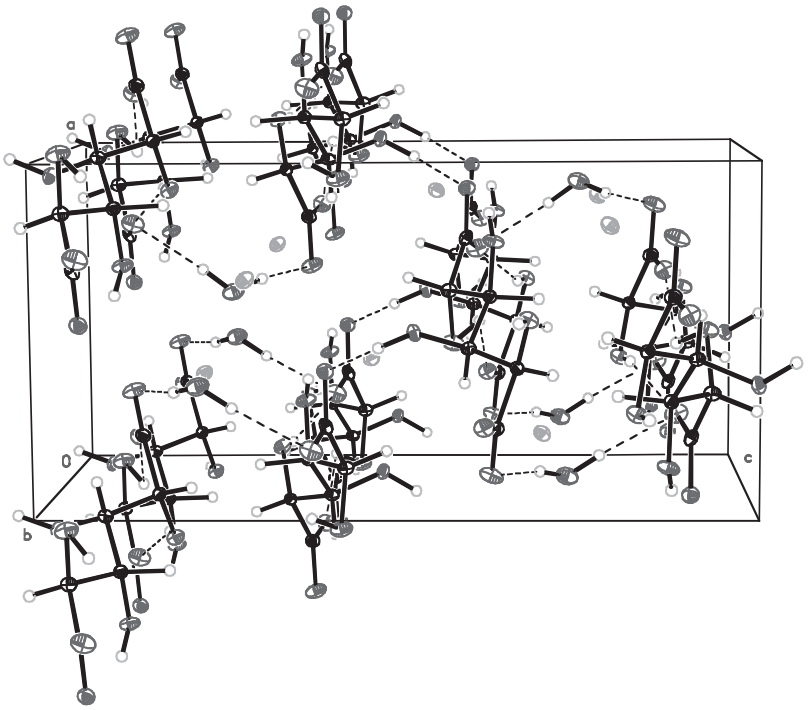


Figure 12. The unit cell associated with the crystal structure of dipotassium D-glucarate monohydrate (**12**) perpendicular to the bc axes showing the hydrogen bonding system associated with the crystal structure.

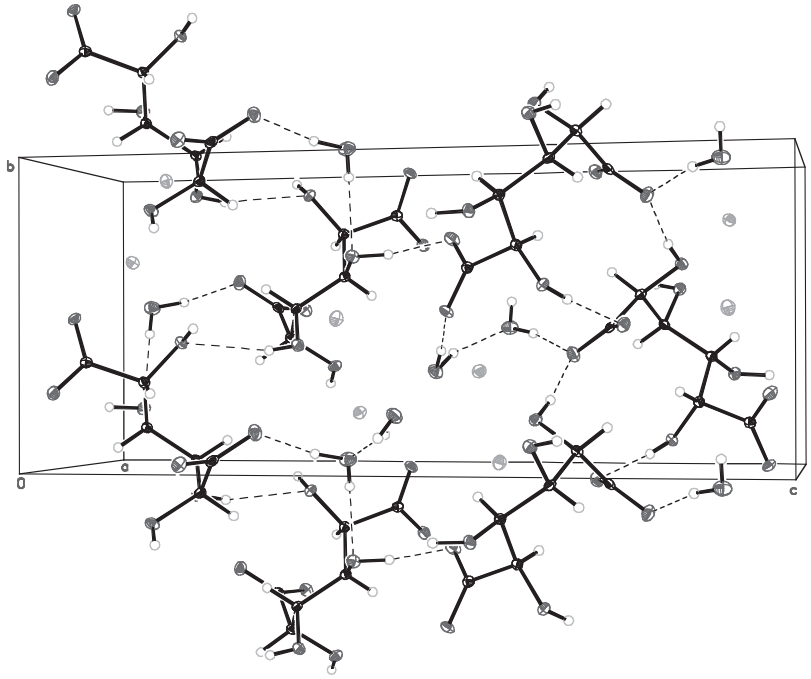


Figure 13. The unit cell associated with the crystal structure of sodium potassium D-glucarate dihydrate (**13**) perpendicular to the bc axes showing the hydrogen bonding system associated with the crystal structure.

cent molecules [d(H23···O15) = 1.790 Å, d(H24···O14) = 1.908 Å and d(H26···O7) = 2.111 Å], while H25 forms an intramolecular hydrogen bond (d(H25···O14) = 1.872 Å). Hydrogen atom H23 forms a weaker intramolecular hydrogen bond [d(H23···O7) = 2.231 Å]. It was also observed that compound **12** crystallized in sheets perpendicular to the ab plane. These sheets are held together by hydrogen bonding to water molecules.

In the hydrogen bonding system associated with the crystal structure of sodium potassium D-glucarate dihydrate (**13**) (Figure 13), all four hydroxyl hydrogen atoms exhibit intermolecular hydrogen bonding [d(H23···O15) = 1.821 Å, d(H24···O8) = 1.788 Å, d(H25···O10) = 2.266 Å and d(H26···O14) = 1.912] but there is no evidence for stabilizing intramolecular hydrogen bonds for ''bent'' **13**. It is noted that potassium sodium salt **13** forms ring-like structures, with the water molecules (Figure 13) and cations located in the cavities.

CONCLUSIONS

Theoretical calculations and ^{1}H NMR solution data show D-glucaramide to have some degree of conformational flexibility, primarily about the C3—C4 and C4—C5 bonds. However, for the most part, the conformational relationship between H15 and

H16 is *gauche*. The conformations that are populated at dielectric constants of 3.5 and 6.5 include several sickle and double-sickle conformations, and to a much lesser extent, extended conformations. In the crystalline state, *N*,*N*′-D-glucaramide and dipotassium D-glucarate are fully extended conformations, while crystalline sodium/potassium D-glucarate has a double-sickle conformation.

Consequently, based on these model experiments, the glucaric acid portion of poly(alkylene D-glucaramides) can in solution be expected to take on a variety of conformations, mostly those with sickle arrangements which give rise to a bend in the glucaric acid monomer unit. The inherent stereoregularity of particular polyamides (*head*, *tail* or *head*, *tail*–*tail*, *head* alignment of the glucaric acid moiety) will also be a large factor in determining the overall polyamide shape. The computational and x-ray structure studies described have provided us with some basic information on the conformational complexity of glucaric acid that should prove useful as we pursue conformational studies on the poly(D-glucamides) themselves.

EXPERIMENTAL

General Methods. All ^{1}H NMR spectra were recorded in D_2O at 400.13 MHz. Chemical shifts are reported as ppm (δ) downfield from 3-(trimethylsilyl)propionic-*2*,*2*,*3*,*3*-d_4 acid, sodium salt (TSP).

D-Glucaramide (1). To a solution of 7N methanolic ammonia (10 mL, 70 mmol) cooled in an ice bath with stirring was added dropwise over a period of 15 min a solution of methyl D-glucarate-6,3-lactone (0.749 g, 3.63 mmol) in distilled methanol (15 mL). The reaction mixture was stirred in an ice bath for 1.5 h, resulting in the formation of a white precipitate. The reaction mixture was then removed from the ice bath, covered with a Kimwipe, and left in a fume hood overnight to allow evaporation of the excess ammonia. The solid was removed by vacuum filtration, washed with methanol (37×10 mL), and dried at reduced pressure for 6 h to give **1** (0.663 g, 3.18 mmol, 87.7%): mp 168–170 °C (lit.[29] 168 °C); ^{1}H NMR δ 4.36 (d, 1H, H–15, $J_{15,16}$ = 3.08 Hz); δ 4.28 (d, 1H, H–18); δ 4.13 (dd, 1H, H–16, $J_{16,17}$ = 4.88 Hz); δ 4.00 (t, 1H, H–17, $J_{17,18}$ = 5.16 Hz). X-ray grade crystals could not be obtained despite multiple recrystallization attempts.

***N*,*N*′-Dimethyl-D-Glucaramide (11).** Methyl D-glucarate-1,4-lactone (0.5034 g, 2.442 mmol) was dissolved in methanol (10 mL). A solution of methylamine (0.5 mL of 40 wt% in water, 180 mg, 5.8 mmol) was added slowly, and the flask was covered with a septum. A shiny white precipitate was observed almost immediately after the addition of the methylamine solution. The reaction mixture was stirred at room temperature for 2 h, and the suspended solid was filtered and washed with methanol (3×5 mL) then acetone (3×5 mL) to give **11** (0.442 g, 1.87 mmol, 76.6%): mp 188–191 °C (lit. 188–190 °C);[30] ^{1}H NMR δ 4.31 (d, 1H, H–15, $J_{15,16}$ = 2.98 Hz); δ 4.25 (d, 1H, H–18); δ 4.10 (dd, 1H, H–16, $J_{16,17}$ = 4.83 Hz); δ 3.96 (t, 1H, H–18, $J_{17,18}$ = 5.16 Hz). X-ray grade crystals were obtained by redissolving a small amount of the white solid in methanol with the aid of a heat gun, then cooling the solution to room temperature and storing at approximately 5 °C for several days.

Table 8. Details of the Data Collection, Solution and Refinement of the Crystal Structures of *N*,*N*′-Dimethyl-D-Glucaramide (**11**), Dipotassium D-Glucarate Monohydrate (**12**) and Sodium Potassium D-Glucarate Dihydrate (**13**)

	11	**12**	**13**
Empirical formula	$C_8H_{16}N_2O_6$	$C_6H_{10}K_2O_9$	$C_6H_{12}KNaO_{10}$
Crystal size (mm)	0.25×0.20×0.20	0.45×0.40×0.20	0.35×0.25×0.25
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions			
a (Å)	8.5371 (18)	7.8798(7)	7.5348(16)
b (Å)	5.2125 (11)	8.6524(16)	7.8276(10)
c (Å)	12.2551 (36)	15.9714(17)	18.9413(29)
α (°)	90	90	90
β (°)	106.88 (2)	90	90
γ (°)	90	90	90
V (Å^3)	521.9 (3)	1087.5(5)	1117.2
Z	2	4	4
Formula weight	236.2	304.3	306.2
$\rho_{calc.}$ (g/cm^3)	1.503	1.859	1.821
abs. coeff (mm^{-1})	0.129	0.908	0.561
F(000)	252	624	632
2θ range (°)	2.0–45.0	2.0–45.0	2.0–45.0
Scan type	ω-2θ	ω-2θ	ω-2θ
Index ranges	$-9 = h = 9$	$0 = h = 8$	$0 = h = 8$
	$-5 = k = 5$	$-9 = k = 9$	$-8 = k = 8$
	$-13 = l = 13$	$-17 = l = 17$	$-20 = l = 20$
Reflections collected	2720	3064	3169
Independent reflections	1362 ($R_{merge} = 3.88\%$)	1393 ($R_{merge} = 1.49\%$)	1465 ($R_{merge} = 2.05\%$)
Observed reflections	944 ($F > 6.0\sigma$)	1393 ($F > 6.0\sigma$)	1358 ($F > 6.0\sigma$)
Extinction correction (χ)	N/A	0.0197 (11)	0.0064 (4)
Min/max transmission	0.7347/0.9894	0.5517/0.6019	0.7965/0.8930
Number of parameters	153	197	213
Final R (observed data)	R = 6.55%	R = 2.11%	R = 2.12%
	wR = 6.04%	wR = 2.48%	wR = 2.20%
Final R (all data)	R = 8.66%	R = 2.15%	R = 2.48%
	wR = 10.97%	wR = 3.43%	wR = 2.59%
Goodness of fit	0.80	0.69	1.11
Largest Δ/σ	0.009	0.001	0.000
Mean Δ/σ	0.001	0.000	0.000
Data to param ratio	6.5:1	7.2:1	6.9:1
Largest diff. peak (eÅ^{-3})	0.71	0.31	0.25
Largest diff. hole (eÅ^{-3})	−0.59	−0.28	−0.28

Dipotassium D-Glucarate·H_2O (12). KOH was added to an aqueous (30 mL) slurry of monopotassium D-glucarate (10.0 g, 40 mmol) until all of the solid had dissolved (pH > 11). The pale yellow mixture was applied to a Bio-Rad AG® 11 AG (50–100 mesh) ion-retardation column. The product (detected by H_2SO_4 char) was contained in fractions 6–10. The fractions were combined and the colorless solution was concentrated at reduced pressure. The residue (11.1 g, 39 mmol, 96%) was crystallized from water to give x-ray grade crystals of **12**.

Anal. Calcd for $C_6H_8K_2O_8 \cdot H_2O$ (386.32): C, 23.68; H, 3.31; K, 25.69. Found: C, 23.86; H, 3.29; K, 25.76.

Sodium Potassium D-Glucarate·$2H_2O$ (13). NaOH pellets (~0.8 g, 20 mmol) were added to monopotassium D-glucarate (5.0 g, 20 mmol) slurried in deionized water. Insolubles were removed by filtration and the filtrate was applied to a Bio-Rad AG® 11 AG (50–100 mesh) ion-retardation column (previously washed with 0.5 M 1:1 KCl–NaCl). Fractions 7–15 (detected by H_2SO_4 char) were combined and concentrated to a clear, colorless syrup. When crystallization did not occur overnight, the syrup was seeded. Crystallization began immediately. The resulting crystals were washed with 1:1 methanol–water. The latter (4.25 g, 16 mmol, 78%) were then recrystallized from 1:1 methanol–water to give x-ray grade crystals of **13**.

Anal. Calcd for $C_6H_8KNaO_8 \cdot 2H_2O$ (270.21): C, 23.53; H, 3.95. Found: C, 23.70; H, 4.02.

Collection of the X-ray Diffraction Data and Solution of the Crystal Structures for 11, 12, and 13. The crystals were sealed into thin-walled glass capillaries, which were then mounted and aligned on an Enraf Nonius CAD4 single crystal diffractometer with κ-geometry. The data were collected with graphite-monochromatized Mo Kα radiation which were subsequently corrected for absorption as well as for Lorentz and polarization effects. Structures 12 and 13 were corrected for extinction by refining the χ parameter.[31] There was no evidence of decay in any of the data collections. Details of the data collection are found in Table 8.

All crystallographic calculations were carried out with the aid of an IBM–PC and the SHELXTL–PC program package.[32] The analytical form of the scattering factors for neutral atoms was used with both of real ($\Delta f'$) and imaginary ($\Delta f''$) components of anomalous dispersion included in the calculations.[33] The positional and anisotropic thermal parameters were refined for all non-hydrogen atoms. Refinement continued until convergence was reached. Each structure was checked by means of a final difference—Fourier synthesis. Specific details are collected in Table 7 or are outlined in the text.

***N,N′*-Dimethyl-D-Glucaramide (11).** A single crystal (dimensions 0.25 mm × 0.20 mm × 0.20 mm) was selected for the study. Cell parameters and Laue symmetry (2/m) revealed that the crystal belongs to the monoclinic crystal system. The systematic absence $0k0$ for $k = 2n + 1$ define the space group as being either the centrosymmetry space group $P2_1/m$ (No. 11) or the noncentrosymmetric space group $P2_1$ (No. 4). Intensity statistics clearly favored the latter case. This was later confirmed by correct solution and refinement of the crystal structure. 2720 reflections were collected which were merged into a unique set of 1362 reflections ($R_{int} = 3.88\%$).

The structure was solved by direct methods. Hydrogen atoms could not be located by direct examination of the difference — Fourier maps. Attempts to locate the hydrogen atoms by using low angle data ($\theta = 1^\circ$ to 10°) failed (the scattering factor of hydrogen atoms drops off quickly with increasing θ). By using only low angle data the contribution from the hydrogen atoms is maximized). The positional and isotropic thermal parameters were refined for both amine hydrogen atoms. All hydrogen atoms bound to carbon atoms were placed at calculated positions in the appropriate staggered geometry.[34] The hydroxyl hydrogen atoms were placed in calculated positions which maximized the intermolecular hydrogen bonding interactions. The positions determined resulted in torsion angles that closely resembled those for the crystal structure of **12** and the theoretically determined conformation **9a** as shown in Table 5. The isotropic thermal parameter of each hydrogen atom was set equal to the U_{eq} value of the atom to which it is bound. Absolute conformation was determined due to the crystal belonging to a noncentrosymmetric space group. This was attempted by the η-refinement procedure. This was later verified by the overlap of the structure with that of dipotassium D-glucarate monohydrate (**12**) (Figure 8).

The refinement converged (largest $\Delta/\sigma = 0.009$) with $R = 6.55\%$ and $wR = 6.04\%$ for those 944 reflections with $F_0 = 6\sigma(|F_o|)$. The final difference — Fourier map showed no anomalous features after refinement, with the residual electron density in the range -0.59 eÅ^{-3} to 0.71 eÅ^{-3}.

Dipotassium D-Glucarate Monohydrate (12). A single crystal (dimensions 0.45 mm×0.40 mm×0.20 mm) was selected for the study. Cell parameters and Laue symmetry (2/m 2/m 2/m) revealed that the crystal belongs to the orthorhombic crystal system. The systematic absences $h00$ for $h = 2n + 1$, $0k0$ for $k = 2n + 1$ and $00l$ for $l = 2n + 1$ uniquely define the space group the noncentrosymmetric space group $P2_12_12_1$ (No. 19). 3064 reflections were collected which were merged into a unique set of 1420 reflections ($R_{int} = 1.49\%$).

The structure was solved by direct methods. All hydrogen atoms were located from difference — Fourier maps and had their positional and isotropic thermal parameters refined. Because the compound crystallized in a noncentrosymmetric space group, absolute conformation needed to be determined. This was accomplished by the η-refinement procedure with $\eta = 0.98(8)$.

The refinement converged (largest $\Delta/\sigma = 0.001$) with $R = 2.11\%$ and $wR = 2.48\%$ for those 1393 reflections with $F_0 = 6\sigma$ ($|F_o|$). The final difference — Fourier map showed no anomalous features after refinement, with the residual electron density in the range -0.28 eÅ^{-3} to 0.31 eÅ^{-3}.

Sodium Potassium D-Glucarate Dihydrate (13). A single crystal (dimensions 0.35 mm×0.25 mm×0.25 mm) was selected for the study. Cell parameters and Laue symmetry (2/m 2/m 2/m) revealed that the crystal belongs to the orthorhombic crystal system. The systematic absences $h00$ for $h = 2n+1$, $0k0$ for $k = 2n + 1$ and $00l$ for $l = 2n + 1$ uniquely define the space group the noncentrosymmetric space group $P2_12_12_1$ (No. 19). 3169 reflections were collected which were merged into a unique set of 1359 reflections ($R_{int} = 2.05\%$).

The structure was solved by direct methods. All hydrogen atoms were located from difference — Fourier maps and had their positional and isotropic thermal parameters

refined. Because the compound crystallized in a noncentrosymmetric space group, absolute conformation needed to be determined. This was accomplished by the η-refinement procedure with $\eta = 1.11(10)$.

The refinement converged (largest $\Delta/\sigma = 0.000$) with $R = 2.12\%$ and $wR = 2.20\%$ for those 1358 reflections with $F_0 = 6\sigma$ (F_o). The final difference—Fourier map showed no anomalous features after refinement, with the residual electron density in the range -0.28 eÅ^{-3} to 0.25 eÅ^{-3}.

SUPPLEMENTARY MATERIAL

Details of x-ray crystallographic data for compounds **11**, **12**, and **13** are included as supplementary material. Tables of atomic coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre. These tables may be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK.

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