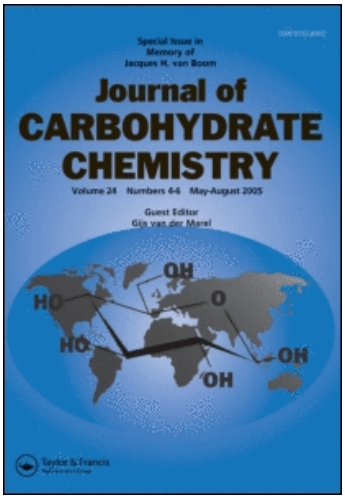

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MM3 Conformational Analysis and X-ray Crystal Structure of 2,3,4,5-Tetra-*O*-Acetyl-*N,N'*-Dimethyl-D-Glucaramide as a Conformational Model for the d-Glucaryl Unit of Poly(Alkylene 2,3,4,5-Tetra-*O*-Acetyl-d-Glucaramides)

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MM3 Conformational Analysis and X-ray Crystal Structure of 2,3,4,5-Tetra-*O*-Acetyl-*N,N′*-Dimethyl-D-Glucaramide as a Conformational Model for the D-Glucaryl Unit of Poly(Alkylene 2,3,4,5-Tetra-*O*-Acetyl-D-Glucaramides)

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This report describes the MM3 conformational analysis and X-ray crystal structure of tetra-*O*-acetyl-*N,N′*-dimethyl-D-glucaramide as a conformational model for the D-glucaryl monomer unit of poly(alkylene tetra-*O*-acyl-D-glucaramides). The driving force for this study was to determine the conformational preferences for the diacid

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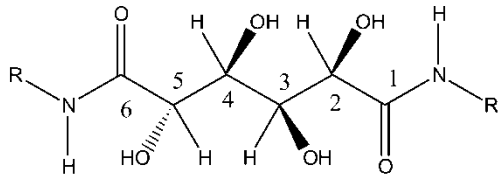
unit as a function of the increasing steric bulk of pendant *O*-acyl groups: acetyl, propanoyl, 2-methylpropanoyl, and 2,2-dimethylpropanoyl. The model dialkyl D-glucaramides all displayed a large vicinal proton coupling between the central backbone glucaryl hydrogens, indicating an essentially fixed *anti* conformational arrangement of these protons. The MM3 molecular mechanics program was then applied to calculate the corresponding low-energy conformations of the structurally simplest of these molecules, tetra-*O*-acetyl-*N*,*N*′-dimethyl-D-glucaramide (**4**). Given the large number of dihedral angles to be considered and the apparent rigidity of these molecules around the central carbons of the glucaryl backbone, a number of conformational approximations based upon model compounds were applied regarding the rotameric disposition of the pendant *O*-acetyl and terminal *N*-methyl groups. The calculated, and dominant, lowest energy conformer has a sickle structure very similar to the global minimum conformation previously calculated for unprotected D-glucaramide. The x-ray crystal structure data from **4** indicated an extended conformation in the solid state and gave solid-state torsion angle information that was comparable to that obtained computationally.

Keywords Molecular mechanics, MM3, Tetra-*O*-acetyl-N, *N*′-dimethyl-D-glucaramide

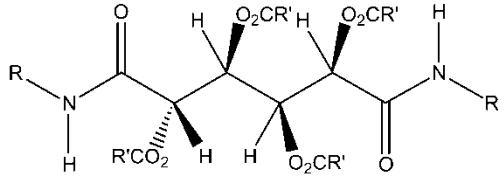
INTRODUCTION

There is considerable interest in this laboratory in a class of carbohydrate-based synthetic polymers entitled polyhydroxypolyamides (PHPAs)[1–9] as structurally variable and biodegradable materials derived in part from agriculturally important carbohydrates, particularly D-glucose from hydrolyzed starch. The polyamides of primary importance are made by condensation polymerization of esterified D-glucaric acid with diamines of choice.

PHPA preparation by way of direct condensation polymerization of unprotected, esterified aldaric acids (tartaric and *meso*-galactaric) with primary diamines was pioneered by Ogata and coworkers,[10–13] with later reports coming from the laboratories of Hashimoto[14,15] and those of the corresponding author.[2–9] One of our interests in the D-glucaric acid PHPAs is in learning more about the shapes of such polyamides in solution as a function of the conformational preferences of the glucaryl monomer unit. In a recent report describing results from an MM3(96) study of D-glucaramide (**1**, Fig. 1) as a model for the repeating D-glucaryl unit in poly(alkylene D-glucaramides),[2] it was found that out of 19,683 starting conformations only 10 were within a minimum energy range of +1 kcal/mol. Two of the ten conformations, the global minimum and the third lowest energy conformation, are almost identical sickle conformations and constitute about 40% of the calculated low-energy conformational population. These two latter conformations are devoid of destabilizing 1,3-eclipsed hydroxyl interactions from C-2 and C-4 that would occur in an extended conformation of D-glucaramide. Two of the three vicinal coupling constants from the glucaryl unit have intermediate

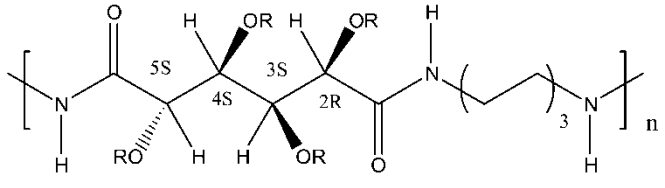


1, R = H; **2**; R = Me; **3**, R = *n*-C_6H_{13}



4 - 7, R = CH_3 R' = Me, Et, *i*-propyl, *t*-butyl

8 - 11, R = *n*-C_6H_{13} R' = as above



12; R = H; **13**; R = Ac

Figure 1: D-Glucaramide (**1**), *N,N'*-dimethyl and dihexyl-D-glucaramide (**2** and **3**), *O*-acyl derivatives (**4–11)** of **2** and **3**, and poly(hexamethylene 2,3,4,5-tetra-*O*-acetyl D-glucaramide) (**13**).

values ($^3J_{16,17} = 4.88$ Hz, $^3J_{17,18} = 5.16$ Hz; atom numbering in Fig. 3) corresponding to vicinal protons that are somewhere between *gauche* and *anti*, consistent with average coupling values from a number of conformations in equilibrium.

We have extended our interests to the poly(alkylene tetra-*O*-acyl-D-glucaramides) in order to probe the conformational distribution of these polyamides as a function of the increasing steric bulk of the pendant acyl groups. To that end *N,N'*-dimethyl (**2**) and dihexyl-D-glucaramide (**3**) were

acylated to give the corresponding tetra-*O*-acetyl, propanoyl, 2-methylpropanoyl, and 2,2-dimethylpropanoyl-D-glucaramides (**4**–**7** and **8**–**11**, respectively).

Unlike the extended, planar zig-zag conformation of adipic acid in nylon 6,6,[16] that of D-glucaric acid in the PHPAs in solution is not typically extended, as concluded from conformational studies carried out on D-glucaramide.[2] Consequently, the added bulkiness of pendant aliphatic *O*-acyl groups on the D-glucaryl unit should make this unit in the corresponding polyamides, and the smaller tetra-*O*-acyl D-glucaramides, even less likely to adopt extended conformations. The steric strain influence of pendant *O*-acyl, and in particular *O*-acetyl groups, on the conformations of derivatized acyclic monosaccharides was established by a number of investigators some years ago using vicinal proton coupling constants as a measure of dihedral angle values.[17–19] Proton coupling constants of *ca*. 2.5 to 4 Hz generally represent vicinal protons in a *gauche* orientation, and those of >7 Hz indicate principally an *anti* orientation of vicinal protons. The above generalities were demonstrated using NMR techniques for fully acetylated pentitols and hexitols,[17] peracetylated hexonitriles,[18] and peracetylated aldohexose dimethyl acetals and diethyl dithioacetals.[19] A similar study was also reported for nonacetylated aldopentose diethyl and diphenyldithioacetals.[20] D-*Gluco* configured derivatives invariably show sickle conformations where the 1,3-destabilizing interaction between acetoxy groups is avoided. The same 1,3-interactions are also reasonable for the title compound and related structures.

To this point, the only conformationally related studies of these PHPAs have been those related to the molecular mechanics (MM3)/^{1}H NMR studies on D-glucaramide[2] and polymers therefrom.[3] In this report we have focused on examining the conformational preferences that occur on the repeating D-glucaryl unit when it is fully *O*-acylated. Eight different tetra-*O*-acyl-*N,N*′-dialkyl-D-glucaramides were prepared and the magnitude of the vicinal proton coupling values (^{1}H NMR 400 MHz) compared in order to assess the influence of increasing steric bulk of *O*-acyl groups on the conformation of the D-glucaryl unit. In addition, tetra-*O*-acetyl-*N,N*′-dimethyl-D-glucaramide (**4**) was conformationally studied using the molecular mechanics MM3 program contained in the Tripos Alchemy 2000 package. Interpretation of vicinal coupling constant data for conformational analysis, as mentioned above, was used to reinforce a "model building" approach[21] applied to molecular modeling aspects of this study. With this method, low-energy conformations of small "building blocks" or "molecular fragments" were first established and those conformational preferences applied to modeling structurally related but larger and conformationally more complex molecules. The results from the ^{1}H NMR studies and the molecular modeling protocol applied to **4** are presented in the following section.

RESULTS AND DISCUSSION

^{1}H NMR Studies

The ^{1}H NMR spectra ($CDCl_3$) of the glucaryl units for both poly(hexamethylene 2,3,4,5-tetra-*O*-acetyl-D-glucaramide) (**13**) and 2,3,4,5-tetra-*O*-acetyl-*N,N* = -dihexyl-D-glucaramide (**8**) are shown in Figure 2. Comparison of the two spectra show that the proton chemical shifts on the polymer (**13**) and the corresponding model compound (**8**) are comparable, but only **8** displays ^{1}H NMR-resolved couplings that can be used to conformationally model the repeating D-glucaryl unit of the polymer (**13**). It was also observed that the ^{1}H NMR spectra of **8** and structurally simpler 2,3,4,5-tetra-*O*-acetyl-*N,N*′-dimethyl-D-glucaramide (**4**) are very similar in the glucaryl unit proton region, thus allowing use of **4** as a conformational model compound for the D-glucaryl unit in the polymer **13**.

Table 1 lists the chemical shifts of H15, H16, H17, and H18 and the vicinal coupling constants for *N,N*′-dimethyl-D-glucaramide (**2**), *N,N*′-dihexyl-D-glucaramide (**3**), their corresponding esters **4**–**7** and **8**–**11**, unprotected polyamide **12**, and *O*-acetylated polyamide **13**. The atom numbers for 2,3,4,5-tetra-*O*-acetyl-*N,N*′-dimethyl-D-glucaramide (**4**), Figure 3, and related diamides were generated from the molecular mechanics study.

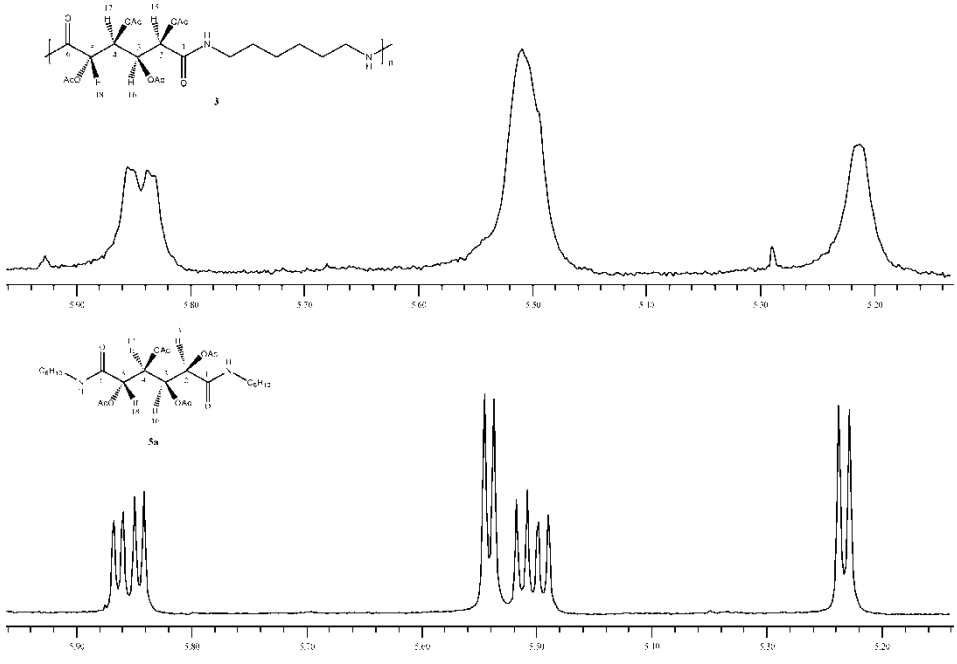


Figure 2: ^{1}H NMR spectra ($CDCl_3$), protons H15–H18, of poly(hexamethylene 2,3,4,5-tetra-*O*-acetyl-D-glucaramide) (**13**) and 2,3,4,5-tetra-*O*-acetyl-*N,N*′-dihexyl-D-glucaramide (**8**).

Table 1: Chemical shifts (δ, ppm) and coupling constants (J, Hz) for compounds **2–13**

Compound	δ (H (16)[a])	δ (H (15)[a])	δ (H (17)[a])	δ (H (18)[a])	$J_{15,16}$	$J_{16,17}$	$J_{17,18}$
2[b,d]	3.86 (m)	3.97 (d)	3.69 (m)	3.91 (t)	3.24	3.89	5.82
3[b,d]	3.85 (m)	3.96 (d)	3.67 (m)	3.90 (t)	3.88	3.24	6.47
4[c]	5.85 (d of d)	5.55 (d)	5.53 (d of d)	5.28 (d)	3.24	7.11	3.89
5[c]	5.85 (d of d)	5.55 (d)	5.54 (d of d)	5.29 (d)	3.23	7.76	3.88
6[c]	5.87 (d of d)	5.55 (d)	5.53 (d of d)	5.31 (d)	2.59	8.41	3.24
7[c]	5.88 (d of d)	5.59 (d)	5.52 (d of d)	5.37 (d)	1.83	8.61	2.75
8[c]	5.86 (d of d)	5.54 (d)	5.50 (d of d)	5.23 (d)	3.23	7.12	3.88
9[c]	5.87 (d of d)	5.56 (d)	5.52 (d of d)	5.26 (d)	3.24	7.12	3.88
10[c]	5.89 (d of d)	5.57 (d)	5.53 (d of d)	5.29 (d)	2.59	7.77	3.24
11[c]	5.88 (d of d)	5.57 (d)	5.50 (d of d)	5.34 (d)	1.90	8.25	2.54
12[b,d]	3.86 (m)	3.98 (t)	3.67 (m)	3.91 (t)	3.23	3.88	5.82
13[c]	5.83 (b)	5.50 (b)	5.50 (b)	5.21 (b)			

[a]Numbers in parentheses are the atom numbers assigned in the molecular mechanics studies.
[b]DMSO-d_6 as solvent.
[c]$CDCl_3$ as solvent.
[d]Coupling constants were obtained after adding a few drops of D_2O to the sample in DMSO-d_6 solution.

All of the tetra-*O*-acyl diamides have large H16–H17 coupling constants (7.11–8.61 Hz), implying large dihedral angles (ca. 180°).[22] H15–H16 and H17–H18 coupling constants are considerably smaller (1.83–3.89 Hz), suggesting a *gauche* arrangement of vicinal protons (ca. 60°).[22] In general, as the acyl groups become bulkier, $J_{16,17}$ becomes larger, indicating a sterically more restricted conformation with the H16 and H17 dihedral angle approaching 180°. In contrast, the corresponding H16–H17 couplings for unprotected **2** and **3** are 3.89 Hz and 3.24 Hz, respectively, values in keeping with an average *gauche* arrangement of H16–H17. Furthermore, $J_{17,18}$ values of 5.82 Hz and

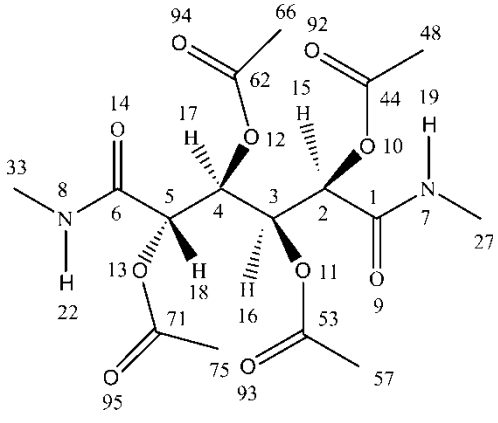


Figure 3: Numbering system for **4**.

6.47 Hz for **2** and **3**, respectively, represent larger average dihedral angles than those of the *O*-acylated diamides indicated above.

The coupling results from **4**–**11** established the following guidelines that were applied in the molecular modeling studies described below; H16–H17 are in a single *anti* arrangement, whereas H15–H16 and H17–H18 can each be in one of two *gauche* relationships.

Conformational Study of 2,3,4,5-tetra-*O*-acetyl-*N,N′*-dimethyl-D-glucaramide (4)

"Building Blocks" Approach Applied to Molecular Mechanics/Conformational Analysis of Compound **4**

Systematic searching for a global minimum by 120° rotations about single bonds of 2,3,4,5-tetra-*O*-acetyl-*N,N′*-dimethyl-D-glucaramide (**4**) would require 14,348,907 (3^{15}) starting conformations, based upon 15 separate torsion angles and typically three staggered conformations of atoms or groups attached to each of the nonterminal atoms. Among the 15 torsion angles, seven are derived from backbone carbons of **4**, while the other eight originate from the acyloxy groups (Table 2 and Figure 3).

For more complex tetra-*O*-acyl-*N,N′*-dimethyl-D-glucaramides (**5**–**8**), additional torsion angles have to be varied, resulting in even more starting conformations. Obviously, for such large and flexible molecules, application of a full conformational search routine represents a significant effort and requires an appropriate high-level computational capability. The alternatives to the full-space systematic search are methods based on random variation of coordinates such as molecular dynamics or Monte Carlo (MC) searching in Cartesian space[21] and MC searching in dihedral space.[21] As neither of these modeling approaches was readily available to us, a simplified "model building approach" to the computational problem was undertaken wherein some of the torsion angles were manually defined using small model

Table 2: Variable torsion angles in **4**

Backbone	Acyloxy moieties
H15-C2-C3-H16	C2-O10-C44-O92
H16-C3-C4-H17	C3-O11-C53-O93
H17-C4-C5-H18	C4-O12-C62-O94
O9-C1-N7-H19	C5-O13-C71-O95
O14-C6-N8-H22	H15-C2-O10-C44
O9-C1-C2-O10	H16-C3-O11-C53
O13-C5-C6-O14	H17-C4-O12-C62
	H18-C5-O13-C71

compounds ("building blocks") to simulate portions of larger **4**. A benefit of this model approach was that it provided us an opportunity to focus on how the individual component ester and amide functional groups and the differences in configurations on the chiral backbone carbons influence the overall conformation of **4** and related molecules. Ultimately we hope to be able to cross check the results we report here using a Monte Carlo searching in dihedral space protocol that we are presently developing for MM3.

Starting Rotamers of **4**

Based on the ^{1}H NMR results from **4,** four starting sickle rotamers were considered, all with the H16–H17 dihedral angle at 180° and the H15–H16 and H17–H18 dihedral angles $\pm$60°. The four rotamers were derived from the extended conformation by a 120° counterclockwise rotation about the C3–C4 bond and a 120° clockwise or counterclockwise rotation about the C2–C3 and C4–C5 bonds. Table 3 lists the dihedral angles set for the starting four rotamers (**4,** Fig. 4). Rules governing assignment of rotamer labels P, ${}_3G_4^+G^+$, etc., are found in reference 20.

"Building Blocks" Studies

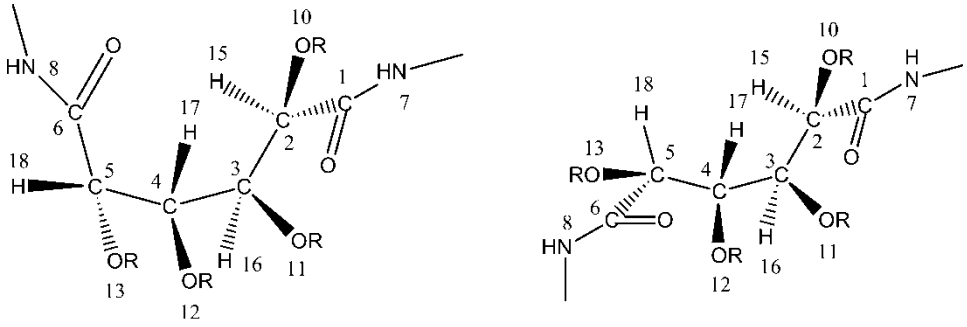
The "building block"molecules (Fig. 5) chosen to structurally mimic various parts of **4** in the conformational study were *N*-methylacetamide (**A**), (2*R* & 2S) *N*-methyl-2-acetoxypropanamide (**B** and **D)**, methyl acetate (**F**), and 2,3-diacetoxybutanes (**G, H**, and **I**).

Model 1: End C Model—N-methylacetamide (A)

N-Methylacetamide was the obvious model to search for the low-energy conformation of the C1–N7 and C6–N8 ends of **4** (Fig. 5). The O9-C1-N7-H19 dihedral angle was increased from 0.0° to 300.0° in 60° increments and the individual conformations were minimized with MM3 at a dielectric constant of 2.0. Two conformations were obtained, a lower-energy *Z* conformation **A2** and a higher-energy *E* conformation **A1**; the energy difference between the two conformers was 2.94 kcal/mol, as previously reported by Allinger and coworkers.[23] Consequently, the O9-C1-N7-H19 and

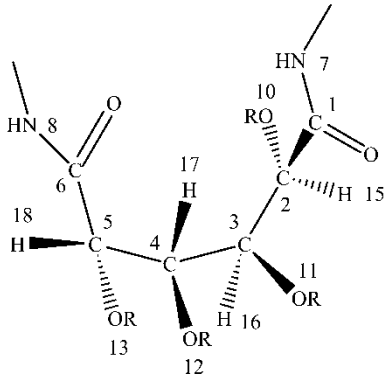
Table 3: Dihedral angles (ω, °) initially set for rotamers 1–4 of 2,3,4,5-tetra-*O*-acetyl-*N,N'*-dimethyl-D-glucaramide (**4)**.

	ω (H15–H16) (°)	ω (H16–H17) (°)	ω (H17–H18) (°)	Conformation
Extended	60	−60	180	P
Rotamer 1	60	180	−60	${}_3G_4^+G^-$
Rotamer 2	60	180	60	${}_3G_4^+G^+$
Rotamer 3	−60	180	−60	${}_2G_3^+G_4^+G^-$
Rotamer 4	−60	180	60	${}_2G_3^+G_4^+G^+$

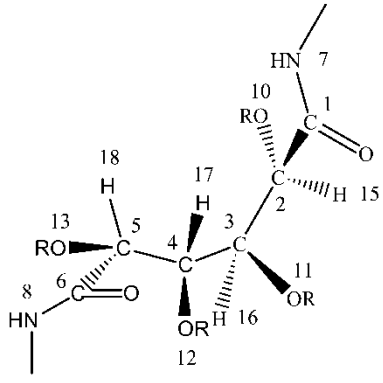


4, rotamer 1 ($_3G^-{}_4G^-$)

4, Rotamer 2 ($_3G^+{}_4G^+$)



4, Rotamer 3 ($_2G^+{}_3G^+{}_4G^-$)



4, Rotamer 4 ($_2G^+{}_3G^+{}_4G^+$)

$R = -C(O)CH_3$

Figure 4: The four starting rotamers of **4**.

O14-C6-N8-H22 dihedral angles on the four tetra-*O*-acetyl-*N,N′*-dimethyl-D-glucaramide (**4**) starting rotamers was set to 180.0°.

Model 2: C1–C2 and C5–C6 Model—N-methyl-2-acetoxypropanamide (B)

Enantiomeric (2*R*) and (2*S*)-*N*-methyl-2-acetoxypropanamide (**B** and **D**) were the models for the terminal acyloxy groups on the chiral carbons (C-2 and C-5) connected to the amide carbonyl groups, considering the O9-C1-C2-O10 and O13-C5-C6-O14 dihedral angles of **4**, respectively. From model **A2**, the H19-N7-C1-O9 dihedral angle of **B** was set to 180.0°, whereas the C2-O10-C44-O92 dihedral angle was set to 0.0° based upon results from the following Acyloxy Rotamer Model (methyl acetate, **F**) study. For the C-1 end of **4**, rotation clockwise about the C1–C2 bond in 60.0° increments from 0.0° to 300.0° generated six conformations of (2*R*)-*N*-methyl-2-acetoxypropanamide, which when minimized yielded two distinct conformations whose energy difference was 2.93 kcal/mol. The relevant dihedral angles for low-energy

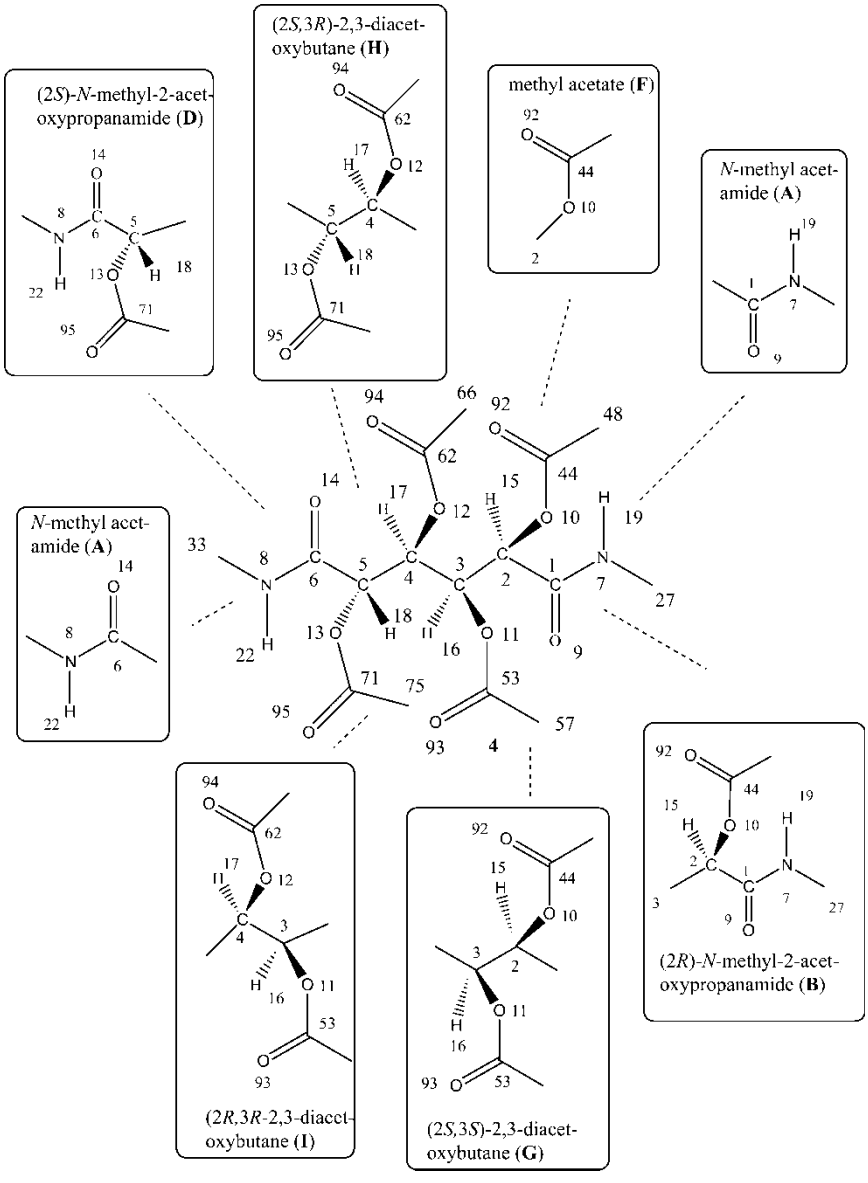


Figure 5: Compound **4**, and compounds **A**, **B**, **D**, **F, G**, **H** and **I** used to model structural component parts of **4**.

enantiomeric conformers of the C-1 and C-6 ends of **4, B1** and **D1**, respectively (Table 4), are the same, but both sets of values are included for clarity.

From the **B** and **D** models, the O9-C1-C2-O10 and O14-C6-C5-O13 dihedral angles were set to $+124.1^\circ$ and -124.1°, respectively, for the four starting rotamers of **4**.

Table 4: Dihedral angles (ω, °) in the **B1** and **D1** conformations of (2*R*)-*N*-methyl-2-acetoxypropanamide (2*S*)-*N*-methyl-2-acetoxypropanamide after MM3 minimization.

	B1		**D1**
ω (O9-C1-C2-C3) (°)	5.8	ω (O14-C6-C5-C4) (°)	−5.8
ω (O9-C1-C2-H15) (°)	−113.4	ω (O14-C6-C5-H18) (°)	113.4
ω (O9-C1-C2-O10) (°)	124.1	ω (O14-C6-C5-O13) (°)	−124.1
ω (N7-C1-C2-C3) (°)	−176.6	ω (N8-C6-C5-C4) (°)	176.6
ω (N7-C1-C2-H15) (°)	64.3	ω (N8-C6-C5-H18) (°)	−64.3
ω (N7-C1-C2-O10) (°)	−58.3	ω (N8-C6-C5-O13) (°)	58.3

Model 3: Acyloxy Rotamer Model—methyl acetate (F)

Methyl acetate served as the model to help determine the orientation of the carbonyl oxygen on each acetoxy group relative to the appropriate glucaryl unit backbone *O*-alkyl carbon, that is., the dihedral angle defined by C2-O10-C44-O92 and similarly the three other acyloxy groups on diamide **4**. Two conformations resulted from changing the C2-O10-C44-O92 dihedral angle of methyl acetate in 60° increments from 0° to 300° followed by MM3 energy minimization. The *Z* conformation (**F1**) was 8.71 kcal/mol lower in energy than the *E* conformation, in agreement with a previously reported energy difference.[24] Based upon this model study, the C2-O10-C44-O92, C3-O11-C53-O93, C4-O12-C62-O94, and C5-O13-C71-O95 dihedral angles were set to 0.0° for each of the starting rotamers of **4**.

Model 4: Vicinal Acyloxy Models—2,3-diacetoxybutanes

The remaining models address the rotameric disposition of the four *O*-acetyl groups on carbons 2–5 of **4** resulting from rotation around the C2-O10, C3-O11, C4-O12, and C5-O13 bonds. By use of conformationally and configurationally different 2,3-diacetoxybutanes as models, we wished to gain insight into the rotameric preferences of two acetoxyl groups on two vicinal chiral carbon atoms. The (2*S*,3*S*)-2,3-diacetoxybutane conformer **G1** was used to mimic diamide starting rotamers 1 and 2 of **4** with a *gauche* arrangement of H15–H16 (dihedral angle ca. +60°), and conformer **G2** was used to mimic starting diamide rotamers 3 and 4 with the second *gauche* arrangement of H15–H16 (dihedral angle ca −60°, Fig. 6). Similarly, conformers **H1** and **H2** of (2*S*,3*R*)-2,3-diacetoxybutane (**H**) were used to model the two *gauche* arrangements of H17–H18 (ca. −60°) on rotamers 1 and 3 and H17–H18 (ca +60°) on rotamers 2 and 4 (Fig. 7). (2*R*,3*R*)-2,3-Diacetoxybutane (**I**) mimicked the *anti* relationship (H16–H17) present in all starting rotamers 1–4 (Fig. 8).

Rotations about the C2-O10, C3-O11, C4-O12, or C5-O13 bonds in 120° increments gave nine, but not all unique, conformations in each case. The relevant dihedral angles generated from the lowest-energy conformer derived from each of the starting diacetoxybutanes (**G**, **H**, and **I**) were on the

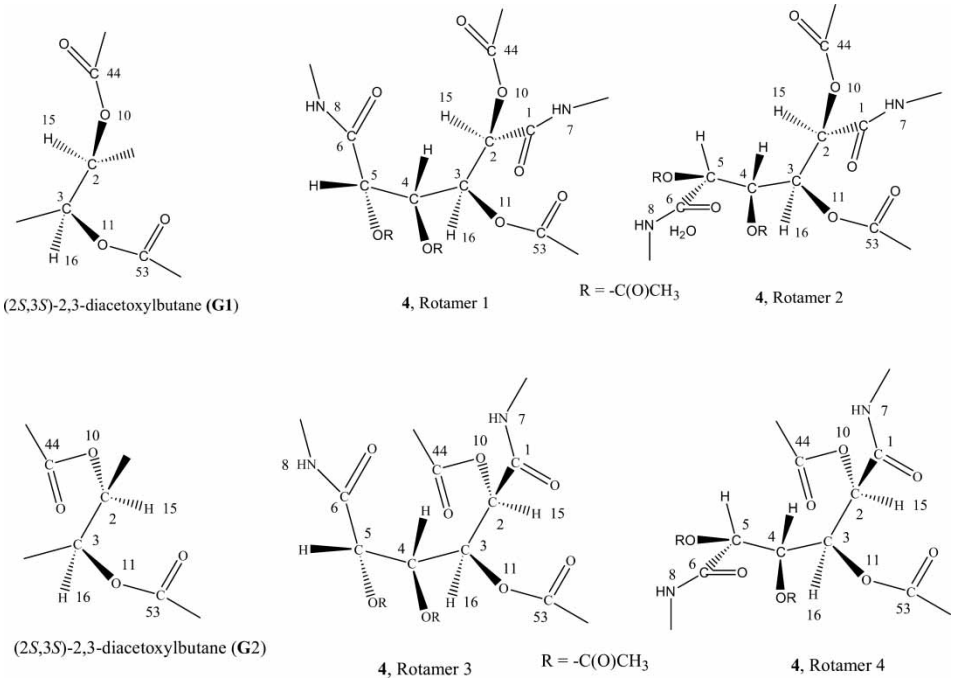


Figure 6: Vicinal Acyloxy Model (2*S*,3*S*)-2,3-diacetoxybutane **G1** (H15–H16 + 60°), for starting rotamers 1 and 2, and Model (2*S*,3*S*)-2,3-diacetoxybutane **G2** (H15–H16 −60°) for starting rotamers 3 and 4.

order of $\pm 40^{\circ}$. In concert with these results, Thibodeaux et al.,[25] using MM3 molecular mechanics and several quantum mechanics protocols, modeled the conformation of acetate groups as found on isopropyl acetate and 3,4,5-triacetoxytetrahydropyran, and concluded that in general these same H-C-O-C (carbonyl) conformations ranged from *eclipsed* to *gauche*. X-ray crystal structure data from penta-*O*-acetyl-β-D-galactopyranose and 164 additional examples in the literature also strongly supported the above conformational preference of acetate groups in the crystal state.[25] Consequently, all combinations of $+40^{\circ}$ and -40° for the H-C-O-C dihedral angles H15-C2-O10-C44, H16-C3-O11-C53, H17-C4-O12-C62, and H18-C5-O13-C71 were applied in the final conformational study of **4**. For each of the four acetoxy groups on **4**, 16 (2^4) conformations were generated from each of the four starting rotamers that were refined from Models 1–3, giving a total of 64 rotamers for computational comparison.

The Calculated Low Energy Rotamers of **4**

Molecular mechanics calculations, the "block diagonal then full matrix minimization" method at dielectric constant 2.0, were carried out on the 64 conformations of **4**. The four lowest energy conformations, **1 m**–**4 m** (Fig. 9), each

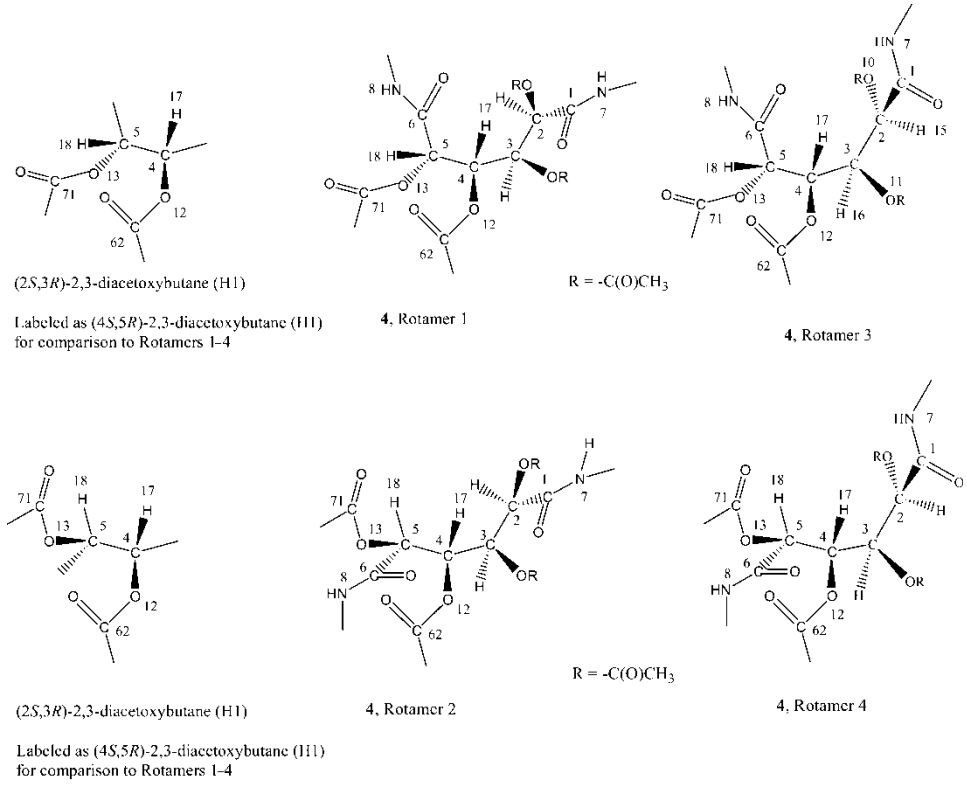


Figure 7: Vicinal Acyloxy Model (2*S*,3*R*)-2,3-diacetoxybutane **H1** (H15–H16, −60°), for starting rotamers 1 and 3, and Model (2*S*,3*R*)-2,3-diacetoxybutane **H2** (H15–H16, +60°), for starting rotamers 2 and 4.

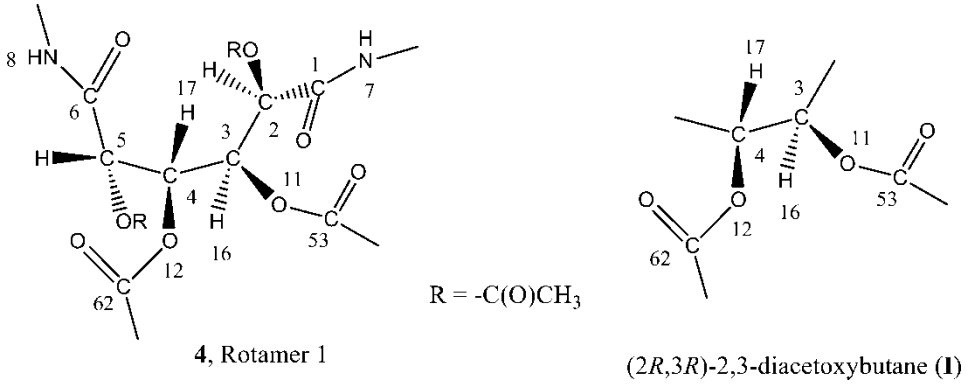


Figure 8: Vicinal Acyloxy Model (2*R*,3*R*)-2,3-diacetoxybutane **I** (H16–C17, +180°), for vicinal C3, C4 acetoxy groups of rotamers 1–4 (only rotamer 1 shown).

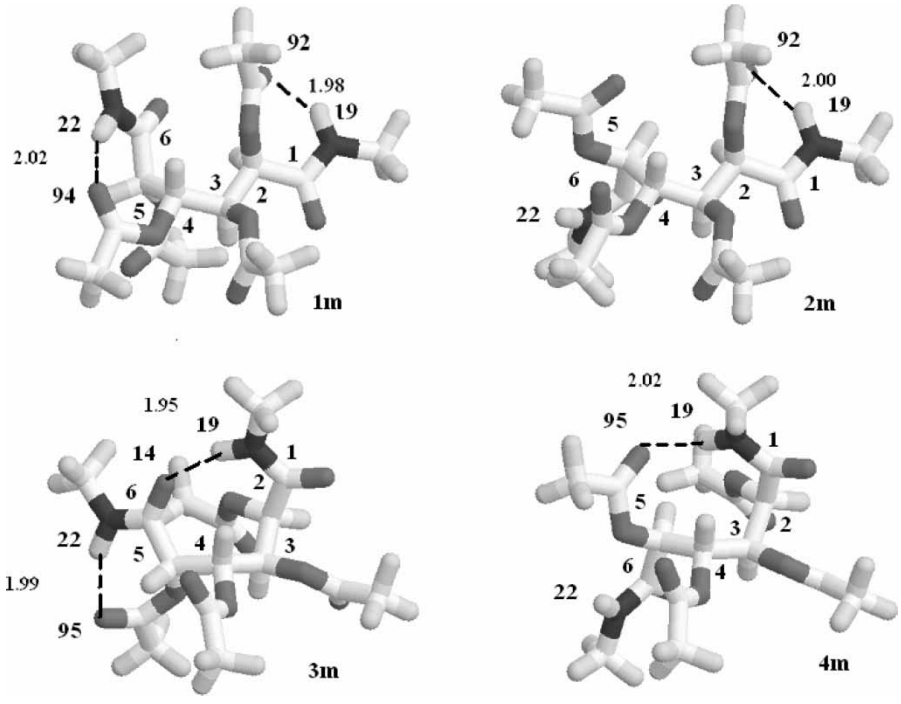


Figure 9: Low-energy conformations **1m**–**4m** derived from starting rotamers 1–4 (**4**) and intramolecular hydrogen bonding interatomic distances (Å).

derived from a different starting rotamer, were within a 1.07 kcal/mol range. The energy differences and calculated populations of these rotamers are shown in Table 5. The rotamer populations were calculated by a previously described method.[26]

The torsion angles suggested from the model studies and those of the low-energy rotamers (**1m**–**4m**) are listed in Table 6. The suggested and calculated angle values are generally comparable. Interestingly, the values from the O9-C1-C2-O10 and O14-C6-C5-O13 dihedral angles for the rotamers indicate that there is free rotation around the terminal C1–C2 and C5–C6 bonds. For example, for rotamer 3 the O9-C1-C2-O10 dihedral angle was set to $+124.1^{\circ}$ and the O14-C6-C5-O13 dihedral angle to -124.1°. However, in minimized

Table 5: Energy differences and calculated percent populations for the four lowest (of 64) energy conformers (**1m**–**4m**) of **4**.

Low energy conformers	**2m**		**4m**		**1m**		**3m**
Energy difference kcal/mol		0.55		0.33		0.19	
Calculated percent population	56.2		22.1		12.7		9.15

Table 6: MM3 calculated torsion angles (ω, °) of the rotamers **1m**–**4m** compared to those from the model studies.

Torsion Angle (ω,°)	1m	2m	3m	4m	X-ray[a]	Suggested	Model
O9-C1-N7-H19	173.4	174.4	−174.1	−174.4	178	180.0	End C Model
O14-C6-N8-H22	178.7	176.2	−171.6	177.7	−174	180.0	End C Model
O9-C1-C2-O10	135.9	132.4	−161.3	−158.1	24	+124.1	C1–C2 and C5–C6 Model
O14-C6-C5-O13	−9.0	151.2	−137.7	159.0	−27	−124.1	C1–C2 and C5–C6 Model
C2-O10-C44-O92	−5.6	−4.2	2.9	−0.5	−6.7	0.0	Acyloxy Rotamer Model
C3-O11-C53-O93	−0.4	0.0	−1.7	−1.6	2.4	0.0	Acyloxy Rotamer Model
C4-O12-C62-O94	−0.3	1.4	0.8	0.8	−6.9	0.0	Acyloxy Rotamer Model
C5-O13-C71-O95	1.3	1.9	5.3	2.1	−7.0	0.0	Acyloxy Rotamer Model
H15-C2-O10-C44	−34.5	−31.7	37.5	39.2	−49	$\sim\pm$40.0	Vicinal Acyloxy Model
H16-C3-O11-C53	−24.1	−25.7	38.0	40.2	22	$\sim\pm$40.0	Vicinal Acyloxy Model
H17-C4-O12-C62	44.6	14.6	36.6	28.1	9	$\sim\pm$40.0	Vicinal Acyloxy Model
H18-C5-O13-C71	−35.7	−40.3	30.5	−31.9	51	$\sim\pm$40.0	Vicinal Acyloxy Model

[a]*Torsion angles involving hydrogen atoms were calculated from torsion angles with C, O, and/or N atoms.*

3m, the set +124.1° angle went to a large negative angle (−161.3°), whereas the minimized second angle (−137.7°) was close to the suggested value. In rotamer **4m**, these same two angles underwent rotation from assigned +124.1° to minimized −158.1°, and −124.1° to +159.0°. The general consistency between the suggested dihedral angles from the models and those calculated from rotamers **1m–4m** suggests that the model approach as applied here is reasonable and should be applicable to similar molecules.

For rotamers **1m**, **3m**, and **4m,** the calculated H17-C4-C5-H18 dihedral angle is between +77° and −95° (Table 7), whereas that angle from lowest-energy rotamer **2m** (61.9°) is close to a typical *gauche* dihedral angle. The origin of the expansion of this angle in **1m**, **3m**, and **4m** from a typical *gauche* angle is clearly due in part to the intramolecular hydrogen bonds that each of these rotamers display at the N8-C6-C5 end of the molecule (Fig. 9) that influence the magnitude of the H17-C4-C5-H18 angle; rotamer **1m** N8-H22---O94═C62 (2.02 Å), rotamer **3m** N8-H22---O95 = C71 (1.99 Å) and C6═O14---H19-N7 (1.95 Å), and **4m** C71═O95---H19-N7 (2.02 Å). Hydrogen bonds were only considered at an interatomic distance of 2.10 Å or less.[27] In contrast, the lowest-energy rotamer **2m** does not exhibit any hydrogen bonding at the C6 end of the molecule and consequently the magnitude of the H17-C4-C5-H18 dihedral angle is essentially established by only steric influences. The dihedral angle differences in all of these rotamers is reflected in their calculated vicinal coupling constants using the Karplus/Altona equation[22] (Table 8). All except rotamer **2m** have a very small calculated H17-C4-C5-H18 coupling constant (0.20–0.93 Hz) consistent with angles that approach 90°. With the H16-C3-C4-H17 dihedral angle approaching 180° for all four rotamers, the calculated couplings are larger, but in the range of the observed value of 7.6 Hz.

Table 7: MM3 calculated dihedral angles (ω, °) from rotamers **1m**–**4m**.

	1m	2m	3m	4m
ω (H15-C2-C3-H16) (°)	60.5	57.1	−54.1	−59.8
ω (H16-C3-C4-H17) (°)	177.2	173.7	−176.6	−174.8
ω (H17-C4-C5-H18) (°)	−95.0	61.9	−82.2	77.0

Table 8: Calculated[22] ^{1}H NMR vicinal coupling constant values (J, Hz) from low energy rotamers **1m**–**4m**, and calculated average and observed values for **1**.

	1m	2m	3m	4m	Calcd average value	Observed ($CDCl_3$)
$J_{15,16}$ (Hz)	0.91	1.23	4.73	3.90	2.10	3.17
$J_{16,17}$ (Hz)	9.93	9.64	10.28	10.34	9.89	7.62
$J_{17,18}$ (Hz)	0.84	2.20	0.73	0.93	1.61	3.81

Comparison of 2,3,4,5-tetra-*O*-acetyl-*N,N′*-dimethyl-D-glucaramide (4) and D-glucaramide (1) - molecular modeling methods and results

A "systematic search"/"grid search" method[21] was applied to conformational studies of D-glucaramide (**1**) at dielectric constant 3.5 generating 19,683 (3^9) starting conformations,[2] from which 2,085 distinct conformations were obtained after MM3 minimization ("block diagonal then full matrix minimization method"). Among the 10 lowest-energy conformations (energy difference within 1 kcal/mol), nine adopt a sickle conformation. A single extended conformation accounts for only 4.7% of the 10 low-energy forms. The global minimum for **1** has a ${}_3G_4^+G^-$ conformation and accounts for 24.0% of the population. An almost identical conformation (**1**–3a) accounts for an additional 16.2%.[21]

The global minimum of D-glucaramide (**1**) and the lowest-energy rotamer of tetra-*O*-acetyl-*N,N′*-dimethyl-D-glucaramide (**2m**) are shown in Figure 10. The two conformers are strikingly similar in the conformational disposition of C1–C5 and the direct substituents on C1–C4. However, relative to **2m**, generation of low-energy conformer **1** involves a 120° counterclockwise rotation around C4–C5, with **1** being stabilized, even at a dielectric constant of 3.5, by a hydrogen bond between C6═O14 and H23-O16. The N7-H19---O92═C44 (2.00Å) **2m** conformer hydrogen bond appears to not alter the conformational disposition of C1–C5 in **2m** compared to **1**, whereas the C6═O14---H23-O16 hydrogen bond of **1** biases the C6 end of the molecule making **1** less extended than **2m**. The conformational similarity between these two low-energy

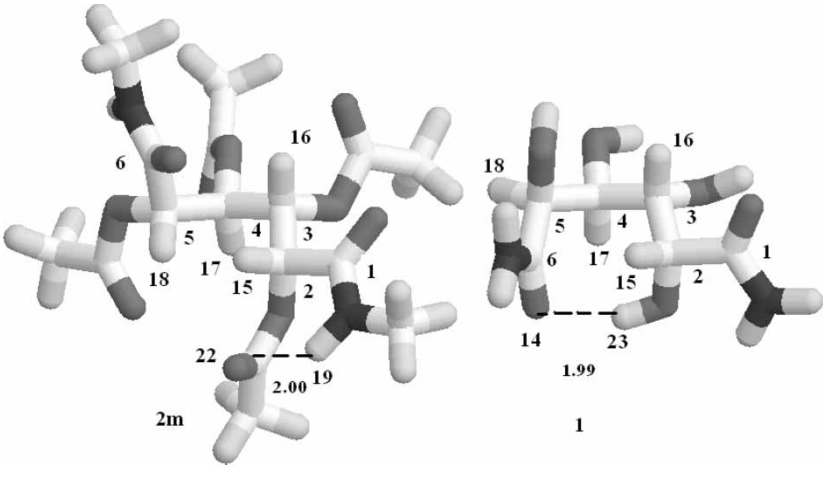


Figure 10: The low-energy conformer **2m** and global minimum conformer of D-glucaramide **1** with intramolecular hydrogen bonds (Å).

structures is further evidence that the relatively simple model approach used here to evaluate **2m** has merit for acyclic molecules of this type.

X-ray Crystal Structure of 4

The solid-state structure of **4** (Fig. 11) has a fully extended conformation with some hydrogen bonding (Fig. 12) between the amide hydrogen atoms on one molecule and the amide carbonyl oxygen atoms on another molecule. Similar extended x-ray crystal structures were recently reported by Styron et al. for the parent molecule, *N,N′*-dimethyl-D-glucaramide, and a dipotassium disalt of glucaric acid.[2]

While the solid-state form of **4** does not match that of the solution form of **4**, the torsion angles suggested by the model compounds described for the low-energy conformers of **4** (Table 7) are reasonably close to those obtained from the x-ray crystal structure data and reinforce the model approach applied here. As previously mentioned, the C1–C2 and C5–C6 models do not work for **4,** or similar amides, because of free rotation around the bond connecting the end two carbons.

Crystal data and structure refinement for tetra-*O*-acetyl-*N,N′*-dimethyl-D-glucaramide (**4**) are presented in Table 9. Tables of atomic coordinates, bond lengths, bond angles, anisotropic displacement parameters, hydrogen

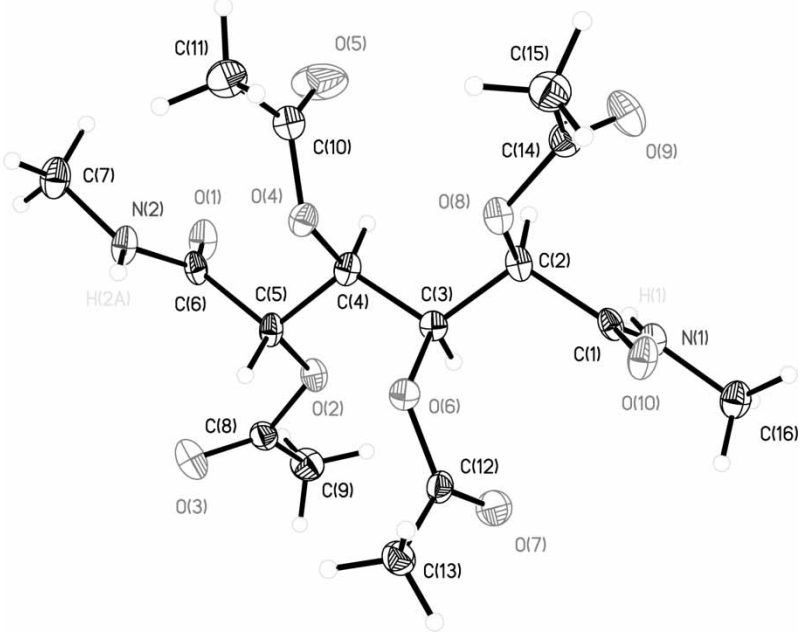


Figure 11: X-ray crystal structure of 2,3,4,5-tetra-*O*-acetyl-*N,N′*-dimethyl-D-glucaramide (**4**).

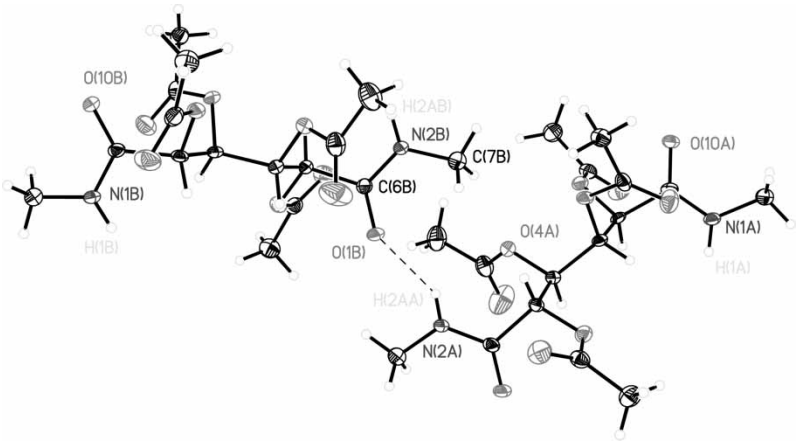


Figure 12: Intermolecular hydrogen bonding between pairs of **4** in the solid state.

Table 9: Crystal data and structure refinement for tetra-*O*-acetyl- *N,N'*-dimethyl D-glucaramide (**4**).

Identification code	DK1	
Empirical formula	C16 H24 N2 O10	
Formula weight	404.37	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.7306(3) Å	$\alpha = 90^\circ$
	b = 9.1545(3) Å	$\beta = 106.910(2)^\circ$
	c = 12.9362(5) Å	$\gamma = 90^\circ$
Volume	989.21(6) $Å^3$	
Z	2	
Density (calculated)	1.358 Mg/m^3	
Absorption coefficient	0.979 mm^{-1}	
F(000)	428	
Crystal size	0.37 × 0.16 × 0.10 mm^3	
Theta range for data collection	3.57 to 66.05°.	
Index ranges	−10 <= h <= 9,	
	−10 <= k <= 10,	
	−13 <= l <= 14	
Reflections collected	4579	
Independent reflections	2899 (R(int) = 0.0474)	
Completeness to theta = 66.05°	93.9%	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	2899/1/259	
Goodness-of-fit on F^2	1.040	
Final R indices (I > 2sigma(I))	R1 = 0.0431, wR2 = 0.1097	
R indices (all data)	R1 = 0.0471, wR2 = 0.1123	
Absolute structure parameter	0.0(2)	
Largest diff. peak and hole	0.254 and −0.222 e.$Å^{-3}$	

coordinates and isotropic displacement parameters, and torsion angles have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK, e-mail deposit@ccde.cam.ac.uk, and are available—CCDC number 296398.

EXPERIMENTAL

General Methods

^{1}H NMR spectra were obtained on a Varian Unity Plus 400 MHz spectrometer. Chemical shifts measured in dimethyl sulfoxide-d_6 and chloroform-d_1 (certified A.C.S. grade) are referenced to nondeuterated solvent signals. Melting points were obtained on a Fisher-Johns melting point apparatus and are reported uncorrected. Solvent evaporations were carried out at reduced pressure. Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia. High-resolution mass spectra (HRMS) were obtained using electrospray ionization (ESI) with a Micromass LCT instrument. All solvents used were reagent grade unless stated otherwise. Hexamethylenediamine was recrystallized from hexanes prior to use. Methanol/diamine solutions were standardized by diluting an aliquot of the solution with water and titrating with standardized hydrochloric acid using a pH meter to determine titration end points. Structures were minimized using MM3 Tripos Alchemy 2000 software and applying the block diagonal minimization method.

Collection of X-ray Diffraction Data and Solution of the Crystal Structure for 4

A suitable crystal of **4** was coated with Paratone N oil, suspended in a small fiber loop, and placed in a cooled nitrogen gas stream at 100 K on a Bruker D8 SMART 1000 CCD sealed tube diffractometer with graphic monchromated CuK_α (1.54178 Å) radiation. Data were measured using a series of combinations of phi and omega scans with 10-second frame exposures and 0.3° frame widths. Data collection, indexing, and initial cell refinements were all carried out using SMART[28] software. Frame integration and final cell refinements were done using SAINT[29] software. The final cell parameters were determined from least-squares refinement of 4,070 reflections.

The structure was solved using direct methods and difference Fourier techniques (SHELXTL, V5.10).[30] Hydrogen atoms were placed in their expected chemical positions using the HFIX command and were included in the final cycles of least squares with isotropic Uij's related to the atoms ridden upon. The C-H distances were fixed at 0.93 Å (aromatic and amide),

0.98 Å (methine), 0.97 Å (methylene), or 0.96 Å (methyl). All nonhydrogen atoms were refined anisotropically. Scattering factors and anomalous dispersion corrections are taken from the *International Tables for X-ray Crystallography*.[31] Structure solution, refinement, graphics, and generation of publication materials were performed by using SHELXTL, V5.10 software.

2,3,4,5-Tetra-*O*-acetyl-*N,N′*-dimethyl-D-glucaramide (4)

Acetic anhydride (3 mL, 31.7 mmol) was added dropwise to a stirred solution of *N,N′*-dimethyl-D-glucaramide (**2**,[2] 307 mg, 1.30 mmol) dissolved in cold (ice bath) anhydrous pyridine (9 mL). The reaction mixture was kept cold and stirred for 30 min, and then stirred at rt overnight. Ice cold water (35 mL) was added to the reaction mixture, which was stirred for 2 h. The aqueous solution was then extracted with dichloromethane (5 × 20 mL) and the combined dichloromethane phases were extracted with deionized water (30 mL), dried over sodium sulfate, concentrated to a syrup to which toluene (4 × 10 mL) was added, and then evaporated under reduced pressure to remove residual pyridine and water. The crude product (white powder) was dried under vacuum overnight and recrystallized from ethanol to give 2,3,4,5-tetra-*O*-acetyl-*N,N′*-dimethyl-D-glucaramide (**4**, 264.5 mg, 0.95 mmol, 50.07%): mp 228–229°C; HRMS: Calcd for $C_{16}H_{24}N_2O_{10}$ $(M + H^+)$ m/z 405.1509. Found: 405.1511.

2,3,4,5-Tetra-*O*-propanoyl-*N,N′*-dimethyl-D-glucaramide (5)

Propanoyl chloride (0.60 mL, 10.6 mmol) was added dropwise to a stirred solution of *N,N′*-dimethyl-D-glucaramide (**2**,[2] 311 mg, 1.32 mmol) dissolved in cold anhydrous pyridine (2.5 mL) (ice bath). The reaction mixture was kept cold and stirred for 3.7 h, stirred at rt for 30 min, and diluted with dichloromethane (6 mL), and the organic phase was washed with saturated aqueous sodium bicarbonate solution (3 × 6 mL). The dichloromethane solution was dried over sodium sulfate, concentrated to a syrup to which toluene (2 × 15 mL) was added, and then evaporated under reduced pressure to remove residual pyridine and water. The crude product (amber syrup) was dried under vacuum overnight and purified by chromatography on a column of silica gel with ethyl acetate/hexane (8:2 v/v) to give chromatographically pure 2,3,4,5-tetra-*O*-propanoyl-*N,N′*-dimethyl-D-glucaramide (**5**, 470.5 mg, 1.02 mmol, 77.45%): mp 115–116°C; HRMS: Calcd for $C_{20}H_{32}N_2O_{10}$ $(M + H^+)$ m/z 461.2135. Found: 461.2148.

2,3,4,5-Tetra-*O*-(2-methylpropanoyl)-*N,N′*-dimethyl-D-glucaramide (6)

4-Dimethylaminopyridine (4.3 mg, 0.02 mmol) was added to a stirred solution of *N,N′*-dimethyl-D-glucaramide (**2**,[2] 94.1 mg, 0.40 mmol) dissolved in cold (ice bath) anhydrous pyridine (1.5 mL). Isobutyric anhydride (0.82 mL, 4.80 mmol) was added dropwise to the solution, and the reaction mixture was allowed to warm to rt and then stirred at 60°C for 24 h. The reaction was then cooled to 0°C, and poured into ice water (4 mL), and the mixture was stirred for 40 min and then diluted with dichloromethane (4 mL). The aqueous phase was extracted with dichloromethane (2 × 4 mL) and the combined dichloromethane solution was dried over magnesium sulfate, concentrated to a syrup to which toluene (4 × 10 mL) was added, and then evaporated under reduced pressure to remove residual pyridine and water. The crude product (light yellow syrup) was purified by chromatography on a column of silica gel with ethyl acetate/hexane (1:1) to give colorless, syrupy 2,3,4,5-tetra-*O*-(2-methylpropanoyl)-*N,N′*-dimethyl-D-glucaramide (**6**, 168.1 mg, 0.33 mmol, 81.69%); HRMS: Calcd for $C_{24}H_{40}N_2O_{10}$ $(M + H^+)$ m/z 517.2761. Found: 517.2746.

2,3,4,5-Tetra-*O*-(2,2-dimethylpropanoyl)-*N,N′*-dimethyl-D-glucaramide (7)

Pivaloyl chloride (240 μL, 1.93 mmol) was added dropwise to a stirred suspension of *N,N′*-methyl-D-glucaramide (**2**,[2] 46.1 mg, 0.20 mmol) in anhydrous pyridine (1.0 mL). 4-Dimethylaminopyridine (2.1 mg) and 1-methylimidazole (4 drops) were added to the reaction mixture, which was stirred at rt for 24 h, diluted with dichloromethane (2 mL), washed with saturated aqueous sodium bicarbonate solution (4 × 2 mL), dried over sodium sulfate, concentrated to a syrup to which toluene (2 × 15 mL) was added, and then evaporated under reduced pressure to remove residual pyridine and water. The crude product (amber syrup) was dried under vacuum overnight and purified by column chromatography with ethyl acetate/hexane (1:3 v/v) to give colorless, syrupy 2,3,4,5-tetra-*O*-(2,2-dimethylpropanoyl)-*N,N′*-dimethyl-D-glucaramide (**7**, 22.3 mg, 0.04 mmol, yield 20.00%): HRMS: Calcd for $C_{28}H_{49}N_2O_{10}$ $(M + H^+)$ m/z 573.3387. Found: 573.3398.

N,N′-Dihexyl-D-glucaramide (3)[32]

n-Hexylamine (10 mL, 75.10 mmol) was added at rt to methyl D-glucarate 1,4-lactone[7] (5.40 g, 26.21 mmol) dissolved in methanol (200 mL). The reaction mixture was stirred for 1 h, and the white solid product was removed by filtration, washed with methanol (2 × 15 mL), and then dried

under reduced pressure at rt for 1.5 h to give *N,N′*-dihexyl-D-glucaramide (**3,** 9.67 g, 25.72 mmol, 98.12%): mp 177.0–177.5°C, (lit mp[13] 170–172°C).

2,3,4,5-Tetra-*O*-acetyl-*N,N′*-dihexyl-D-glucaramide (8)

Acetic anhydride (3 mL, 31.8 mmol) was added dropwise to a stirred solution of *N,N′*-dihexyl-D-glucaramide (**3**; 325.1 mg, 0.87 mmol) dissolved in cold (ice bath) anhydrous pyridine (9 mL). The reaction mixture was stirred cold for 30 min and then at rt overnight. Ice cold water (35 mL) was added to the reaction mixture, which was then stirred for 2 h and extracted with dichloromethane (5 × 20 mL). The combined dichloromethane solution was extracted with deionized water (30 mL), dried over sodium sulfate, concentrated to a syrup to which toluene (4 × 10 mL) was added, and then evaporated under reduced pressure to remove residual pyridine and water. The crude product (white powder) was dried under vacuum overnight and recrystallized from ethyl acetate/hexane to give 2,3,4,5-tetra-*O*-acetyl-*N,N′*-dihexyl-D-glucaramide (**8,** 277.5 mg, 0.51 mmol, yield 58.93%): mp 107.5–110.5°C; HRMS: Calcd for $C_{26}H_{45}N_2O_{10}$ $(M + H^+)$ m/z 545.3074. Found: 545.3085.

2,3,4,5-Tetra-*O*-propanoyl-*N,N′*-dihexyl-D-glucaramide (9)

Propanoyl chloride (0.60 mL, 6.88 mmol) was added dropwise to a stirred solution of *N,N′*-dihexyl-D-glucaramide (**3**; 321 mg, 0.85 mmol) dissolved in cold (ice bath) anhydrous pyridine (2 mL). The chilled reaction mixture was stirred for 3.5 h, warmed to rt and stirred for 30 min, and diluted with dichloromethane (6 mL), and the organic phase was washed with saturated aqueous sodium bicarbonate solution (3 × 6 mL). The dichloromethane solution was dried over sodium sulfate, concentrated to a syrup to which toluene (2 × 10 mL) was added, and then evaporated under reduced pressure to remove residual pyridine and water. The crude product (amber syrup) was dried under vacuum overnight and purified by chromatography on a column of silica gel with ethyl acetate/hexane (4:6 v/v) to give pure, syrupy solid, 2,3,4,5-tetra-*O*-propanoyl-*N,N′*-dihexyl-D-glucaramide (**9**; 380 mg, 0.63 mmol, 74.12%): HRMS: Calcd for $C_{30}H_{53}N_2O_{10}$ $(M + H^+)$ m/z 601.3700. Found: 601.3683.

2,3,4,5-Tetra-*O*-(2-methylpropanoyl)-*N,N′*-dihexyl-D-glucaramide (10)

Isobutyryl chloride (0.63 mL, 6.55 mmol) was added dropwise to a stirred solution of *N,N′*-dihexyl-D-glucaramide (**3**, 306 mg, 0.81 mmol) dissolved in cold (ice bath) anhydrous pyridine (1.6 mL). The chilled reaction mixture was

stirred for 4 h, warmed to rt and stirred for 3 h, diluted with dichloromethane (6 mL), and the resulting solution was washed with saturated aqueous sodium bicarbonate solution (2 × 6 mL). The dichloromethane solution was dried over sodium sulfate, concentrated to a syrup to which toluene (2 × 15 mL) was added, and then evaporated under reduced pressure to remove residual pyridine and water. The crude product (amber syrup) was dried under vacuum overnight and purified by column chromatography with ethyl acetate/hexane (4:6 v/v) to give pure syrupy 2,3,4,5-tetra-*O*-(2-methylpropanoyl)-*N,N′*-dihexyl-D-glucaramide (**10,** 250 mg, 0.38 mmol, 46.89%): HRMS: Calcd for $C_{34}H_{61}N_2O_{10}$ $(M + H^+)$ m/z 657.4326. Found: 657.4353.

2,3,4,5-Tetra-*O*-(2,2-dimethylpropanoyl)-*N,N′*-dihexyl-D-glucaramide (11)

Pivaloyl chloride (1.2 mL, 9.74 mmol) was added dropwise to a stirred solution of *N,N′*-dihexyl-D-glucaramide (**3,** 310 mg, 0.83 mmol) dissolved in cold (ice bath) anhydrous pyridine (1.6 mL). The chilled reaction mixture was stirred for 4 h and warmed to 60°C for 5.5 h. A 10% pyridine solution of 4-dimethylaminopyridine (5 drops) was added to the reaction mixture, which was then stirred at rt for 13 h, diluted with dichloromethane (6 mL), washed with saturated aqueous sodium bicarbonate solution (2 × 6 mL), dried over sodium sulfate, and concentrated to a syrup. Toluene (2 × 10 mL) was then added to the syrup and the solution concentrated under reduced pressure to remove residual pyridine and water. The crude product (amber syrup) was dried under vacuum overnight and purified by column chromatography with ethyl acetate/hexane (2:8 v/v) to give pure syrupy solid, 2,3,4,5-tetra-*O*-(2,2-dimethyl)propanoyl)-*N,N′*-dihexyl-D-glucaramide (**11,** 224 mg, 0.31 mmol, yield 39.09%): HRMS: Calcd for $C_{38}H_{69}N_2O_{10}$ $(M + H^+)$ m/z 713.4952. Found: 713.4982.

Poly(hexamethylene 2,3,4,5-tetra-*O*-acetyl-D-glucaramide) (13)

Acetic anhydride (3 mL, 31.8 mmol) was added dropwise to a stirred solution of poly(hexamethylene D-glucaramide)[7] (**12**, 200 mg, 0.69 mmol) dissolved in cold (ice bath) anhydrous pyridine (8 mL). The reaction mixture was stirred for 24 h at rt. Deionized water (35 mL) was added to the reaction mixture, which was stirred for another 2 h and then extracted with dichloromethane (3 × 35 mL). The combined organic solution was extracted with deionized water (20 mL), dried over sodium sulfate, concentrated to a syrup to which toluene (4 × 10 mL) was added, and then evaporated under reduced pressure to remove residual pyridine and water. The white solid was dried

under vacuum at rt to crude poly(hexamethylene 2,3,4,5-tetra-*O*-acetyl-D-glucaramide) (**13**, 146 mg, 0.32 mmol, 46.38%) used directly for ^{1}H NMR analysis.

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