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Conformational Preferences of *cis*-1,3-Cyclopentanedicarboxylic Acid and Its Salts by ^{1}H NMR Spectroscopy: Energetics of Intramolecular Hydrogen Bonds in DMSO

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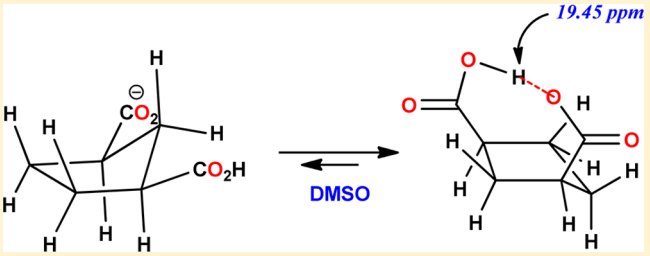
Supporting Information

ABSTRACT: The conformational populations of *cis*-1,3-cyclopentanedicarboxylic acid (**1**) and its mono- and dianion were established in DMSO solution by comparing the vicinal proton−proton coupling constants ($^3J_{HH}$) obtained in solution to their theoretical counterparts. Geometries used for $^3J_{HH}$ theoretical estimation (using Karplus-type equations) were obtained from optimized structures at the B3LYP/6-31G-(2d,2p) level. The diacid (**1**) adopted many conformations, whereas the ionized species (**1A** mono- and **1B** dianion) assumed single conformations. A downfield chemical shift of 19.45 ppm ($\Delta\delta_H$ = 7.43 ppm) observed at −60 °C was indicative of intramolecular hydrogen bonding in **1A**, which was later corroborated by determining the ratio of the first (K_1) to the second (K_2) ionization constants. K_1/K_2 in DMSO (1.3×10^7) was significantly larger than the value in water (2×10). In addition, K_1/K_E = 200 (where K_E is the acidity constant of the monomethylester of **1**) was greater than the intramolecular hydrogen bonding threshold value of 2. The calculated intramolecular hydrogen bond strength of **1A** was ∼3.1 kcal mol^{-1}, which is ∼2.7 kcal mol^{-1} more stable than the values for *cis*-1,3-cyclohexanedicarboxylic acid (**2A**). Thus, the relative energies of intramolecular hydrogen bonding in the monoanions **1A** and **2A** suggests that 1,3-diaxial conformers are more favored for cyclopentane than for cyclohexane rings.



INTRODUCTION

The conformational analysis of cycloalkanes has been an integral part of physical organic chemistry. Modern organic chemistry texts often provide detailed analysis of the various conformations of cyclohexanes with respect to the stereochemistry of six-membered rings, but those of cyclopentanes have received much less attention. Yet many natural products including steroids, prostaglandins, sugars, and nucleotides consist of or possess five-membered rings. The reason for this neglect stems from the conformational complexities associated with cyclopentanes as opposed to that of cyclohexanes, which adopt "rigid" conformations.[1,2] For instance, it takes more than 10 kcal mol^{-1} of energy to displace cyclohexane from its chair conformation,[2,3] and hence, the quantitative measurements of the different conformers of cyclohexanes have been achieved by dynamic NMR spectroscopic methods.[4,5] Similar quantifications for cyclopentanes are difficult because the energy barriers to ring flipping between the distinct conformers are low. By taking advantage of cyclohexane's rigidity, Winstein et al.[6] developed a numerical scale called the "*A* value", which represents the averages of the equilibria for equatorial to axial in monosubstituted cyclohexanes. With these *A* values, it is possible to predict the dominant chair isomer of a substituted cyclohexane with a high level of accuracy. However, similar rules are not applicable to cyclopentanes. For example, a number of studies concluded that chlorine prefers the axial position in chloropentane,[7−9] whereas in cyclohexane, a chlorine substituent has been found to be more stable in the equatorial position.[10] Similar results were found for methylcyclopentane. On the basis of the ^{13}C chemical shifts of methylcyclopentane, Roberts et al.[11] suggested that the most stable form has an axial methyl group, although the *A* value for methyl group in cyclohexane is 1.70 kcal mol^{-1} more in favor of the equatorial isomer.[12]

The ring strains in planar cyclopentane are partially relieved by puckered conformations. There are two symmetrical puckered conformations, the envelope **E** and the half-chair or twist **T**, with C_s and C_2 symmetry groups, respectively (Figure.1). Because of the low-energy barriers between conformers in cyclopentane, the puckered atom can easily rotate from one position to the other around the ring by pseudorotation through the *E* and *T* conformations.[13]

Pseudorotation leads to the formation of numerous puckered conformations in which each atom can assume many relative positions.[14] As described by Eliel and Wilen,[12] the cyclopentane ring is "in a conformational flux between the two conformations above and also among other in-between structures". The introduction of substituent groups may simplify the conformational analysis because certain conformers may become

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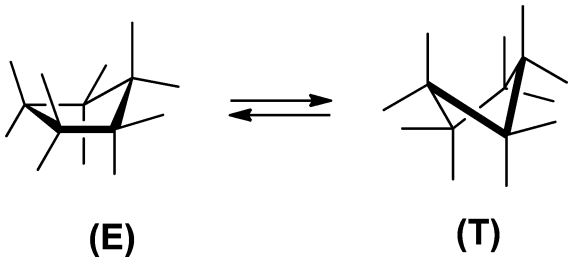
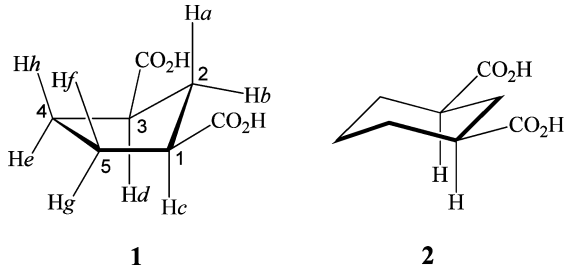


Figure 1. Envelope (**E**) and half-chair/twist (**T**) conformations of cyclopentane.

energetically favored. Substituent groups can induce such preferences either through steric effects or intramolecular interaction. However, there are no standard depictions for the conformational preferences in five-membered rings, as in the case of the predictable cyclohexanes, for which the chair is almost always the preferred geometry. The cumbersome approach is to consider all possible conformers.

There have been few reports on the conformations of *cis*-1,3-disubstituted cyclopentanes;[15−18] however, that of *cis*-1,3-cyclopentanedicarboxylic acid (**1**) has apparently not been previously investigated. Recently, we reported the conformational studies of *cis*-1,3-cyclohexanedicarboxylic acid (**2**) by means of NMR spectroscopy.[19] In the present paper, we extend our conformational investigations to **1** as a function of its ionization states in DMSO. Comparisons were made between **1** and **2** (Figure 2).



1 **2**

Figure 2. Structures of **1** and **2**, including proton labeling used for **1**.

RESULTS AND DISCUSSION

Spectral Assignment and Simulation. The symmetry of **1** caused five separate signals in DMSO-d_6 to be observed using a 600 MHz NMR spectrometer (Figure 3). The only obvious assignments were the methylene α-protons (H*c* and H*d*) at 2.70 ppm, which occurred as a complex multiplet. Two separate sets of doublet of triplets at 2.10 and 1.87 ppm were assigned to the H*a* and H*b* protons located on C2. H*a* was assigned to the lower frequency (1.87 ppm) on the basis of the simulated spectra and the assignments in *cis*-cyclopentane-1,3-diol.[20] The iterative simulation of H*a* and H*b* as a 4-spin system using gNMR[21] provided the essential vicinal J_{ac}(9.36 Hz), J_{ad}(9.20 Hz), J_{bc}(8.01 Hz), and J_{bd}(8.20 Hz) coupling constants. The J_{ab} geminal (−12.95 Hz) couplings were supplied by simulation as well. However, H-*e,f* and H-*g,h* on C4 and C5, respectively, were overlapping and too complex to be directly iterated as a 10-spin system. Hence, H-*c,d* (at 2.70 ppm) were decoupled to provide a much simpler spectrum, which was simulated using the AA′BB′ rule. All assignments were confirmed by two-dimensional NMR techniques (namely, HSQC and COSY).[22] See Supporting Information for other $^3J_{HH}$ and $^2J_{HH}$ coupling constants, including $^4J_{ae}$(0.45 Hz) and $^4J_{cd}$(0.09 Hz) long-range couplings.

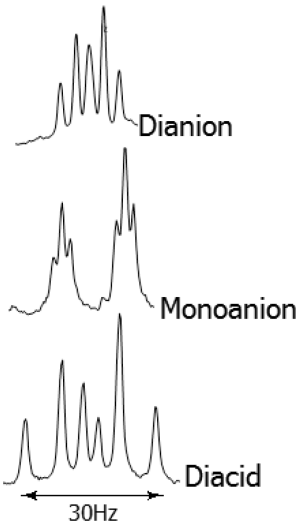


Figure 3. Experimental 600 MHz ^{1}H NMR spectra of **1** showing doublets of triplets patterns of the H*b* protons as a function of the diacid ionization states.

For the ionized species, the monoanion (**1A**) and dianion (**1B**), interferences from overlapping signals of the counterion [tetrabutylammonium ($^+$NBu$_4$)] precluded the full-line shape analyses of H-*e,f* and H-*g,h* peaks. However, the H-*a,b* and H-*c,d* signals were visible and, thus, provided sufficient spectral data (i.e., coupling constants) to fully identify the conformations of **1A** and **1B**.

Conformational Analysis of the Diacid (1). The coupling constants from the iteratively simulated spectra were used to estimate the conformational equilibria of the diacid (**1**). Because of lack of structural information on the conformations of **1** in solutions, we have resorted to computer-aided geometries. The conformational search for **1** was performed first by Monte Carlo molecular mechanics calculation (using SPARTAN 10s MMFF94), followed by full DFT optimization using Gaussian-09 programs.[23] The "conformer distribution" option in SPARTAN was implemented. Duplicate conformers and those with unreasonably high energy (i.e., 5 kcal mol^{-1} above the most stable forms) were not considered for further optimization. The selected conformers were then re-optimized by DFT calculation at the recommended B3LYP/6-31G-(2d,2p).[24] In each conformer, both the *E* and *Z* carboxylic acids are possible, and the isomer with the lower energy was selected. In all cases, except for the monoanion, the *ZZ* diacid isomers were found to be most stable. To account for solvation effects in the DFT calculation, the integral equation formalism polarizable continuum model (IEF-PCM, solvent = DMSO)[25] option was used. Four low-energy conformers **1**(***eaZZ***), **1**′(***aeZZ***), **1**(***eeZZ***), and **1**′(***eeZZ***) were identified from the computational search for **1** (Figure 4). All of these conformers are of the envelope family, but the positions of the carboxyl groups are different, as will be seen in Figure 4.

The H−H dihedral angles involving C_1-C_2, C_2-C_3, and C_4-C_5 fragments of these conformers in DMSO were used to estimate their respective theoretical vicinal $^3J_{HH}$ coupling constants according to eqs 1 and 2:

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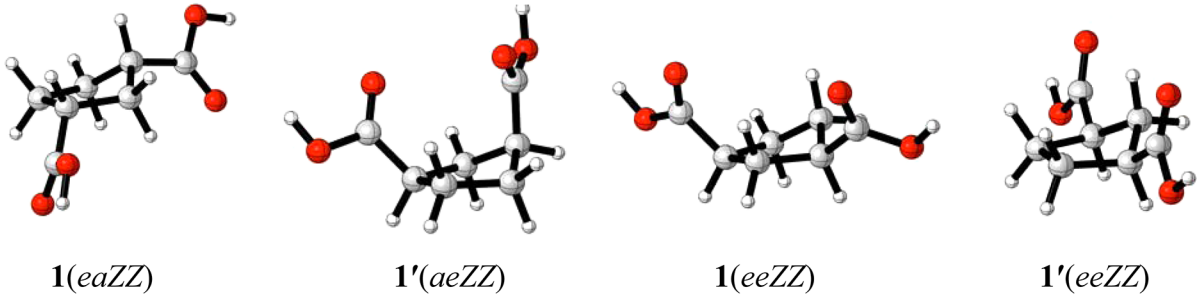

Figure 4. DFT-optimized low-energy conformers of *cis*-1,3-cyclopentanedicarboxylic acid (**1**). Here, the "*a*" and "*e*" notations are of axial and equatorial positions, respectively, and the calculations show that it is possible to have different energies for *ae* and *ea* and also for two different *ee*, and as expected the *ee* conformers are more stable than *ae* and *ea*.

Table 1. Experimental and Calculated Vicinal Coupling Constants $^3J_{HH}$ (Hz) of the Diacid (1)

conformer	$(J_{ac} + J_{ad})/2$	$(J_{bc} + J_{bd})/2$	$(J_{ef} + J_{gh})/2$	J_{eg}	J_{fh}
theoretical					
1(***ea*ZZ**)	10.91	7.32	5.64	7.95	7.73
1′(***ae*ZZ**)	1.37	8.26	5.76	7.45	7.63
1(***ee*ZZ**)	8.66	9.03	6.72	5.77	5.50
1′(***ee*ZZ**)	12.07	5.71	6.00	10.65	10.65
experimental[a]	9.28	8.11	6.57	7.76	7.62

[a]Experiments were performed with DMSO-d_6 as solvent.

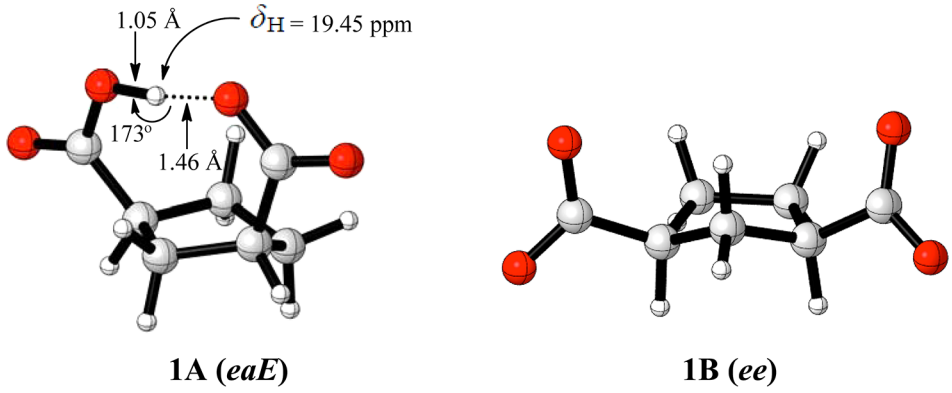

Figure 5. DFT-optimized low-energy conformers of the monoanion **1A** (***ea*E**) and the dianion **1B** (***ee***). Note that "*a*" and "*e*" notations denote axial and equatorial positions, respectively.

$$^3J_{HH} = 14.63\cos^2\varphi_{ij} - 0.78\cos\varphi_{ij} + 0.60 + \sum \lambda_i[0.34 - 2.31\cos^2(\zeta_i\varphi_{ij} + 18.4|\varphi_i|)] \quad (1)$$

$$^3J_{HH} = 11.16\cos^2\varphi_{ij} - 1.28\cos\varphi_{ij} + 0.77 \quad (2)$$

Applied only to the C_1−C_3 portions of the ring, is the Haasnoot, de Leeuw, and Altona (HLA)[26] equation (eq 1), which takes into account the orientation and electronegativity of substituent groups. The values for the empirical electronegativity variables (λ) for -CH_2 (ring) and -CO_2H substituent groups in DMSO have been derived elsewhere.[19] The parameter ζ_i can take the values +1 or −1 depending on the relative orientation of the substituent *i*. On the other hand, eq 2 is a Karplus-type equation derived by Abraham and Koniotou[20] and has been found to give better prediction of vicinal coupling constants for "CH_2-CH_2" fragments of cyclohexane and cyclopentane rings. The estimated coupling constants calculated using both equations are summarized in Table 1. The process of estimating these coupling constants can be simplified by the use of MestReJ PC software.[27] Because not all the isomers have a plane of symmetry, it is necessary to average J_{ac},J_{bc}, J_{ad},J_{bd}, and J_{ef},J_{gh} sets of coupling constants in order to generate equivalent sets of protons. This averaging is valid because the derived J_{av} will be independent of structural stereoisomerism. Abraham and co-workers found this manipulation beneficial in the conformational study of *cis*-1,3-cyclopentanediol.[20]

Because computational modeling has shown that **1** may consist of four low-energy conformers, the experimentally observed coupling constants should be the weighted average of the respective couplings in these conformers **1**(***ea*ZZ**), **1**′(***ae*ZZ**), **1**(***ee*ZZ**), and **1**′(***ee*ZZ**) as described in eq 3:

$$J^i_{(exp)} = \sum n_j J^i_j \quad (3)$$

where n_j are the respective fractions of the conformers **1**(***ea*ZZ**), **1**′(***ae*ZZ**), **1**(***ee*ZZ**), and **1**′(***ee*ZZ**), respectively, while J^i_j are these conformers' respective vicinal coupling constants for *i* species. The sum of the distinct conformer

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Table 2. Experimental and Calculated Vicinal Coupling Constants [$^3J_{HH}$] of 1A and 1B in hertz

conformer	method	J_{ac}	J_{ad}	J_{bc}	J_{bd}	$(J_{ac} + J_{ad})/2$	$(J_{bc} + J_{bd})/2$
1A	DFT	2.40	0.96	10.47	8.11	1.68	9.29
	exptl	2.40	1.20	9.87	8.83	1.80	9.35
1B	DFT	12.33	12.08	5.00	5.77	12.21	5.39
	exptl	12.35	12.10	4.99	5.77	12.23	5.38

Table 3. Ionization Constants of 1, 2, and Succinic Acid (SA) in Water and DMSO; Acidity Constants of the Monomethylesters of These Acids in DMSO (pK_E) Are Also Shown

	DMSO					water		
acid	pK_1	pK_2	K_1/K_2	pK_E	K_1/K_E	pK_1	pK_2	K_1/K_2
1	10.2[a]	17.3[a]	1.3×10^7	12.5[a]	200	4.23[c]	5.53[c]	20
2	11.6[b]	14.4[b]	630	11.9[b]	2	4.10[b]	5.46[b]	23
SA	9.5[b]	16.7[b]	1.6×10^7	11.6[b]	126	4.20[b]	5.55[b]	22

[a]This work. [b]Reference 18. [c]Reference 33.

populations (n_i) must be equal to 1 if the above statement is to hold (eq 4).

$$\sum n_i = n_{\mathbf{1}(eaZZ)} + n_{\mathbf{1}'(aeZZ)} + n_{\mathbf{1}(eeZZ)} + n_{\mathbf{1}'(eeZZ)} = 1 \quad (4)$$

The averaged experimental and theoretical coupling constants compiled in Table 1 consist of five equations with four unknowns. Inspection of these values shows clearly that no single conformer matched the experimental values; hence, no single conformer is likely dominant. Solving for the four unknown populations by combining any four equations provided consistent distribution for **1**(*eaZZ*), **1**′(*aeZZ*), **1**(*eeZZ*), and **1**′(*eeZZ*) with the average values of 1%, 11%, 58%, and 33%, respectively. This distribution is congruent with eq 4 in the sense that the total sums of the four distributions are 100 ± 3%.

Conformational Analysis of the Ionized States. The conformational search for the ionized species monoanion (**1A**) and dianion (**1B**) were performed in a similar way as described above. Unlike the disparate array of conformers calculated for **1**, the search produced only single low-energy conformer for each **1A** and **1B**, which suggests that these conformers may have been influenced by electrostatic interactions or for **1A** formation of intramolecular hydrogen bonding.

In the case of the **1A**, the *ab initio* DFT-optimized structure at the B3LYP/6-31G(2d,2p) level showed an asymmetric, favorable intramolecular hydrogen bond with distances of 1.05 Å for the O−H bond and 1.46 Å for the O···H bond (Figure 5). In addition, the O−H···O angle was calculated to be linear (173°), and the O−O distance (2.50 Å) was less than the sum of the van der Waal radii (3.04 Å). These parameters are consistent with "normal" intramolecular hydrogen bonding.[28] The finding of an asymmetric hydrogen bond is in accord with prevailing literature reports that suggest symmetrical hydrogen bonds in monoanion of dicarboxylic acids are very rare in solution.[29]

The conformations of both **1A** and **1B** in DMSO were confirmed by comparing the theoretical vicinal coupling constants ($^3J_{HH}$) derived from the HLA equation to their respective experimental values obtained from iterative simulated spectra. These data are summarized in Table 2. The theoretical coupling constants calculated using the DFT-derived geometries agreed with the experimental values for both **1A** and **1B**. As a result, conformers ***eaE*** and ***ee*** (shown in Figure 5) can be assumed as the dominant single forms of the monoanion and the dianion in DMSO, respectively. The possibility of intramolecular hydrogen bonding in **1A** seems very possible, not because such intramolecular hydrogen bond interaction was not observed for **2A**,[19] but rather because pseudorotation is known to have low activation energy for cyclopentane compared to the much more rigid cyclohexane ring. In the case of **1B** (*ee*), it is not unreasonable to assume that electrostatic repulsion between the negatively charged carboxylates could have caused this conformation to adopt an *ee* preference in which the two anions are forced farther apart, but there is no clear experimental evidence for **1B** (*ee*) in Table 2 (DFT/exptl) to show that might occur to an observable degree.

Determination of Ionization Constants: K_1, K_2, and K_E. The ratios of the ionization constants K_1/K_2 and K_1/K_E can provide evidence of intramolecular hydrogen bonding in dicarboxylic acids. Note that K_1 and K_2 are the first and second ionization constants of the acid protons, respectively, and K_E is the ionization constant of the monomethyl ester. According to the thermodynamic studies by Westheimer,[30] intramolecular hydrogen bonding may be significant only when $K_1/K_2 > 10^4$ and $K_1/K_E > 2$. This is certainly true for succinic acid in DMSO.[31] Because water molecules solvate anions well, intramolecular hydrogen bonds in aqueous media are typically overwhelmed by solute−water hydrogen bonding of the carboxylate, hence $K_1/K_2 \ll 10^4$. However, the caveat of overreliance on K_1/K_2 is that large values may also be obtained if the dianion is destabilized, as is the case with (±)-2,3-di-*tert*-butylsuccinic acid.[32] In order to avoid this pitfall, it is suggested that K_1/K_2 could be complimented by measuring K_1/K_E. The statistical ratio of K_1/K_E is 2; hence, $K_1/K_E > 2$ is suggestive that the monoanion is stabilized by intramolecular hydrogen bonding. The acidities of **1** and its monoanion and monomethyl ester derivatives were determined by the previously reported ^{1}H NMR method using standards with known pK_a in DMSO.[33,34] These results are summarized in Table 3.

On the basis of the experimentally determined pK_a values, **1A** is about 7.1 pK_a units more acidic than the diacid (**1**) in DMSO, but in water this difference is only 1.3 pK_a units.[35] Such a discrepancy caused by solvation is reminiscent of intramolecular hydrogen bonding in **1A**, which is present in DMSO, but not in water.[28] Because DMSO solvates anions poorly compared to water, the formation of hydrogen bonds is much more favorable in DMSO than in water. DMSO is only a hydrogen bond acceptor, while water is both an acceptor and a

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donor. Also, the calculated K_1/K_E in DMSO is much greater than the threshold value of 2, which is a further indication of intramolecular hydrogen bond formation. The ratios of ionization constants for *cis*-1,3-cyclopentanedicarboxylic acid (**1**) are notably different from those calculated for **2**[19] but quite similar to the succinic acid values.

At this point, all evidence seems to suggest that intramolecular hydrogen bonding in **1A** is significant. An additional way to establish this is by a variable-temperature (VT) ^{1}H NMR experiments performed in THF-d_8. At −60 °C, the hydrogen-bonded proton of **1A** became visible at 19.45 ppm (Figure 6), which is in contrast to **1**, where the analogous

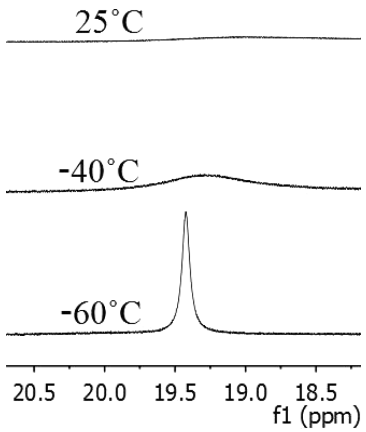

Figure 6. Variable-temperature ^{1}H NMR of the hydrogen-bonded proton of the monoanion of **1** (depicted as ***eaE*** in Figure 5) taken in THF.

resonance was observed at 12.02 ppm in DMSO at room temperature. The 19.45 ppm downfield shifts (corresponding to $\Delta\delta_H$ = 7.43 ppm) can result from protons that become less shielded from the oxygen lone pairs when the O−H bond is stretched, which is the usual case for protons bridging two carboxylates involved in hydrogen bonding.[32] As a result, **1A** is involved in an intramolecular hydrogen bonding. We note that in the optimized structures the O−H bonds were calculated to be 0.97 and 1.05 Å in **1** and **1A**, respectively, indicating an O−H bond expansion of 0.08 Å due to hydrogen bonding.

Both the ratios of the ionization constants (K_1/K_2 and K_1/K_E; see Table 3) and the chemical shift of the bridging proton in **1A** agree with the proposed intramolecular hydrogen-bond geometry ***eaE***. Further information that **1A** is involved in an intramolecular hydrogen bond is provided by the agreement of the experimental coupling constants derived from iterative simulations with their theoretically counterparts for **1A** (Table 2). The implication of this finding is that transannular intramolecular hydrogen bond in a 1,3-dicarboxylic acid is quite possible. The question then becomes why was no such interaction noted for the monoanion of **2**?

Energetics of Intramolecular Hydrogen Bonds in 1A and 2A. According to Garza et al.,[19] both $^3J_{HH}$ data and DFT studies indicated that the monoanion of **2** (**2A**) adopts nearly 100% diequatorial (***ee***) preference in DMSO, a form in which an intramolecular hydrogen bond is not geometrically feasible. In fact, unlike in **1**, no conformational changes were observed in **2** when singly or doubly ionized, and it was suggested that the strong *syn*-1,3-diaxial steric repulsions between the carboxylic groups were responsible for the high preference for diequatorial form.

This repulsion effect can be predicted on the basis of Winstein's *A* values for -CO_2H for the diacids (i.e., the *ee* isomer should be 2.70 kcal mol^{-1} more stable than the *aa* counterpart). However, in the monoanion **2A** (*ee*), one would expect that the stabilization due to the plausible intramolecular hydrogen bond could be at least partially compensated for the *syn*-1,3-diaxial repulsions. However, this was not the case when the energetics of the hydrogen bonds in **1A** and **2A** in DMSO were compared.

In aprotic solvents, the stabilization of these monoanions by intramolecular hydrogen bonding acts to increase K_1 values of the diacids and renders the first step of their deprotonation more favorable. Such stabilization decreases the experimental pK_1 (pK_{obs}) values from the figures for the "intrinsic" (pK_{int}). This criterion, that is, differences between pK_{obs} and pK_{int}, has been used to quantify the strength of hydrogen bonds according eq 5.[36] The intrinsic pK_{int} represents the pK_a of a given carboxylic diacid expected in the absence of hydrogen bonding, and these values were obtained by assuming the pK_{int} of the monomethyl esters of **1** and **2** are equal to pK_E. From this data we can use eq 5 to show the difference between the free energies of **1** and **2** (Table 4).

$$\delta G_{HB} = -RT \ln(K_{obs}/K_{int}) \quad (5)$$

Table 4. Hydrogen Bond Strengths (in kcal mol^{-1}) Derived from the pK_a Data in DMSO

compound	pK_{obs}	pK_{int}	K_{obs}/K_{int}	ΔG_{HB}(kcal/mol)
1	10.2	12.5	200	3.1
2	11.6	11.9	2	0.4

The decrease in the acidity of **1A** by 2.3 pK_a units from the pK_{int} value (10.2 vs 12.5) corresponds to stabilization of the monoanion, relative to the diacid, by 3.1 kcal/mol per single hydrogen bond. In contrast, **2A** is stabilized by only 0.4 kcal/mol relative to the diacid (**2**). The difference in the hydrogen bond strengths between **1A** and **2A** is about 2.7 kcal/mol per hydrogen bond, which is approximately the energy required to place two CO_2H groups in the axial position of cyclohexane according to Winstein's *A* values (A_{COOH} = 1.35 kcal/mol).[12] Clearly, the inability of **2** to form intramolecular hydrogen bonding favorably is the result of the energetic penalty associated with *ee*−*aa* equilibrium in cyclohexane, which could otherwise result from the difference in rigidities of the cyclohexane and cyclopentane rings.

■ CONCLUSIONS

The conformer populations of *cis*-1,3-cyclopentanedicarboxylic acid (**1**) and the mono- and dianion were determined in DMSO by comparing their experimental vicinal coupling constants ($^3J_{HH}$) derived from iterative simulation to their respective theoretical values obtained by computational modeling at the B3LYP/6-31G(2d,2p) level. In the diacid of **1**, no single conformer was dominant in solution, and conformational distributions of 1%, 11%, 58%, and 33% were calculated for **1**(***eaZZ***), **1′**(***aeZZ***), **1**(***eeZZ***), and **1′**(***eeZZ***), respectively. However, in the ionized mono- and dianion states, these species tend to adopt single forms. In the case of **1A**, the theoretical $^3J_{HH}$ (shown in Table 2) of conformer ***eaE*** was in good agreement with experimental values. In addition, K_1/K_2 ratios were large in DMSO (1.3×10^7) but small in H_2O (20), which agrees with the findings of intramolecular hydrogen

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bonding in DMSO. The low-field chemical shift of the bridging proton (19.45 ppm) further corroborated our findings. The occurrence of intramolecular hydrogen bonding in **1A** was unanticipated because even in glutaric acid (pentanedioic acid), which is the simplest form of 1,3-dicarboxylic acid, no intramolecular hydrogen bonding was reported for the monoanion.[37] In comparison to *cis*-1,3-cyclohexanedicarboxylic acid, it appears that the cyclopentane ring (in **1**) maximizes 1,3-diaxial contact, giving an intramolecular hydrogen bond more easily than cyclohexane.

This work demonstrates the elegance of proton NMR techniques, in conjunction with computational modeling, to depict conformer preferences in solution. The techniques described in this paper may be applicable to the conformational study of many biologically active natural products whose important conformations in solution have remained elusive.

EXPERIMENTAL SECTION

Preparation of Samples in DMSO. The diacid, 1,3-*cis*-cyclopentanedicarboxylic acid (**1**) and its monomethyl ester were synthesized according to literature procedures.[38] The corresponding monoanion and dianion salts were prepared by mixing a CH_3OH solution of the above acid with 1 and 2 equiv of tetrabutylammonium hydroxide solution (1.0 M in CH_3OH), respectively. Both H_2O and CH_3OH were subsequently removed by evaporation under reduced pressure, followed by heating the sample (~70 °C) for 1−2 h under high vacuum to yield white solids. Dried samples were then stored in a positive pressure glovebox for subsequent use. The solute concentration used for NMR analysis in 99.9% DMSO-d_6 was about 0.01 M or less in all samples.

Measurement of Ionization Constants in DMSO. In order to determine the ionization constant in DMSO, we followed the procedure previously reported by Choi et al.[33] Also, Garza et al.[19] has recently applied this method to determine the pK_1 and pK_2 of **2** in DMSO.

Spectra Measurements. NMR spectra were recorded with an NMR spectrometer using the default pulse sequence in the software. Low-temperature experiments were performed on a 500 MHz NMR spectrometer. Typical spectra parameters for ^{1}H spectra: 16 scans, spectral width 9600 Hz, relaxation delay of 1 s, and acquisition time of 4 s. Unless otherwise stated, all measurements were at a regulated temperature of 25 °C. Decoupling was performed using the default parameter in the 600 MHz NMR: relaxation delay = 1 s, pulse sequence = 2.95 μs, irradiation (offset) = 2.70 ppm, and decoupler power level (pwr) = 28.5. Line shape simulations were performed using the gNMR software.[21]

Theoretical Calculations. Conformational distributions were performed using the latest SPARTAN 10 program. The selected pre-optimized conformers were then fully optimized by DFT methods using the Gaussian-09 package.[23] All energy minima were verified to have 0 imaginary frequencies by vibrational frequency analysis at the same level as the optimized structures.

ASSOCIATED CONTENT

Supporting Information

Experimental and simulated NMR spectra, coupling constants, and Cartesian coordinates of the optimized structures used in the theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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