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A Theoretical and Experimental Investigation of Vicinal Tricarbonyl Systems and Their Hydrates

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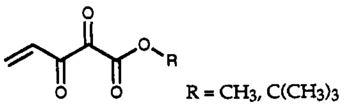
The conformational preferences of the vinyl vicinal tricarbonyl reagent (VTC) and related triketones have been examined in the context of ab initio molecular orbital theory in order to better understand the properties of these reactive polyelectrophiles. The preferred conformation of the VTC methyl ester has been calculated to have the glyoxal unit twisted almost perpendicular to the plane of the ester unit. These results support the recent conclusions of Schreiber and co-workers on the activity of FK-506 and related compounds for inhibition of the rotamase enzyme. The origin of the enhanced reactivity has been examined via an analysis of the charge density distributions of the triketones and the corresponding hydrates. Electrostatic stabilization appears to be the main driving force for the stability of the hydrates. The energy of hydration for VTC has been calculated to be similar to that of activated aldehydes such as fluoral and chloral. Experimental values are also presented for the energy of hydration of chloral and VTC in acetone solution.

Introduction

Vicinal tricarbonyls have intrigued chemists over the years, and recently their value to organic synthesis has been enhanced with their use as synthetic building blocks and their presence in the medicinally important compounds FK-506^1 and rapamycin.^{2} The vicinal tricarbonyl unit as well as the vinyl vicinal tricarbonyl reagent (VTC) have been used extensively in the preparation of various natural products.^{3} The applicability of the vinyl vicinal tricarbonyl reagent to synthesis arises from its innate polyelectrophilicity and the exploitation of this electrophilic nature.



VTC (A)

The unusual reactivity of vicinal tricarbonyls has been under periodic investigation since the synthesis of 1,3-diphenylpropane-1,2,3-trione over 100 years ago.^{4} Predictions of ground-state conformers by Calvin and Wood in 1940 were based on comparison of the UV spectra of 2,3,4-pentanetrione with biacetyl and acetone.^{5} In the 1970s, semiempirical methods and photoelectron spectra were used by Kroner and Strack to predict a helical conformation of pentanetrione which was calculated to be lower in energy than the planar s-trans,s-trans structure by 21.8 kcal-mol^{-1}.^{6} Following the work of Kroner and Strack, Wolfe and co-workers prepared $PhC(Me)_2COCOCOPh$ in order to determine whether the stereomutation of vicinal tricarbonyls proceeds through a symmetric or asymmetric process.^{7} The study indicated that the transition state for rotation about the carbonyl chain was lower in energy than that observable by NMR methods (i.e., less than 7 kcal-mol^{-1}). Wolfe's subsequent semiempirical study of mesoxaldehyde (1,2,3-propanetrione) suggested an asymmetric transition state structure for stereomutation with an energy of 3.90 kcal-mol^{-1}. It has been recognized that force fields used in molecular mechanics calculations lack the proper parameters for vicinal carbonyls, and recently, Gleiter, Irngartinger, and co-workers have proposed a method using dipole moments, while ignoring torsional and van der Waals potentials, to obtain minima close to those found experimentally.^{8} To this date, though, there has been no extensive ab initio study of the vicinal tricarbonyl moiety.^{9}

It is interesting that the most potent immunosuppressant to date, FK-506, contains a vicinal tricarbonyl unit in which the terminal carbonyl has formed a hemiacetal. It has been proposed that the conformation of the keto–amide bond in the vicinal tricarbonyl region of FK-506

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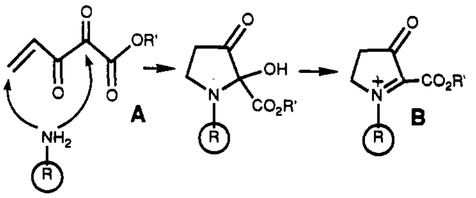
mimics the twisted amide bond transition state which is essential to inhibition of the rotomase enzyme.[10] The use of vicinal tricarbonyls in organic synthesis and their presence in biologically active compounds requires a better understanding of this special moiety. The limited experimental information on vicinal tricarbonyls can be bolstered by theoretical studies bearing on their preferred conformations, electron density distributions, and the source of their unique reactivity.

We have therefore completed an ab initio molecular orbital study of the vicinal tricarbonyl unit and our vinyl vicinal tricarbonyl reagent **A**. The reagent **A** is a stable hydrate and has been used directly in reactions as a polyelectrophile.[1c] Equilibrium between hydrated and nonhydrated forms presumably provides the highly activated central carbonyl for reaction. For example, primary amines add to **A** by 2-fold addition to the central carbonyl and, in a conjugated manner, to the vinyl group. A hydroxypyrrolidinone carboxylate is then formed which can be utilized in further reactions presumably via pyrrolinium ion **B**.



Methods

All ab initio calculations were performed with Gaussian 90,[11] and geometries were completely optimized within the symmetry specified. The 6-31G*[12] basis set was used for all optimizations. In some cases MP2/6-31G* geometry optimizations were carried out, and here all electrons were correlated. Single-point calculations (designated single-point level//optimized geometry) at the 6-31+G** level were also carried out. Correction for electron correlation was performed with Møller–Plesset perturbation theory through second (MP2) and third (MP3) orders. The frozen-core approximation was used for the single-point calculations. Some stationary points were characterized by analytical evaluation of the Hessian matrix in order to obtain the harmonic vibrational frequencies. The calculated zero-point vibrational energy (ZPE) was scaled by 0.9 in order to account for the overestimation of the vibrational frequencies at the RHF level.[13] Electron density analysis was performed with the Atoms In Molecules Package (AIMPAC)[14] and, in particular, PROAIM.[15] Covalent bond orders were calculated with a modified version of BONDER.[16]

Table I. Relative Energies of 1,2,3-Propanetrione Conformers

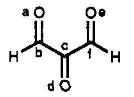
						6-31+G**//6-31G*[d]		
	6-31G*	MP2/6-31G*	freq[b]	ZPE	μ	RHF	MP2	MP3
1	0.0	0.0	99.2	29.0	1.87	0.0	0.0	0.0
2[c]	0.6	0.4	83.9*i*	29.0	2.22	1.0	1.2	1.1
3	1.0	0.5	59.5	29.2	2.28	1.3	1.2	1.2
4	8.2	6.3	48.8	28.9	4.35	8.4	6.6	7.0

[a] Energies in kcal/mol, ZPE (scaled by a factor of 0.9) in kcal-mol^{-1}, μ in D (at the RHF/6-31G* level). [b] Lowest frequency at the 6-31G* level. [c] This conformer (**2**) is a transition state (one imaginary frequency) at RHF/6-31G*. [d] Scaled ZPE is included.

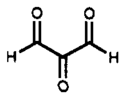
Results

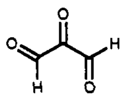
In order to obtain a better understanding of the conformational preferences of VTC as well as its energies of hydration and electron distribution, we have studied a series of vicinal tricarbonyls and their monohydrates. This investigation begins with the smallest vicinal tricarbonyl unit: 1,2,3-propanetrione. Next, the vinyl and methoxy groups are appended to the vicinal tricarbonyl system individually and then together to give our vinyl vicinal tricarbonyl ester, VTC. We shall discuss each system in turn.

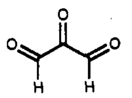
1,2,3-Propanetrione. Mesoxaldehyde (or 1,2,3-propanetrione) was prepared years ago and studied in the gas phase. It was found that it quickly polymerized.[17] Four conformations of the trione (**1**–**4**) were examined at the RHF/6-31G* level. The planar conformers **3** and **4** were found to be minima. The other planar conformer, **2**, was found to be a transition state for the interconversion of the chiral conformers corresponding to **1**. The latter was found to possess a helical twist with a torsional angle (O–C–C–O) of 149° which effectively reduces the oxygen-oxygen repulsion of carbonyls 1 and 3 in **2**.[18]



1 (C_2)
s-trans, s-trans
∠abcd, ∠efcd = 149°


2 (C_{2v})
s-trans, s-trans


3 (C_s)
s-cis, s-trans


4 (C_{2v})
s-cis, s-cis

Relative energies for the 1,2,3-propanetrione conformations at RHF/6-31G* and MP2/6-31G* are given in Table I. The effect of correcting for electron correlation on the relative energies was small both at the MP2 and MP3 levels, and the effect of including diffuse functions at carbon and oxygen (6-31+G**) also was small. Further, the relative energies of these conformers did not change significantly when the zero-point energy (ZPE) correction was applied. The twisted conformer **1** was found to have the lowest energy, and the planar structure **2** was ~1 kcal-mol^{-1} higher in energy. The planar s-cis,s-trans structure **3** was ~1 kcal-mol^{-1} higher in energy than **1**, and planar s-cis,s-cis **4** was ~7 kcal-mol^{-1} higher.

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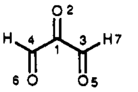
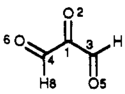
[18] Geometry optimization at the HF/3-21G level found **2** to be a minimum and did not find conformation **1**. This level of theory was found to be generally unsatisfactory for the compounds in this report.

Table II. Comparison of Selected Geometrical Data for 1,2,3-Propanetrione, 1-4



1, 2



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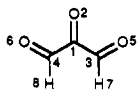


4

	$r(C_1{=}O_2)$	$r(C_3{=}O_5)$	$r(C_4{=}O_6)$	$r(C_1\text{-}C_3)$	$r(C_1\text{-}C_4)$	$r(C_3\text{-}H_7)$	$r(C_4\text{-}H_8)$	∠(CCC)
6-31G*:								
1	1.187	1.182	1.182	1.524	1.524	1.090	1.090	119.7
2	1.189	1.180	1.180	1.527	1.527	1.092	1.092	123.5
3	1.184	1.185	1.182	1.521	1.534	1.090	1.087	118.4
4	1.180	1.181	1.181	1.533	1.533	1.093	1.093	117.8
MP2/6-31G*:								
1	1.228	1.221	1.221	1.520	1.520	1.106	1.106	120.3
2	1.230	1.219	1.219	1.522	1.522	1.107	1.107	122.9
3	1.225	1.224	1.222	1.517	1.531	1.105	1.101	118.2
4	1.222	1.221	1.221	1.531	1.531	1.107	1.107	117.8
X-ray structure of 1,3-diphenylpropane-1,2,3-trione:[a]								
	1.213	1.209	1.216	1.523	1.522			117.3

[a] Reference 19.

In the 1,2,3-propanetrione series, the dipole moments (Table I) are related to the energetic ordering of the conformers. Structure **4** has the highest dipole moment (4.35 D) and is the least stable, while structures **2** and **3** have roughly the same dipole moment (2.22 and 2.28 D) and are close in energy. Structure **1** has the lowest dipole moment (1.87 D) as well as the lowest energy. This relationship between energy and dipole moment is expected for these gas-phase calculations.

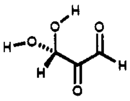
Some geometrical parameters for the different conformers of 1,2,3-propanetrione are listed in Table II along with the corresponding data from the X-ray structure of 1,3-diphenylpropane-1,2,3-trione[19] for comparison. The data are consistent for each conformer, and for the most part unextraordinary, with the exception of the C-C-C angle. Structure **2** with its 1,3 carbonyl oxygen repulsion consistently has a larger C-C-C angle than the other three structures. This greater C-C-C angle which pulls the 1,3 carbonyl oxygens away from one another would help to stabilize the planar s-trans,s-trans structure resulting in only ~1 kcal-mol^{-1} energy difference between the planar conformer **2** and the twisted s-trans,s-trans conformer, **1**. The C=O bond lengths are calculated to be too short at the RHF/6-31G* level.[12] This deficiency is corrected by electron correlation, and the MP2/6-31G* level gives C=O bond distances close to those of the X-ray structure.[19] The outer C=O bonds of the calculated triones are the same length by symmetry; however, the X-ray structure of 1,3-diphenyl-1,2,3-propanetrione has outer C=O bond lengths of 1.2086 and 1.2162 Å. The difference in these distances in the X-ray structure is probably due to crystal-packing forces.

The monohydrates of 1,2,3-propanetrione were examined, and the relative energies for seven structures at the RHF/6-31G* level, as well as the lowest frequency obtained from vibrational frequency analysis and the ZPE (both at the 6-31G* optimized geometry) for the three lowest energy structures, are given in Table III.

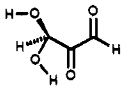
Without the inclusion of ZPE at the 6-31G* level, the most favorable site for hydration appears to be the aldehyde. However, when the ZPE is taken into account, the hydrate at the central carbonyl is the most stable, albeit by a very small amount (less than 0.1 kcal). Correction for electron correlation (Table III) plus the ZPE correction shows **7** to be more stable than **5** and **6** by nearly 1 kcal-mol^{-1}. This effect of ZPE correction on the relative energies of the hydrates was notable throughout our study; however, the nonhydrated tricarbonyls have similar ZPEs, and thus the relative energies are hardly affected. In this case, the C_2 symmetric structure (**7**) with hydration at the central carbonyl has a considerably smaller ZPE than acetals **5** and **6**.

The energy of hydration (Table III) was found to be −11.2 kcal-mol^{-1} at RHF/6-31+G**//6-31G*+ZPE and −14.5 kcal-mol^{-1} at MP3/6-31+G**//RHF/6-31G*+ZPE

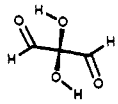
Table III. Relative Energies[a] of 1,2,3-Propanetrione Hydrates



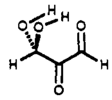
5 (C_1)



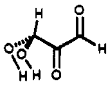
6 (C_1)



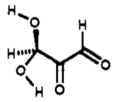
7 (C_2)



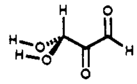
8 (C_s)



9 (C_s)



10 (C_1)



11 (C_s)

	6-31G*	frequency[b]	ZPE[c]	6-31+G**//6-31G*[e] RHF	MP2	MP3
5	0.0	97.4	47.0	0.5	1.8	1.0
6	0.2	82.8	46.8	0.0	1.4	0.7
7	1.0	98.0	46.1	0.0	0.0	0.0
8	2.0					
9	3.6					
10	4.7					
11	8.9					

	6-31G*	6-31+G**//6-31G*[e] RHF	MP2	MP3
	Energy of Hydration[d]			
1 → **5**	−18.1	−10.7	−12.1	−13.5
1 → **6**	−17.9	−11.1	−12.5	−13.8
1 → **7**	−17.1	−11.2	−13.9	−14.5

[a] Relative energies are given in kcal-mol^{-1}. [b] Lowest vibrational frequency at 6-31G*. [c] ZPE, in kcal/mol, is scaled by a factor of 0.9. [d] Energies of hydration are given in kcal-mol^{-1}. [e] Scaled ZPE is included.

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Table IV. Energies of Hydration for Some Carbonyl Compounds[a]

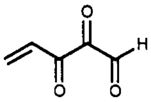
	6-31G*	MP2/ 6-31G*	+ZPE
1,2,3-propanetrione → 1-hydrate (6)	−17.9	−19.2	−15.0
1,2,3-propanetrione → 2-hydrate (7)	−17.1	−19.6	−15.4
trans-malonaldehyde → hydrate	−14.2	−17.3	−12.0
acetaldehyde → acetaldehyde hydrate	−10.7	−12.4	−7.3
acetone → acetone hydrate	−6.6	−10.3	−5.7

[a] In kcal-mol^{-1}. Geometry optimizations were carried out at the indicated theoretical levels.

for the lowest energy conformations ($1 + H_2O \rightarrow 7$).[20] Structures 5 and 6 had energies of hydration of −13.5 and −13.8 kcal-mol^{-1}, respectively, at the MP3 level. As expected, the three preferred structures of 1,2,3-propanetrione hydrate (5–7) have an anomeric orientation of their hydroxyl groups.[21] In fact, the anomeric orientation was found consistently in the lower energy conformations of all the hydrates studied.

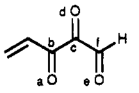
For a comparison of the energy of hydration of 1,2,3-propanetrione, we have calculated the energy of trans malonaldehyde in its keto form and its hydrate. It should act as a model of 1,2,3-propanetrione without the central carbonyl. The energies of hydration for acetone,[22] acetaldehyde,[17] malonaldehyde (keto form), and 1,2,3-propanetrione at the MP2/6-31G* level are given in Table IV. With the ZPE correction, the energy of hydration for *trans*-malonaldehyde is −12.0 kcal-mol^{-1} compared to −15.4 kcal-mol^{-1} for 1,2,3-propanetrione. Both acetaldehyde and acetone give considerably less exothermic hydrations, in part because they do not have the possibility for internal hydrogen bonding. Thus, as seen in this progression toward more exothermic energies of hydration, the electron-withdrawing effect of the carbonyl group is an important factor in the driving force for hydration.

2,3-Dioxo-4-pentenal. Vinyl vicinal diketo aldehyde C (2,3-dioxo-4-pentenal) does not appear to have been reported; however, as part of our study we examined this unknown compound by ab initio molecular orbital methods. The relative energies of five conformations of 2,3-dioxo-4-pentenal at the RHF/6-31G* level are listed in Table V along with the three lowest energy conformers at the MP3/6-31+G**//6-31G* level.


C

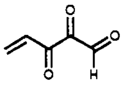
In the process of finding stationary points, both C_s and C_1 symmetric structures were considered; in nearly all cases, the initial C_1 geometry was optimized to the C_s symmetric geometry with the exception of the lowest energy conformer 12. Structure 12 displays a geometry similar to the twisted mesoxaldehyde conformer 1 with the vinyl group remaining in plane with the adjacent carbonyl. The enone and aldehyde carbonyl are twisted 39° and 32° out of plane, respectively, with regard to the central carbonyl which compares well to the 31° deviation from planarity found for the lowest energy conformation of 1,2,3-propanetrione, 1. The planar structures 14 and 15 are transition states, while 13 is a minimum. Both structures 14 and 15 have a planar 1,3 interaction, and conformation 13 does not. In the case of 14, there is a 1,3 carbonyl interaction, while in the case of 15, there is a 1,3 ene–carbonyl interaction. It follows that structure 16 should be a transition state as well due to its two 1,3 π interactions. This is also observed.

Table V. Relative Energies of 2,3-Dioxo-4-pentenal Conformers (kcal/mol)

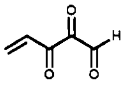


∠abcd = 141°, ∠efcd = 148°

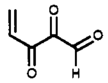
12 (C_1)



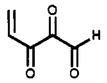
13 (C_s)



14 (C_s)



15 (C_s)



16 (C_s)

	6-31G*	6-31+G**//6-31G*[a] RHF	MP2	MP3	freq[b]	ZPE[c]	μ[d]
12	0.0	0.0	0.0	0.0	47.0	49.5	2.33
13	0.7	1.2	1.6	1.4	32.9	49.6	3.83
14	1.7	2.5	2.8	2.5	70.7*i*	49.5	2.91
15	2.4	2.6			39.2*i*	49.6	3.32
16	4.2				76.4*i*	49.5	3.45

[a] These energies include the zero-point energies. [b] Lowest vibrational frequency at the RHF/6-31G* level. [c] Zero-point energy in kcal-mol^{-1} at the RHF/6-31G* level and scaled by a factor of 0.9. [d] μ in D at the RHF/6-31G**//RHF/6-31G* level.

From Table V, we can see a preference for an s-cis enone (compare 13 and 15; 14 and 16) by ~2 kcal-mol^{-1}. This system parallels the unsubstituted 1,2,3-propanetrione system except that the s-cis,s-trans structure 13 is ~1 kcal-mol^{-1} lower in energy than the s-trans,s-trans conformer 14, while their counterparts 2 and 3 in the 1,2,3-propanetrione series have the opposite preference by ~0.4 kcal-mol^{-1} and are nearly isoenergetic as electron correlation is added (see Table I). The preference for conformer 13 over 14 arises from relief of the O–O repulsion in 14.

The monohydrates of 2,3-dioxo-4-pentenal were examined, and the relative energies of five low-energy structures are presented in Table VI along with their lowest vibrational frequency and ZPE at the 6-31G* level. Of the five structures presented, two have the hydrate at the aldehydic carbonyl, two have the hydrate at the central carbonyl, and one has the hydrate at the enone carbonyl. All optimized geometries were found to be minima by a vibrational frequency analysis, and all display an anomeric arrangement of the hydrate.

The aldehyde hydrates 17 and 18, which differ in intramolecular hydrogen-bonding patterns, have the same relative energy at the RHF/6-31G**//6-31G* level with the ZPE correction. Hydrate 17 possesses a 6-membered ring hydrogen-bonding interaction, while hydrate 18 has a 5-membered ring interaction. Both structures are 0.3 kcal-mol^{-1} higher in energy than the lowest energy structure, 19, which has the hydrate on the central carbonyl and an s-cis enone conformation. Hydrate 20 also has a hydrate at the central carbonyl and differs from hydrate 19 in the conformation of the enone portion which is s-trans for conformer 20. The s-cis enone 19 is 1.1 kcal-mol^{-1} lower in energy than the s-trans enone 20 at RHF/6-31G**/

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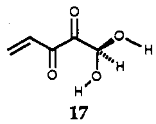
(20) For the RHF/6-31G* geometry of water, the corresponding total energies are as follows: RHF/6-31G*, −76.010 75; RHF/6-31+G**, −76.031 14; MP2(fc)/6-31+G**, −76.232 60; and MP3(fc)/6-31+G**, −76.237 25 hartrees. The MP2(fu) geometry optimization gave −76.199 24 hartrees. The scaled ZPE is 12.98 kcal-mol^{-1}.

(21) (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: Berlin, 1983. (b) Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* 1989, *111*, 4821 and references cited therein.

(22) Wiberg, K. B.; Morgan, K. M.; Maltz. H., manuscript in preparation.

Table VI. Relative Energy of 2,3-Dioxo-4-pentenal Hydrates (kcal/mol)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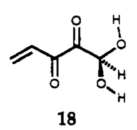
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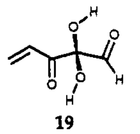
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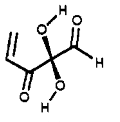
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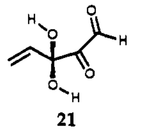

21

	6-31G*	6-31+G**//6-31G*[a] RHF	6-31+G**//6-31G*[a] MP2	freq[b]	ZPE[c]
17	0.0	0.5	2.5	43.5	67.5
18	0.4	0.2	2.3	41.5	67.2
19	0.9	0.0	0.0	63.8	66.6
20	1.9	1.2	0.7	76.3	66.7
21	7.9				

[a] These relative energies include the zero-point energy correction. [b] Lowest vibrational frequency at the RHF/6-31G* level. [c] Zero-point energy in kcal-mol^{-1} at the RHF/6-31G* level and scaled by a factor of 0.9.

Table VII. Energies of Hydration (ΔH, kcal/mol)[a]

trione	hydrate	carbonyl position	6-31+G**//6-31G* RHF	6-31+G**//6-31G* MP2	6-31+G**//6-31G* MP3
1	**7**	central	-11.2	-13.9	-14.5
1	**6**	aldehyde	-11.1	-12.5	-13.8
1	**5**	aldehyde	-10.7	-12.1	-13.5
12	**19**	central	-10.9	-14.5	
12	**17**	aldehyde	-10.4	-12.0	
12	**21**	enone	-8.1[b]		
22	**28**	central	-11.9	-14.2	
22	**29**	aldehyde	-9.4	-10.9	
34	**35**	central	-11.1	-14.8	
34	**37**	enone	-2.4	-6.6	

[a] Energies of hydration include the scaled ZPE of the optimized structure at 6-31G* except where noted. [b] ZPE correction is not included.

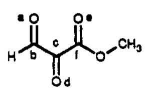
/6-31G*+ZPE. The ZPE correction, as seen above, is very important for the relative energies of the hydrates. Throughout this series, the relative energetic ordering does not change when electron correlation is included (see Table VI). However, the relative energies of aldehyde hydrates **17** and **18** are raised to 2.3 and 2.5 kcal-mol^{-1} at the MP2 level relative to **19**. As would be expected, the hydrate at the enone carbonyl, **21**, is much higher in energy (~7 kcal-mol^{-1}) than the hydrate at the central carbonyl, **19**.

The energies of hydration for 2,3-dioxo-4-pentenal at the MP2/6-31+G**//RHF/6-31G* level are given in Table VII. The most exothermic hydration occurs at the central carbonyl to give a ΔH of -14.5 kcal-mol^{-1} (for **12** + H_2O → **19**). Hydration at the aldehyde to yield hydrate **17** is exothermic by -12.0 kcal-mol^{-1}. Hydration at the enone would be less exothermic.

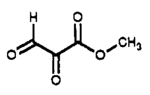
1-Methoxy-1,2,3-propanetrione. The preparation of 1-ethoxy-1,2,3-propanetrione has been reported recently in the literature, and it was isolated as the hydrate.[23]

The results of the ab initio conformational analysis of 1-methoxy-1,2,3-propanetrione (**D**) with geometries optimized with the 6-31G* basis set are listed in Table VIII.

Table VIII. Relative Energies for 1-Methoxy-1,2,3-propanetrione (kcal/mol)



(∠abcd,∠efcd)
22 (180°,82°) 6-31G*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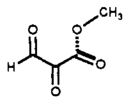
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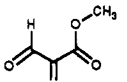
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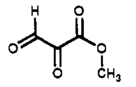
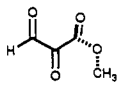
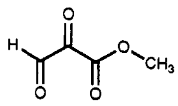

26


27

	6-31G*	6-31G*	6-31+G**//6-31G* RHF	6-31+G**//6-31G* MP2	6-31+G**//6-31G* MP3	freq[a]	ZPE[b]
22	0.0	0.0	0.0	0.0	0.0	22.9	49.7
23	2.1	2.2	2.9	3.0	2.6	28.2	49.8
24	*c*						
25	4.5						
26	*d*						
27	8.1						

[a] Lowest vibrational frequency at the RHF/6-31G* level. [b] Zero-point energy in kcal-mol^{-1} at the RHF/6-31G* level and scaled by a factor of 0.9. [c] Geometry optimization at 6-31G* level starting from the 3-21G optimized geometry gave structure **22**. [d] Although a stationary point was found at the 3-21G* level, it was not found at 6-31G*.


D

Selected single point calculations with electron correlation or better basis sets are also listed for the low energy conformers.

Six possible conformers (**22–27**) of 1-methoxy-1,2,3-propanetrione were examined at the 6-31G* level. The minimum energy conformation was found to be **22** in which the glyoxal and ester components of the tricarbonyl ester are orthogonal to one another with a torsional angle of 82°. This result had initially surprised us, and the parallel to the twisted FK-506 keto–amide bond and its mode of rotomase inhibition is of special interest. Geometry optimization for conformer **24** led to **22**, and conformer **26** was found not to be a stationary point.

The lowest energy conformer, **22**, is more than 2 kcal-mol^{-1} lower in energy than the next lowest conformer *s-cis,s-trans,s-cis*-**23**. The all s-cis conformer **25** is 4.5 kcal-mol^{-1} higher in energy than conformer **22b**. Structure **25** can be compared to the *s-cis,s-cis*-1,2,3-propanetrione (**4**), which is 8.3 kcal-mol^{-1} higher in energy than the lowest energy conformer **1**. When comparing these two systems, it is interesting to note that the C–C–C angle for the s-cis,s-cis conformation **4** of 1,2,3-propanetrione is 117.8°; while for the s-cis,s-cis,s-cis methoxy derivative **25**, the C–C–C angle is a nondistorted 119.8°.

The hydrates of the dicarbonyl ester, 1-methoxy-1,2,3-propanetrione, were examined, and the relative energies for six structures at the RHF/6-31G* level, as well as the lowest frequency obtained from the vibrational frequency analysis and the ZPE, are shown in Table IX.

The molecule with the hydrate on the central carbonyl, **28**, has two hydrogen-bonding interactions between the hydroxyl hydrogens and the adjacent carbonyl oxygens. Structure **32**, which also has the hydrate at the central

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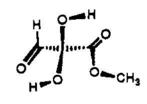
(23) Ihmels, H.; Maggini, M.; Prato, M.; Scorrano, G. *Tetrahedron Lett.* **1991**, *32*, 6215–6218.

Table IX. Relative Energies of 1-Methoxy-1,2,3-propanetrione Hydrates (kcal/mol)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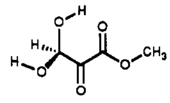
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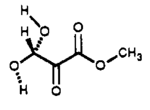
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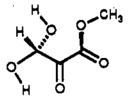
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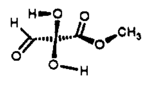
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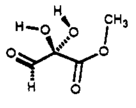
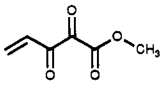

33

	6-31G*	6-31+G**//6-31G*[a] RHF	6-31+G**//6-31G*[a] MP2	freq[b]	ZPE[c]
28	0.0	0.0	0.0	62.1	66.9
29	1.2	2.5	3.3	44.7	67.7
30	1.7	2.3	3.3	40.5	67.4
31	3.2				
32	5.4				
33	*d*				

[a] These relative energies include the zero-point energies. [b] Lowest vibrational frequency at the RHF/6-31G* level. [c] Zero-point energy in kcal-mol^{-1} at the RHF/6-31G* level and scaled by a factor of 0.9. [d] This was a stationary point at the 3-21G* level, but not at 6-31G*.

Table X. Relative Energies of VTC and Hydrates (kcal/mol)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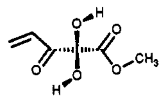
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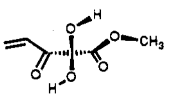
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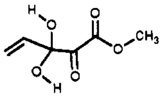
37

	6-31G*	6-31+G**//6-31G*[a] RHF	6-31+G**//6-31G*[a] MP2	freq[b]	ZPE[c]
34				22.3	70.2
35	0.0	0.0	0.0	55.2	87.2
36	1.1	1.1	1.5	53.8	87.2
37	9.3	8.6	8.2	32.4	87.0

[a] These relative energies include the zero-point energies. [b] Lowest frequency at the 6-31G* level. [c] ZPE in kcal-mol^{-1} and scaled by 0.9.

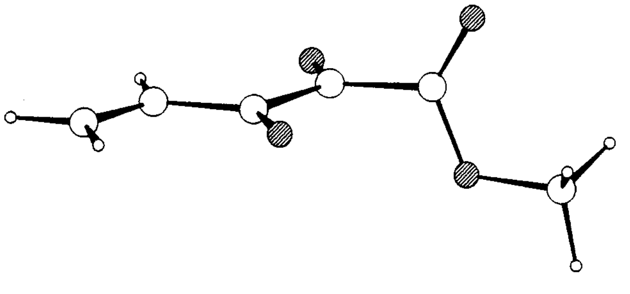

Figure 1. Calculated RHF/6-31G* geometry for the VTC methyl ester (**A**). The oxygen atoms are shaded for clarity.

carbonyl, is 5.5 kcal-mol^{-1} (6-31G**//6-31G*) higher in energy than conformer **28** and has a hydrogen bonding interaction between the hydroxyl proton and the methoxy oxygen. Three of the structures (**29–31**) have the hydrate at the aldehydic carbonyl carbon. The aldehyde hydrate conformers **29**, **30**, and **31** have hydrogen-bonding patterns which involve a 6-membered ring interaction for **29** and a 5-membered ring interaction for **30** and **31**. As seen previously with **5** and **6** of 1,2,3-propantrione hydrate and **17** and **18** of 2,3-dioxo-4-pentenal hydrate, the relative energies of **29** and **30** are very similar (~0.3 kcal-mol^{-1}). The aldehyde hydrate **31** of 1-methoxy-1,2,3-propanetrione has the same intramolecular hydrogen-bonding pattern as conformer **30** but an s-cis relationship between the central ketone and the ester, and **31** is 1.5 kcal-mol^{-1} higher in energy than hydrate **30** at the 6-31G**//6-31G* level. Structure **33** with an s-trans (*E*) ester is very destabilized in comparison to **28**.

The energies for hydration of 1-methoxy-1,2,3-propantrione are given in Table VII. The ΔH of hydration for the lowest energy conformer **28**, which is hydrated on the central carbonyl, is −14.2 kcal-mol^{-1} at the MP2 level in comparison to the lowest energy conformer **22**. The ΔH of hydration for the aldehyde hydrate **29** at the same level is −10.9 kcal-mol^{-1}.

Vinyl Vicinal Tricarbonyl Ester (VTC). In searching for the lowest energy conformer of VTC (**A**), the preceding conformational analyses of 2,3-dioxo-4-pentenal **C** and 1-methoxy-1,2,3-propanetrione **D** were considered. The s-cis (*Z*) enone is favored over the s-trans enone in the case of 2,3-dioxo-4-pentenal, and the central ketone and aldehyde of the molecule tended toward a slightly twisted s-trans configuration. The conformational analysis of 1-methoxy-1,2,3-propanetrione displayed a tendency toward an s-cis (*Z*) ester which is orthogonal to the planar s-trans glyoxal unit. With this information in hand, the vinyl tricarbonyl ester (VTC) was studied, and relative energies at the RHF/6-31G* level are listed in Table X for the unhydrated and hydrated forms of VTC. The effect of electron correlation on the relative energies is also shown in Table X.

Structure **34** was found to be a minimum for VTC (R = Me). The conformation consists of an s-cis enone which is in-plane with the adjacent central ketone and an ester group which is orthogonal to this keto–enone unit (Figure 1). In Table X two hydrates on the central carbonyl and one hydrate at the enone carbonyl have been studied. The lower energy hydrate, **35**, has two intramolecular hydrogen bonds between the two hydrogens of the hydrate and the adjacent carbonyl oxygens. VTC hydrate **36** has a hydrogen-bonding interaction with the methoxy oxygen instead of the carbonyl oxygen of the ester group and is ~1 kcal-mol^{-1} higher in energy than hydrate **35**. The third conformer **37** has the enone carbonyl hydrated and is ~9 kcal-mol^{-1} higher in energy than the lowest energy structure **35**. With electron correlation included, the energy differences change slightly, but the trends remain the same. The relative energies of hydrates **35**, **36**, and **37** are 0.0, 1.5, and 8.2 kcal-mol^{-1} at the MP2/6-31+G**//RHF/6-31G* level. Thus, hydration of the central carbonyl group is preferred.

Selected geometrical data for the VTC reagent and 1,3-diphenylpropanetrione are given in Table XI. The geometry of the lowest energy VTC hydrate, **35**, is very similar to that shown in the X-ray crystal structure of the hydrate of *tert*-butyl ester VTC, **39** (Figure 2). The hydrogen bonding in the crystal structure has been shown to be intermolecular instead of intramolecular as seen in the calculated structures.[24] The small difference in bond angles between the X-ray crystal structure **39** and the

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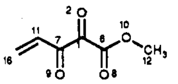
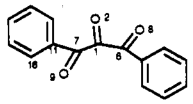
[24] The X-ray crystal structure of VTC (R = *tert*-butyl) showed intermolecular distances between the hydrogen atoms of the hydrate and the carbonyl (1.843 Å) and hydroxyl oxygen (1.894 Å) of an adjacent molecule in the unit cell within the range indicating hydrogen-bonding interactions.

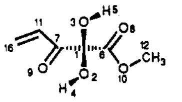
Table XI. Selected Geometrical Data for VTC and 1,3-Diphenylpropanetrione



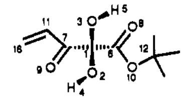
6-31G* optimized geometry **34**



X-ray structure **38**



6-31G* optimized geometry **35**



X-ray structure **39**

	$r(C_1–O_2)$	$r(C_6–O_8)$	$r(C_7–O_9)$	$\angle(C_7C_1C_6)$	$\angle(C_{16}C_{11}C_7)$	$\angle(O_9C_7C_1)$	$\angle(C_{12}O_{10}C_6)$
34	1.1843	1.1826	1.1923	115.38	120.35	117.37	117.03
38	1.2125	1.2162	1.2086	117.25	120.29	114.06	
35		1.1879	1.1932	112.89	120.71	118.41	117.39
39		1.1932	1.2045	109.87	122.46	118.00	121.37

	$\angle(O_8C_6C_1)$	$\tau(C_{16}C_{11}C_7O_9)$	$\tau(O_9C_7C_1O_2)$	$\tau(O_2C_1C_6O_8)$	$\tau(O_8C_6O_{10}C_{12})$
34	122.38	0.49	177.91	−84.87	−1.78
38	114.82	1.44	107.39	123.26	
35	122.28	−5.62			−2.61
39	123.87	−0.88			−3.19

	$r(C_1–O_2)$	$r(O_2–H_4)$	$r(C_1–O_3)$	$r(O_3–H_5)$	$\tau(H_5O_3C_1O_2)$	$\tau(H_4O_2C_1O_3)$
35	1.3724	0.9536	1.3749	0.9520	79.14	104.19
39	1.3709	1.0894	1.3953	0.9527	63.86	70.59

calculated structure of VTC hydrate **35** can be accounted for by the difference in hydrogen bonding and the difference between "crystal packing forces" in the crystalline environment of the X-ray structure and the gas-phase environment of the ab initio molecular orbital calculations.

The torsional angles, $O_9–C_7–C_1–O_2$ and $O_2–C_1–C_6–O_8$, for the calculated, nonhydrated VTC structure **34** display the enone and central carbonyl as nearly planar (177.9°) and the ester group as orthogonal to that keto–enone unit (−84.9°). In contrast, the X-ray crystal structure of 1,3-diphenylpropanetrione, **38**, has torsional angles which differ greatly from those of the calculated VTC structure **34** and are reported at 107.4° and 123.3°. The inherent difference between those compounds (phenyl substituents as opposed to vinyl and methoxy groups) and the crystal-packing forces for structure **38** may account for the difference in carbonyl torsional angles. Crystal-packing forces are operative in structure **38** as is evident from the different lengths of the outer carbonyl C=O bonds (1.2162 and 1.2086 Å) in the X-ray structure.

The energy of hydration for the vinyl tricarbonyl reagent is −13.7 kcal-mol^{-1} at the RHF/6-31G**//6-31G*+ZPE level and −14.8 kcal-mol^{-1} at the MP2/6-31+G**//RHF/6-31G* level and can be compared to the energies of hydration for activated aldehydes (i.e., chloral, mesoxaldehyde).

The energies of hydration for the lower energy conformers of all systems studied are listed in Table VII. It is interesting to note that the energies for hydration at the central carbonyl are all within 0.9 kcal-mol^{-1} at the MP2/6-31+G**//RHF/6-31G* level: −13.9, −14.5, −14.2, and −14.8 kcal-mol^{-1} for 1,2,3-propanetrione, 2,3-dioxo-4-pentenal, 1-methoxy-1,2,3-propanetrione, and VTC (R = Me), respectively. The vinyl substituent and the methoxy substituent do not have a substantial effect on the Δ*H* of hydration. The aldehyde hydrates, not surprisingly, also have values within a narrow range: −12.5 kcal-mol^{-1} for 1,2,3-propanetrione, −12.0 kcal-mol^{-1} for 2,3-dioxo-4-pentenal, and −10.9 kcal-mol^{-1} for 1-methoxy-1,2,3-propanetrione. The central hydrate is the lowest energy structure in all cases and thus gives the most exothermic reaction.

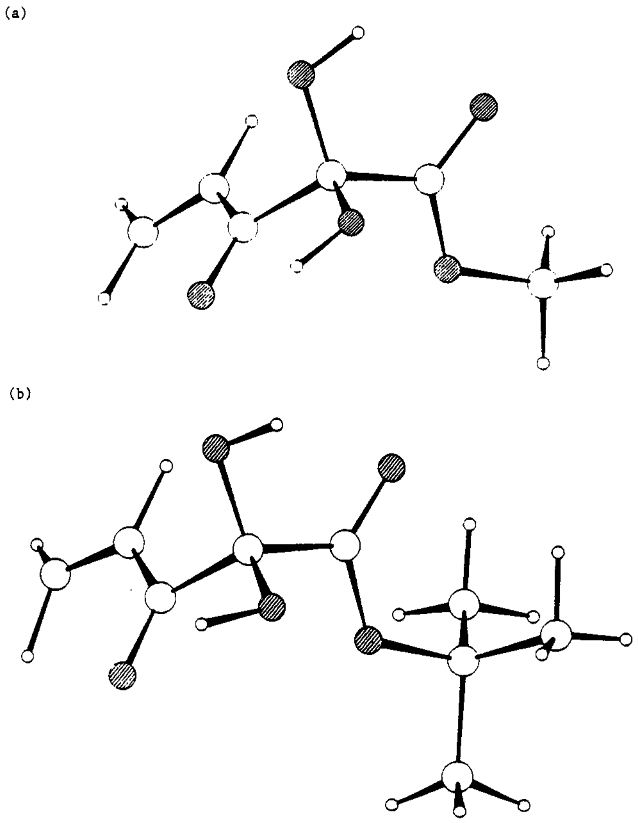


Figure 2. Comparison of (a) the calculated RHF/6-31G* geometry for the hydrate at the central carbonyl of the VTC methyl ester and (b) the X-ray crystal structure of the hydrate of the VTC *tert*-butyl ester. The oxygen atoms are shaded for clarity.

Experimental Results

In order to obtain an experimental value for the energy of hydration ($\Delta H_{\text{hydration}}$) of the vicinal tricarbonyl reagent

VTC, we have performed some ^1H NMR experiments as well as reaction calorimetry. The latter has been used successively in determining accurate energies for ketalization of carbonyl compounds.[25] It was not possible to study the vicinal tricarbonyl reagent calorimetrically as the dehydrated VTC could not be isolated. Instead, trans-hydration experiments using hydrated VTC and non-hydrated chloral (CCl_3CHO) were performed in order to determine the equilibrium constant for reaction (1). The

$$\mathrm{VTC{\cdot}H_2O + Cl_3CCHO \rightleftharpoons VTC + Cl_3C(OH)_2H} \quad (1)$$

ΔH of hydration of chloral was determined by reaction calorimetry as chloral, and its hydrate could be easily isolated as pure compounds. Together, the methods would provide a reasonable value for the energy of hydration of VTC.

The reaction calorimetry on chloral entailed the following steps:

$$\mathrm{CCl_3CHO(l) + H_2O(soln) \rightarrow CCl_3C(OH)_2H(aq)} \quad (2) \quad \Delta H_2$$

$$\mathrm{CCl_3C(OH)_2H(s) + H_2O(soln) \rightarrow CCl_3C(OH)_2H(aq)} \quad (3) \quad \Delta H_3$$

$$\mathrm{CCl_3CHO(l) + acetone(soln) \rightarrow CCl_3CHO(soln)} \quad (4) \quad \Delta H_4$$

$$\mathrm{CCl_3C(OH)_2H(s) + acetone(soln) \rightarrow CCl_3C(OH)_2H(soln)} \quad (5) \quad \Delta H_5$$

$$\mathrm{H_2O(l) + acetone(soln) \rightarrow H_2O(soln)} \quad (6) \quad \Delta H_6$$

$$\mathrm{CCl_3CHO(acetone) + H_2O(acetone) \rightarrow CCl_3C(OH)_2H(acetone)} \quad (7) \quad \Delta H_7$$

where ΔH_7, the energy of hydration for chloral in acetone solution, is equal to $\Delta H_2 - \Delta H_3 - \Delta H_4 + \Delta H_5 - \Delta H_6$. From reaction calorimetry, the enthalpy values for reactions 2 through 6 are −11 354 ± 19, 1026 ± 12, −630 ± 20, 428 ± 10, and 900 ± 20 cal-mol^{-1}, respectively. Therefore, the $\Delta H_{\mathrm{hydration}}$(chloral) in acetone solution is −12 222 ± 37 cal-mol^{-1}.

We initially desired an experimental value for the energy of hydration of chloral in the gas phase. While there is a published value for the heat of vaporization of chloral hydrate,[26] we are quite skeptical of its accuracy since chloral hydrate will not be stable in the gas phase. We have therefore resorted to comparing the experimental hydration energies in acetone solution with our ab initio values.

We have also calculated the ab initio energies of hydration for fluoral (CF_3CHO)[27] and chloral.[28] The resulting $\Delta H_{\mathrm{hydration}}$(fluoral) at the RHF/6-31+G** and MP2(fc)/6-31+G** levels (with the inclusion of the scaled ZPE correction at the RHF/6-31G* level) are −11.1 and −12.3 kcal-mol^{-1}, respectively, while $\Delta H_{\mathrm{hydration}}$(chloral) are −6.9 and −9.6 kcal-mol^{-1}, respectively. The calculations suggest that the energy of hydration for fluoral and chloral are not the same (contrary to the usual assumption). Indeed, the hydration of these aldehydes seems to be dominated by the greater electron-withdrawing effect of the CF_3 group and perhaps also the larger steric bulk of the CCl_3 group. While our calculated, gas-phase $\Delta H_{\mathrm{hydration}}$ for chloral can not be compared directly with the experimental value in acetone solution (−12.22 ± 0.04 kcal-mol^{-1}), both values are in reasonable agreement.

^1H NMR trans-hydration experiments between VTC *tert*-butyl ester hydrate and chloral were performed in dry acetone-d_6. The equilibrium constant (K_{eq}) was obtained for eq 1 from the peak integrals for all of the components. ΔH was then obtained as a function of temperature (T(°C), K_{eq}: 8.65, 3.52; 24.85, 2.72; and 41.25, 2.17) from a least-squares analysis (r 0.999 92) of ln (K_{eq}) vs $1/T$, a line whose slope is $-\Delta H/R$. For the trans-hydration reaction (1), the experimental ΔH was found to be −2.6 ± 0.1 kcal-mol^{-1}, and therefore, chloral is preferentially hydrated over VTC in acetone-d_6.

Therefore, the $\Delta H_{\mathrm{hydration}}$ of VTC *tert*-butyl ester is −9.6 kcal-mol^{-1} in acetone solution which compares to our theoretical results for the VTC methyl ester (−14.5 kcal-mol^{-1} at the MP2/6-31+G**//6-31G* level) in the gas phase. Thus, while there are insufficient data for best comparison of the experimental $\Delta H_{\mathrm{hydration}}$ to the calculated value (for example, heats of fusion and vaporization), our calculated values do show the correct trends. The heats of solvation of VTC and its hydrate are neglected, but we anticipate that the solvation effect will not be the only factor responsible for the difference between the calculated and experimental values. Our theoretical and experimental studies do show, however, that the hydration of the VTC reagent is very exothermic and on a similar scale as activated aldehydes such as fluoral and chloral.

Origin of the Differences in Hydration Energies. A unique feature of the tricarbonyl compounds is that they prefer to hydrate at the center carbonyl in preference to an aldehydic carbonyl. Although the preference is often not large, it should be remembered that aldehydes are normally hydrated in preference to ketones by about 2 kcal/mol.

We were interested in examining the reasons for the differences in hydration energies that have been uncovered in this investigation. It seemed likely that the changes in charge distribution would play a role in determining the relative energies. Therefore, we have investigated the charge distributions for both the carbonyl compounds and their hydrates making use of Bader's theory of atoms in molecules.[14] Here, one first locates the bond critical points (the points having the minimum charge density along the path joining pairs of atoms). Starting at one of these points, rays are developed perpendicular to the bond path for which the charge density decreases most rapidly. The set of such rays provides a surface separating the pair of atoms. This is done for all bonded atom pairs, and the set of surfaces thus produced serves to separate the molecule

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[25] (a) Wiberg, K. B.; Squires, R. R. *J. Am. Chem. Soc.* **1979**, *101*, 5512. (b) Wiberg, K. B.; Squires, R. R. *J. Am. Chem. Soc.* **1981**, 4103, 4473. (c) Wiberg, K. B.; Martin, E. J.; Squires, R. R. *J. Org. Chem.* **1985**, *50*, 4717.

[26] Stephenson, R. M.; Malanowski, S. *Handbook of the Thermochemistry of Organic Compounds*; Elsevier: New York, 1987.

[27] The RHF/6-31G* geometry for each compound was used. The total energies for fluoral are as follows: RHF/6-31+G**, −449.502 861, and MP2(fc)/6-31+G**, −450.453 647 hartrees. The total energies for fluoral hydrate are as follows: RHF/6-31+G**, −525.559 117, and MP2(fc)/6-31+G**, −526.713 342 hartrees. The scaled ZPE are 20.9 and 38.6 kcal-mol^{-1} for fluoral and fluoral hydrate, respectively.

[28] The RHF/6-31G* geometry for each compound was used. The total energies for chloral are as follows: RHF/6-31+G**, −1529.588 291, and MP2(fc)/6-31+G**, −1530.433 665 hartrees. The total energies for chloral hydrate are as follows: RHF/6-31+G**, −1605.637 683, and MP2(fc)/6-31+G**, −1606.688 792 hartrees. The scaled ZPE are 17.7 and 35.2 kcal-mol^{-1} for chloral and chloral hydrate, respectively.

Table XII. Change in Carbon Charge on Hydration[a]

carbon type	transformation	C(keto)	C(hydrate)	Δq
a. 1,2,3-propanetrione				
aldehyde	$1 \rightarrow 5$	1.311	1.402	0.096
center	$1 \rightarrow 7$	1.157	1.313	0.156*
b. 2,3-dioxo-4-pentenal				
aldehyde	$12 \rightarrow 17$	1.312	1.402	0.090
center	$12 \rightarrow 19$	1.162	1.317	0.155*
enone	$12 \rightarrow 21$	1.221	1.314	0.093
c. 1-methoxy-1,2,3-propanetrione				
aldehyde	$22 \rightarrow 29$	1.295	1.406	0.111
center	$22 \rightarrow 28$	1.236	1.370	0.134*
d. VTC				
center	$34 \rightarrow 35$	1.230	1.369	0.139*
enone	$34 \rightarrow 37$	1.198	1.299	0.101

[a] The preferred site of hydration is shown by an asterisk.

into atomic regions. The electron population in each region is obtained by numerical integration of the charge density.

The populations may be converted into charges by subtracting them from the atomic number of the atoms involved. These charges have been obtained for the atoms of all of the compounds in this study and are available as supplementary material. The most interesting changes in charge on going from a carbonyl compound to its hydrate was found at the carbonyl carbons, and these data are summarized in Table XII for the formation of the hydrates from the more stable tricarbonyl conformers. The charges may at first seem large, but it must be remembered that the oxygens withdraw charge from the carbons via both the σ and π systems, and this results in a large charge shift from carbon to oxygen.

In each case, the change in charge at the carbonyl carbon on hydration is given, and it can be seen that the largest increase in charge is correlated with the most favorable reaction. In the hydrates, there is an advantage in having as large an increase in carbon charge as possible, since this leads to a large stabilizing internal coulombic interaction with the two attached oxygens having partial negative charges. This type of stabilization has been found in many other cases, such as with heterosubstituted allyl anions,[29] acetyl derivatives,[30] and polyfluorinated alkanes.[31]

A general discussion of the factors that control hydration equilibria will be given at a later time when we present our experimental and computational results for the hydration of a number of carbonyl compounds.

Conclusions

In summary, our theoretical calculations have revealed some interesting conformational preferences for these trione systems. The s-cis (*Z*) enone was found to be favored over the s-trans (*E*) enone in calculations of 2,3-dioxo-4-pentenal by $\sim$1.4 kcal-mol^{-1} at the RHF/6-31+G**//6-31G* level. The s-cis ester was favored over the s-trans ester in 1-methoxy-1,2,3-propanetrione by $\sim$8 kcal-mol^{-1} at the RHF/6-31G* level. The lowest energy conformer for 1-methoxy-1,2,3-propanetrione **22b** was found to be a structure bisected, as such, into planar s-trans glyoxal and s-cis ester components which are twisted 82° relative to one another. This suggests a stereoelectronic relationship of this structure to the tricarbonyl section of FK-506 which incorporates a similarly twisted amide–ketone bond.

The regiochemistry for hydration in the model systems, 1,2,3-propanetrione, 2,3-dioxo-4-pentenal, and 1-methoxy-1,2,3-propanetrione was found, in all cases, to favor the central carbonyl at the RHF and MP2/6-31+G**//6-31G* levels with ZPE correction. It is interesting to note that in the case of 1,2,3-propanetrione and 2,3-dioxo-4-pentenal hydrates, energies considered without the ZPE correction favored hydration at the terminal aldehyde carbonyl over hydration at the central carbonyl; however, energies considered with the ZPE correction favored the central carbonyl hydrates. The 1-methoxy-1,2,3-propanetrione hydrates remained in the same relative energetic order with and without ZPE correction. The 6-31+G** basis set gave slightly greater differences in relative energies than the 6-31G** basis set. Electron correlation increased the energy differences between conformers to an even greater extent, but the relative trends at the HF level with ZPE correction were unchanged (see Table VII).

Analysis of the charge density distributions of the vicinal tricarbonyls has shown that the driving force for hydration is the large electrostatic stabilization that is created in the hydrates when the (positively charged) hydrated carbon is flanked by two large negative oxygen charges. Hydration of the ester unit is less favored as two negative charges stabilize the ground state, and less stabilization is gained on going to the hydrate. This stabilization may also explain the geometric distortions in VTC, and analogously FK-506. The ester unit is well stabilized electrostatically by itself, and as a result, it is twisted nearly perpendicular to the rest of the carbonyl system. The hydrate at the central carbonyl is favored over the others as a larger positive charge at the central carbonyl carbon is generated upon hydration, and therefore, a larger degree of electrostatic stabilization is created.

The hydration process for VTC has been found, by calculation, to be highly exothermic and on the scale of activated aldehydes such as fluoral and chloral. Calorimetric results for the hydration of chloral has yielded an experimental $\Delta H_{\text{hydration}}$ of -12.22 ± 0.04 kcal-mol^{-1} in acetone solution. Our calculated $\Delta H_{\text{hydration}}$(g) for fluoral going to fluoral hydrate is -12.3 kcal-mol^{-1} at the MP2/6-31+G**//6-31G* level (with ZPE), while the calculated $\Delta H_{\text{hydration}}$(g) for chloral to chloral hydrate is -9.6 kcal-mol^{-1}. These are in reasonable agreement with the experimental value obtained for chloral hydration in acetone solution. Trans-hydration experiments between VTC *tert*-butyl ester and chloral in acetone showed that VTC *tert*-butyl ester has an experimental energy of hydration which is 2.6 ± 0.1 kcal-mol^{-1} less exothermic than chloral. Thus, VTC *tert*-butyl ester has a $\Delta H_{\text{hydration}}$ of -9.6 kcal-mol^{-1} in acetone solution, while our gas-phase, calculated $\Delta H_{\text{hydration}}$ is -14.5 kcal-mol^{-1} at the MP2/6-31+G**//6-31G* level for the VTC methyl ester.

Experimental Section

VTC *tert*-butyl ester was prepared according to ref 3. Chloral hydrate was obtained commercially from Fisher and used without further purification. Chloral was prepared by shaking the hydrate with concentrated sulfuric acid, separating the two layers, and then distilling.[32] The calorimetry stock medium was deionized with distilled water or dry acetone. Water used for calorimetry

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ampules was distilled once more. Acetone-d_6 was dried over 4-Å molecular sieves and used without further purification. p-Toluenesulfonic acid monohydrate was dehydrated by heating under vacuum.

Purity of all compounds was determined on a Hewlett-Packard 5890A analytical gas chromatograph equipped with a crosslinked methyl silicone fused silica capillary column (50 m × 0.20 mm × 0.33 μm). All compounds used for calorimetry and NMR experiments were found to be >99.5% pure prior to use.

The automated calorimetry system has been described previously.[33] Chloral and water were vacuum transferred into preweighed spherical ampules, flame sealed under vacuum, and then reweighed. Chloral hydrate was crushed to a fine powder and added to the ampule via a small funnel. A Mettler analytical balance, reproducible to 0.000 005 g, was used for weighings. In each calorimetry run, 100 mL of stock solution was placed in the cell, and one ampule was placed in the sample holder. After equilibrium was reached, the ampule was broken. The temperature, measured to 0.0001 °C with a quartz probe, was recorded every 10 s starting roughly 10 min before initiation of the reaction and until the reaction was complete (nominally an additional 30 min). An electrical calibration directly followed each reaction run. Each calorimetric reaction was performed five to six times to ensure reproducible results.

Solutions for NMR experiments were prepared by adding a weighed quantity (~0.01 g) of VTC–H_2O into a 1-mL volumetric flask, followed by a weighed quantity (~0.3–0.4 g) of acetone-d_6. Chloral was added by volumetric microsyringe (5–10 μL), and the solution was transferred to an NMR tube containing 1 crystal of anhydrous *p*-toluenesulfonic acid. The solution was then degassed and sealed under vacuum. ^1H NMR spectra were taken on a Bruker 500-MHz NMR spectrometer at temperatures around 10, 25, and 40 °C. Temperatures were calibrated with a MeOH standard using the equations of Ammann, Meier and Merbach.[34] The receiver delay was set to 10 s to ensure proper relaxation of all signals in order to have accurate integrals.

Acknowledgment. This investigation was supported by the National Institutes of Health. We are indebted to the Pittsburgh Supercomputing Center and to Cray Research for generous grants of computer time. C.M.H. thanks the Fannie and John Hertz Foundation for a predoctoral fellowship.

Supplementary Material Available: Tables of atomic charges and bond orders for the tricarbonyl compounds and their hydrates (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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