5.0, 12.7 Hz, H-3eq of NeuAc), 3.45–4.13 (m), 4.48 (d, J = 8.0 Hz, H-1 of Gal), 4.49 (d, J = 8.0 Hz, H-1 of Gal), 5.0–5.04 (m), 5.18–5.22 (m), 5.38–4.42 (m).

General Procedure for Bromohydration with NBS. To a solution of 1 mmol of glucal in a mixture of 3.6 mL of CH_3CN–1.5 mL of H_2O was added 1 mmol of NBS at room temperature. The reaction was continued for 3 h at the same temperature. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel column chromatography. The products were converted to peracetates by pyridine and acetic anhydride in the presence of a catalytic amount of 4-(dimethylamino)pyridine and purified by silica gel column chromatography for characterization.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1,4)-1,3,6-tri-*O*-acetyl-2-bromo-2-deoxy-D-glucopyranose (5a) and -D-mannopyranose (5b). According to the general procedure, a 1:2.5 mixture of **5a** and **5b** (30 mg, 78%) was obtained from Galβ-(1,4)glucal 4 (17 mg). The ratio of **5a** and **5b** was determined from the integrated ratio of the anomeric protons. **5a** and **5b** were obtained as α:β anomeric mixtures: **5a** (α:β = 3.5), **5b** (α:β = 5:2).

Methyl 5-Acetamido-2,4,7,8,9-penta-*O*-acetyl-3-bromo-3,5-dideoxy-β-D-*erythro*-L-*manno*-2-nonulopyranosonate (2) and Methyl 5-Acetamido-2,4,7,8,9-penta-*O*-acetyl-3-bromo-3,5-dideoxy-α-D-*erythro*-L-*gluco*-2-nonulopyranosonate (3). Chemical bromohydration was carried out according to the general procedure, and the products were converted to peracetate, followed by esterification with methyl iodide in the presence of an equimolar amount of secium carbonate to obtain a mixture of **2** and **3** (155 mg, 74%). The production ratio of **2** and **3** was determined from the integral ratio of methyl ester protons.

^{1}H-NMR spectra of **2** and **3** were in good agreement with a previous report.[25]

Compound **3**. ^{1}H-NMR ($CDCl_3$) δ: 1.90, 2.03, 2.08, 2.10, 2.12, 2.15, (3 H, s, each OAc and NHAc), 3.78 (3 H, s, $COOCH_3$), 4.04 (1 H, dd, J = 6.0, 12.4 Hz, H-9), 4.09 (1 H, d, J = 10.0 Hz, H-3ax), 4.33 (1 H, ddd, J = 10.0, 10.6, 10.7 Hz, H-5), 4.36 (1 H, dd, J = 2.4, 12.4 Hz, H-9′), 5.10 (1 H, ddd, J = 2.4, 6.0, 6.1 Hz, H-8), 5.25 (1 H, dd, J = 2.5, 10.7 Hz, H-6), 5.30 (1 H, dd, J = 10.0, 10.6 Hz, H-4), 5.38 (1 H, dd, J = 2.5, 6.1 Hz, H-7), 5.90 (1 H, d, J = 10.0 Hz, NH).

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Enol Oxalacetic Acid Exists in the *Z* Form in the Crystalline State and in Solution†

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Because of inconsistencies in the literature regarding the structure of the enol form of oxalacetic acid (OAA), this subject has been reinvestigated. It was approached initially by attempting to determine the crystal structure of enol OAA directly by X-ray crystallography. This approach failed due to the poor quality of enol OAA crystals. The subject was then approached indirectly as follows. First, the structure of enol di-*tert*-butyl OAA in the crystalline state was determined to be *Z* by X-ray crystallography. Second, the solution structure of enol di-*t*-butyl OAA was determined to also to be *Z* by ^{1}H and ^{13}C-NMR studies combined with the results from X-ray crystallography of enol di-*tert*-butyl OAA. Third, the solution structure of enol OAA was determined to be *Z* by ^{13}C-NMR studies using enol di-*tert*-butyl OAA as a reference. Fourth, the structure of enol OAA in the crystalline state was determined to be *Z* by ^{1}H-NMR studies using freshly dissolved enol OAA solutions at low temperature. Finally, the structure of enol OAA in aqueous solution was inferred to be *Z* on the basis of is activity as a substrate for fumarase A. The previous reports in the literature of crystalline (*E*)-enol OAA are in error.

Introduction

Oxalacetic acid (OAA) is an important primary metabolite. It can exist in the keto, enol (which could be cis(*E*) or trans(*Z*)), and hydrated *gem*-diol forms each of which can also exist in several ionization states. A number of investigators have attempted to identify the particular forms of OAA present in the crystalline state and in solution. Although there is general agreement on the nature of the equilibrium between the keto, enol, and hydrated *gem*-diol forms in solution,[1-3] there is little known about the structure of the enol in solution and considerable disagreement over the structure of the enol of OAA in the crystalline state.[4-10]

The earliest studies on the various forms of OAA were those of Wohl and co-workers who reported that crystalline OAA existed as the enol. Depending on the concentration of H_2SO_4 in the mother liquor, they claimed that the (*Z*)-enol melting at 182 °C or the (*E*)-enol melting at 152 °C would crystallize out of solution.[4,5]

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Consistent with Wohl's results, Heidelberger and Hurlburt have reported the synthesis of both the (*E*)-enol and the (*Z*)-enol of OAA by starting, respectively, with sodium diethyloxalacetate which gave a crystalline product with a melting point of 151–2 °C and with di-*tert*-butyl OAA which gave a crystalline product with a melting point of 182–4 °C.[6,7] They also claim that the (*Z*)-enol could be converted to the *E* by dissolving it in water and reisolating it as quickly as possible. *The Merck Index* under the entry oxalacetic acid also states that the (*E*)-enol OAA can be crystallized from water and in addition states one can obtain (*E*)-enol OAA from ethyl acetate + carbon tetrachloride and (*Z*)-enol OAA from acetone + benzene.[8] However, the only evidence for the (*E*)-enol and (*Z*)-enol given in these references is the similarity in the melting points to those reported by Wohl's group. The OAA of commerce is claimed to be the (*E*)-enol by one manufacturer. The 1990 Sigma Catalog under number O 4126 indicates the OAA they sell is *cis*-hydroxymaleic acid.

During a reinvestigation of the Wohl group's findings, Gruber and co-workers prepared crystalline samples of OAA melting at 152 and 182 °C according to Wohl's procedure and found these samples had identical infrared spectra.[9] They concluded that these samples had the same structure and that the melting point of the lower melting sample was due to impurities, not because it was isomeric to the high melting sample. These results were corroborated by Banks who also noted the absence of a peak in the infrared spectrum at 2.8 μ characteristic of the enolic OH group and concluded that in the crystalline state the enolic OH was involved in a hydrogen bond that affected its stretching frequency.[10] Banks argued from this that the crystalline form of OAA the studied was *Z*, since only in this form would the enolic OH group be in position to form an intramolecular hydrogen bond to a carboxyl oxygen cis across the double bond.

NMR investigations into the species of OAA present in solution have been made, and resonances characteristic of an enol were observed; however, the stereochemistry of the enolic species was not investigated.[2,3,11] In each investigation only one vinylic proton resonance was observed. Since the vinylic proton of (*E*)-enol OAA which is cis to a hydroxyl group and the vinylic proton of (*Z*)-enol OAA which is cis to a carboxyl group whould be expected to have different chemical shifts, this must mean only one isomer is present in these solutions at levels detectable by NMR. This is puzzling because both the (*E*)- and (*Z*)-enol tautomers would be expected in solution if they are as readily interconvertible as the literature suggests.

We became interested in this problem while studying the oxalacetate keto–enol isomerase activity of *E. coli* fumarase A. We wanted to know which isomer of the enol OAA we were using as a substrate for this enzyme. Due to the inconsistencies in the literature on this subject, we have reinvestigated this problem. Our initial attempts to solve this problem by X-ray crystallography failed because of the poor quality of crystals of OAA. Next, an indirect multistep approach to finding the structure of enol OAA was undertaken as described in this paper.

Experimental Section

Synthesis of Di-*tert*-butyl Oxalacetate. Di-*tert*-butyl OAA was prepared by a modification of the method of Heidelberger and Hurlburt.[6,7] The reaction vessel was heated without stirring for 24 h in an oil bath at 110 °C. The reaction mixture was acidified with aqueous HCl, extracted with ether, and recrystallized repeatedly from ether. This gave crystals suitable for X-ray crystallography. The compound was stored at −20 °C since it slowly decomposed at room temperature.

X-ray Crystallography. A colorless cubic crystal with dimensions 0.46 × 0.47 × 0.47 mm was obtained by saturating a diethyl ether solution at its boiling point and cooling to 4 °C. The crystal was mounted in a glass capillary under N_2 and placed on an Enraf-Nonius CAD4 diffractometer equipped with a Mo Kα graphite monochromator, and gas-cooled low temperature unit operating at T = −70 °C. The diffractometer routines indicated a monoclinic cell with dimensions a = 5.980 (1) Å, b = 9.869 (1) Å, c = 11.786 (2) Å, β = 95.65 (1)° which were verified by partial rotation photographic projections along each of the three reciprocal axes. With Z = 2 the calculated density for $C_{12}H_{20}O_5$ is 1.172 g/cm^3.

A total of 1705 data were collected over the range $3.5° \leq \theta \leq 55.0°$ using the ω scan method with a scan width = 1.20–1.90° ω and scan speed = 1.80–5.00°/min. The data were treated in the usual manner for Lorentz-polarization as well as for two standards collected 13 times. With μ(Mo) = 0.85 cm^{-1} absorption effects were negligible. The merged data yielded 1158 unique reflections with $I \geq 3.0\sigma(I)$. Systematic absences of $h0l, l$ odd and $0k0$, k odd indicate the space group is $P2_1/c$ (no. 14).

The solution was accomplished via direct methods (MULTAN). The coordinates and thermal parameters were refined via full-matrix least-squares analysis on F with scattering factors taken from the *International Tables for Crystallography*, Vol. IV. The final refinement allowed anisotropic temperature factors for all non-hydrogen atoms, and isotropic factors for the hydrogen atoms (122 parameters) yielded R = 0.041, Rw = 0.045 with the standard deviation of an observation of unit weight 1.89. The maximum shift/error in the last cycle was 0.05 and the largest residual density on the final difference map was 0.17 e/Å^3 near atom C1.

Results and Discussion

X-ray Crystal Structure of Di-*tert*-butyl Oxalacetate. A summary of the crystal data, refinement results, bond distances, and bond angles are given in the supplementary material along with a complete set of parameters from the crystal structure determination. The data show that di-*tert*-butyl OAA is the (*Z*)-enol in the crystalline state and that the asymmetric unit consists of one-half the molecule lying on an inversion center through the central C=C bond. This disorders the enol oxygen over two sites in the crystal lattice. Excellent thermal and coordinate parameters were obtained by simply half-weighting the enol hydroxy moiety in the refinement to reflect the disorder across the inversion center; however, the obscured vinylic proton was excluded. The C=C bond distance is as expected (1.34 Å) for a C—C=C—C system, but the enolic carbon–oxygen bond distance is shorter than expected. This is most likely a consequence of the disorder and the superimposition of the oxygen with the vinylic proton.

Analysis by NMR Spectroscopy. The NMR of di-*tert*-butyl OAA in solution was investigated next in anticipation of using the results as a reference point to interpret the NMR of OAA in solution. The diester was dissolved in d_6-acetone, and a ^{1}H NMR spectrum was run immediately. The spectrum showed resonances at δ 1.523 and 1.526 (*tert*-butyl groups), 5.77 (vinylic proton), and 11.66 ppm (OH). After 24 h at room temperature, three new peaks appeared at δ 1.452, 1.534, and 3.70 ppm, while the previous signals were diminished in intensity. These changes are due in all probability to the tautomerization of some of the enol to the keto form with two new *tert*-butyl groups and the methylene signal of the keto ester. From 24 to 96 h there was very little additional change; at equilibrium, the enol–keto ratio was 7:3. Since the formation of keto di-*tert*-butyl OAA in acetone occurs over a period of hours, and the keto form would necessarily be an intermediate in the conversion of the (*Z*)-enol to the

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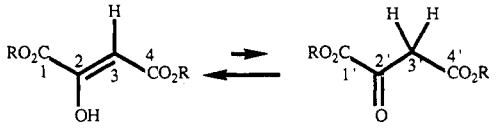
Table I. ^{13}C NMR data for OAA and Di-*tert*-butyl OAA[a]

	R = H		R = *t*-Bu[b]	
C	δ	(J_{CH}, Hz)	δ	(J_{CH}, Hz)
1	162.85	(3.5)	161.05	(3.5, 8[c])
2	161.81	(2.5)	161.43	(2, 3.5[c])
3	96.51	(173)	97.83	(174, 3[c])
4	174.18	(≤0.5)	172.63	(≤0.05, ≤0.5[c])
1′	161.60	(1)	159.99	(1)
2′	189.22	(6.5)	188.44	(6.5)
3′	45.12	(132)	47.09	(129)
4′	168.36	(7.5)	166.55	(7.5)

[a] OAA was obtained from Sigma, and di-*tert*-butyl OAA was made as described in this paper. [b] *tert*-Butyl groups: 27.89, 27.96, 28.11, and 28.24 ppm (CH_3), 82.38, 83.23, 83.46, and 84.23 ppm (C); $^1J_{CH}$ = 127 Hz, $^2J_{CH}$ = $^3J_{CH}$ = 4 Hz. [c] Coupling constants to the OH proton. Confirmed by eliminating this interaction through weak irradiation at the δ 11.66 frequency during acquisition (ref 15).

Scheme I



(*E*)-enol, it is certain that the initial solution proton NMR spectrum is of (*Z*)-enol di-*tert*-butyl OAA. Furthermore, this same (*Z*)-enol is the only enolic species in solution that is detectable by NMR after several days. The (*E*)-di-*tert*-butyl OAA appears to be a much higher energy form in acetone than the (*Z*)-enol.

The ^1H NMR spectrum of OAA in d_6-acetone was investigated next. An enol–ketone equilibrium mixture (ratio 7:3) is formed by the time the sample is dissolved and placed in the NMR spectrometer (the isomerization is acid-catalyzed). Vinylic and methylene proton signals appear at 5.97 and 3.85 ppm, respectively. The strong similarity in the chemical shift of the vinylic proton of OAA and (*Z*)-enol di-*tert*-butyl OAA in d_6-acetone is evidence that the enol form of OAA in acetone is also *Z*.

An independent line of investigation into the enol form of di-*tert*-butyl OAA and OAA was made by measuring their ^{13}C NMR spectra in d_6-acetone. The results are shown in Table I. (Scheme I illustrates the numbering system used in Table I and facilitates the discussions of the results.)

After equilibrium had been reached, the ^{13}C NMR spectrum of di-*tert*-butyl OAA and OAA exhibited chemical shifts characteristic of both the keto and enol forms (CH_2 at 47.09 and 45.12; and CH at 97.53 and 96.51 ppm for di-*tert*-butyl OAA and OAA, respectively). A full analysis of the long-range carbon-hydrogen couplings is only consistent with the configuration for these enols being *Z*. The most important parameter for this assignment is the 3.5-Hz three-bond coupling consistant in each case between C-1 and the olefinic proton, H-3, of the enol forms which shows that these two nuclei are in each case in a cis relationship. If the enols were *E*, the C-1 and the olefinic protons would be trans to each other, and the $^3J_{CH}$ would be expected to be 9 Hz or larger.[12-14] These conclusions with respect to di-*tert*-butyl OAA are in complete agreement with the results of the X-ray crystal structure determination of di-*tert*-butyl OAA coupled with the ^1H NMR studies which showed the same enolic species exists in acetone solution in equilibrium with the keto form as exists in the crystalline state. Thus, two independent approaches both demonstrate that the form of the enol of di-*tert*-butyl OAA is (*Z*) in acetone solution as well as in the solid state. This information coupled with the strong similarity between the ^{13}C NMR spectrum of the enol of OAA with that of enol di-*tert*-butyl OAA, and particularly the virtual identity of the coupling constants between C-1 and the olefinic proton, H-3, of the enol form of di-*tert*-butyl OAA and OAA shows that in acetone solution the enol form of OAA is also *Z*.

An attempt was made to detect (*E*)-enol OAA in solution by incubating an acetone solution of OAA at 45 °C before and during the measurement of its ^1H-NMR spectrum. Again, no enolic resonances other than that of the (*Z*)-enol were detected indicating (*E*)-enol OAA must be considerably higher in energy than the (*Z*)-enol.

The data presented to this point show that the enol form of di-*tert*-butyl OAA in the crystalline state and in acetone solution is *Z* and the enol form of OAA in acetone solution is also *Z*. Next we investigated the form of enol OAA in crystals with solid-state NMR using di-*tert*-butyl OAA as a reference. However, the marked differences in chemical shifts of di-*tert*-butyl OAA and OAA between solution and the solid state made it very difficult to determine the enol form of OAA in crystals by solid-state NMR.

Since it was clear from the ^1H-NMR spectrum of OAA in solution at room temperature that the rate of isomerization of the enol and keto forms was slow on the NMR time scale, the possibility occurred to us of identifying the crystalline form of enol OAA by working in solution at temperatures low enough to completely suppress the isomerization to the keto form. In this way, the enolic form of OAA present in the crystalline state would be "trapped" in solution long enough to allow its identification by NMR. OAA from Sigma was dissolved in d_6-acetone at −78 °C, and its ^1H- and ^{13}C-NMR spectra were measured at that temperature. Since the spectra lacked resonances characteristic of the keto form, no isomerization had occurred; therefore, the enol present was of necessity the same form as that which existed in crystals (since the keto form is an obligate intermediate in the isomerization of enol forms). The chemical shifts of the enol in solution at −78 °C were identical with those of the (*Z*)-enol OAA present in solution at room temperature. This proves that crystalline OAA obtained from Sigma is the (*Z*)-enol.

Analysis by IR and Raman Spectroscopy. Infrared and Raman spectra were obtained on di-*tert*-butyl OAA and OAA from Sigma. Of particular interest with regard to which form crystalline OAA takes is the frequency of the C=C stretch. In the case of simple olefinic compounds, the C=C stretch of *trans*-CHR^1=CHR^2 is generally 16 cm^{-1} higher than *cis*-CHR^1=CHR.[16] Di-*tert*-butyl OAA exhibited a C=C stretch at 1632 cm^{-1}, and OAA from Sigma exhibited a C=C stretch at 1640 cm^{-1}. Since we have shown that the di-*tert*-butyl OAA is *Z*-(trans), we would expect the C=C stretch of OAA to be similar to that of di-*tert*-butyl OAA if it were *Z* and 10–20 cm^{-1} lower than that of di-*tert*-butyl OAA if it were *E*. That the frequency of the C=C stretch in OAA is 8 cm^{-1} higher than that of di-*tert*-butyl OAA is evidence that crystalline OAA has the same conformation around the double bond as di-*tert*-butyl OAA, namely *Z*. A possible

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Table II. Melting Points of OAA Samples

sample	expected isomer	expected mp (°C)	obsd mp (°C)
(1) OAA prepared from di-*tert*-butyl oxalacetate	*Z*	182–4	182
(2) OAA recrystallized from ethyl acetate + carbon tetrachloride	*Z*	182–4	180
(3) OAA prepared from sodium diethyl oxalacetate	*E*	151–2	179
(4) OAA recrystallized from acetone + toluene	*E*	151–2	179
(5) OAA obtained from Sigma	*E*	151–2	182
(6) OAA obtained from Sigma recrystallized one time from H_2O	*E*	151–2	173
(7) OAA obtained from Sigma recrystallized two times from H_2O	*E*	151–2	165
(8) OAA obtained from Sigma recrystallized three times from H_2O	*E*	151–2	160
(9) OAA obtained from Sigma recrystallized four times from H_2O	*E*	151–2	159

complication in this reasoning would be if there was an electronic effect arising from differences in hydrogen bonding of the enol in crystalline OAA and di-*tert*-butyl OAA that countered the expected shift to a lower frequency in the case the cis form of the double bond. However, the results reported in the following paragraph suggest that the hydrogen bonding of the enol is similar in crystalline OAA and di-*tert*-butyl OAA.

Two C=O stretches were observed for the carboxyl carbonyl groups of OAA at 1690 and 1717 cm^{-1}, and two C=O stretches were observed for the carboxyl carbonyl groups of di-*tert*-butyl OAA at 1650 and 1725 cm^{-1}. The two different C=O stretches for these two compounds most likely arise because in each case one of the carbonyl groups is hydrogen bonded to the enolic proton which modifies the C=O stretch.

While not completely definitive, the most straightforward interpretation of these IR and Raman measurements is that OAA exists as the (*Z*)-enol in the crystalline state also.

Physical Properties of OAA Samples. To this point it has been demonstrated that both di-*tert*-butyl OAA made by us and OAA obtained from Sigma are the (*Z*)-enol in the crystalline state. This means the Sigma sample was not hydroxylmaleic acid (i.e., (*E*)-enol OAA) as claimed by the manufacturer. A deliberate attempt was made to prepare (*E*)-enol OAA by three methods reported in the literature to give this form. We hoped to be able to measure the spectroscopic properties of the (*E*)-enol OAA prepared by these methods. Since the primary criteria cited in the literature to distinguish (*E*)- and (*Z*)-OAA is their melting points[4-10] the melting points of our preparations are summarized and compared with the literature values in Table II. The samples of OAA made by methods which are claimed by Heidelberger and Hurlbert[6] and by *the Merck Index*[8] to give (*E*)-enol OAA, i.e., (1) hydrolysis of sodium diethyl OAA, (2) recrystallization from H_2O, or (3) recrystallization from ethylacetate + carbon tetrachloride, all melt at much higher temperatures than that reported for the (*E*)-enol. We were not able to obtain a pure compound by any of these methods that melted as low as 151–152 °C, the reported melting point of the (*E*)-enol. This is of particular significance because one would conclude from the literature that the (*E*)-enol was the more stable form[6-8] and should be easily obtained from the (*Z*)-enol.

How can the reports in the literature that there are two forms of enol OAA be reconciled with the results reported in this paper? As shown in Table II, the melting point of OAA recrystallized from H_2O initially decreases with recrystallization. This behavior is consistent with impurities accumulating in the OAA sample during recrystallization from H_2O. Others as well as ourselves have noticed that impurities (including pyruvate and citroylformate) are readily formed in aqueous solutions of OAA.[2,3] This is not unexpected given that OAA is a β-keto acid. This leads us to suspect that all previously reported samples of enol OAA with melting points lower than 182 °C were not (*E*)-enol OAA, but were in fact samples of crystalline (*Z*)-enol OAA whose melting points had been lowered by impurities.

All the samples prepared by the methods shown in Table II were dissolved in acetone at −78 °C and their ^1H-NMR spectra were run at that temperature immediately after the samples were dissolved. Again, no isomerization to the keto form occurred in any of the sample. The spectra of the enol present in each of these samples were identical indicating they were all same form of the enol in the crystalline state. Combined with the results reported earlier in this paper, one can conclude that the enol form of OAA in all these samples is *Z*. New peaks appear in the NMR spectra of the samples that were repeatedly recrystallized, but these are clearly not attributable to the (*E*)-enol. The new peaks are characteristic of the decomposition products mentioned above.

The frequency of the C=C stretch in IR spectra of all the samples in Table II was also measured and found to be the same; again indicating the form of the enol is the same in all these samples.

Finally, the form of enol OAA in aqueous solution was investigated. Our data as well as others show that there is only one enolic form of OAA detectable in aqueous solution,[2,3] Since we have shown that the enol form that crystallizes out of aqueous solution is *Z*, this implies (but does not prove) that the form in solution is also *Z*. Stronger evidence in this regard is our recent results which show that enol OAA in aqueous solution readily binds to the active site fumarase A, and that this enzyme catalyzes the isomerization of enol and keto OAA.[17] Since the active site of this enzyme binds the trans four-carbon dicarboxylic acid fumarate, but does not bind the cis four-carbon dicarboxylic acid maleate,[18] the most straightforward interpretation is that the form of enol OAA in aqueous solution is *Z*.

Summary and Conclusion

Starting with the work of Wohl's group and based on a difference in melting points between OAA samples recrystallized under different conditions, a concept was introduced into the literature (and has persisted to this day) that both (*E*)-enol OAA and (*Z*)-enol OAA exist in the crystalline state. In spite of several papers in the literature on the topic, no definitive evidence for the existence of these two forms has ever been reported in the literature. We have shown that di-*tert*-butyl OAA exists as the (*Z*)-enol in the crystalline state and by two independent means that the enol form of di-*tert*-butyl OAA in acetone solution is also *Z*. Using di-*tert*-butyl oxalacetic acid as a reference, we have shown that enol OAA in acetone solution is *Z* and that the enol form of OAA in the crystalline

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state is also *Z*. In all the samples we have purchased or prepared, some of which were reputed to give (*E*)-enol OAA, we have failed to find any evidence for the (*E*)-enol. In all probability the lower melting form of OAA that others have taken to be (*E*)-enol OAA is really (*Z*)-enol OAA contaminated with impurities which readily form in solution during recrystallization efforts and depress the melting point. Based primarily on enzymatic evidence, the form of enol OAA in aqueous solution appears to also be *Z*.

Supplementary Material Available: Crystal data for di-*tert*-butyl oxalacetate and an ORTEP plot of (*Z*)-enol oxalacetic acid (4 pages). This material is contained in many 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.

Chemistry of Oxaziridines. 18. Synthesis and Enantioselective Oxidations of the [(8,8-Dihalocamphoryl)sulfonyl]oxaziridines[1,2]

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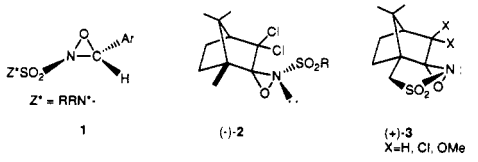
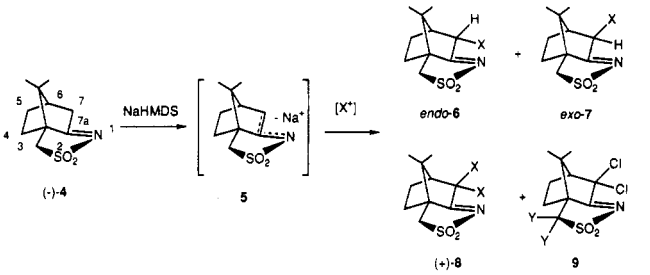
The synthesis and enantioselective oxidations of [(8,8-dihalocamphoryl)sulfonyl]oxaziridines [8,8-dichloro-1,7,7-trimethyl-2′-(phenylsulfonyl)spiro[bicyclo[2.2.1]heptane-2,3′-oxazinidine]] **13** are reported. These reagents are prepared in two steps from the (camphorylsulfonyl)imine **4** by treatment of the corresponding azaenolate with electrophilic halogen sources followed by biphasic oxidation of the resulting dihalo imine **6–9** with *m*-CPBA/K_2CO_3. Of these oxaziridines the dichloro reagent **13b**, available on a multigram scale, affords the highest enantioselectivities for the asymmetric oxidation of sulfides to sulfoxides (42–74%) and for the hydroxylation of enolates (often better than 95% ee). In general the molecular recognition is predicted and explained in terms of minimization of nonbonded steric interactions in the transition states. For the asymmetric oxidation of sulfides to sulfoxides, secondary electronic factors related to the polarity of the sulfide and oxaziridine also play a role. Definitive evidence for chelation of the metal enolate with the C–X bond in **13** is not found. The molecular recognition is interpreted in terms of the higher reactivity of the reagents and an active-site structure which is sterically complementary with the enolate. For the asymmetric hydroxylation of the *Z*- and *E*-enolates of propiophenone (**16a**), the *Z*-enolate exhibits much higher stereoselectivity than the *E*-enolate: >95% vs 22% ee.

Enantiopure *N*-sulfonyloxaziridines **1–3** are important asymmetric oxidants for the reagent controlled synthesis of enantiomerically enriched α-hydroxy carbonyl compounds, sulfoxides, selenoxides, and epoxides.[3] Not only is the product stereochemistry predictable, but the ee's often exceed 95%. Reflecting their dissimilar active site structures, these reagents exhibit quite different stereoselectivities in their asymmetric oxidations. Particularly useful in maximizing the efficiencies of these reagents has been the systematic modification of their active sites which has also provided important information concerning the origins of the molecular recognition. This has been especially true of the (camphorylsulfonyl)oxaziridine derivatives **3**, which are superior to types **1** and **2** for the asymmetric hydroxylation of enolates, where the dichloro and dimethoxy analogs (X = Cl, OMe) have been employed in the enantioselective syntheses (>95% ee) of biologically significant α-hydroxy carbonyl compounds.[4-8]



Scheme I



a, X = F; **b**, X = Cl; **c**, X = Br; **d**, Y = Cl

a, X = F; **b**, X = Cl; **c**, X = Br

This paper concerns the synthesis of the [(monohalocamphoryl)sulfonyl]oxaziridines **11–12** and [(dihalocamphoryl)sulfonyl]oxaziridines **13**, their stereoselective oxidations, and rationale for the molecular recognition.

Results and Discussion

Synthesis of the [(Halocamphoryl)sulfonyl]imines. The starting material for the synthesis of all the (camphorylsulfonyl)oxaziridine derivatives **3** is the (−)-(camphorsulfonyl)imine **4**, readily prepared on a large scale in two steps (>90%), from (+)-10-camphorsulfonic acid.[9,10]

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