The Configuration of 1,3-Dioximinoacetone and 1-Oximinoacetone

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The configuration of 1,3-dioximinoacetone prepared by the nitrosation of acetone dicarboxylic acid has been determined by spectral and acidity studies to be syn–syn. 1-Oximinoacetone prepared by the nitrosation of acetone has been determined to be anti.

1,3-Dioximinoacetone (1,3-diisonitrosoacetone, mesoxaldehyde dioxime, DIA) was first described by Pechmann and Wehsarg[1] in 1886 and studied more recently by Geissman, Schlatter, and Webb.[2] Because of the important use of this substance as a colorimetric reagent,[3] we have undertaken to determine the geometry of this compound and, because of its relationship to the above compound, we have also studied 1-oximinoacetone.

Three forms of DIA are possible—syn–syn, syn–anti, and anti–anti—and all possibilities may be present depending upon energy and spatial relationships. It is known from nmr studies that the C–H resonance frequencies differ for syn and anti forms of propionaldoxime with the syn form having the lower field signal.[4] Thin layer chromatography studies indicate that DIA prepared according to the method of Geissman[2] is over 95% one isomer; indication of trace amount of two other substances are present and these might be other isomers but they do not give the characteristic color reactions of DIA.[3] The same spectral characteristics are shown by a number of different preparations, fractions, crude products, as well as the "heat and ultraviolet light stable isomer" of Pechmann.[1] The nmr spectrum for DIA in 20% solution in dimethyl sulfoxide gives only two signals, equal area peaks: a sharp singlet at 8.13 ppm assigned to the aldehydic proton and a broad singlet at 11.8–12.8 ppm assigned to the hydroxyl proton. The simple spectra with only one type of carbon-bound proton serves to exclude the possibility of the syn–anti isomer but does not permit a decision between the other two isomers although the anti–anti might be favored because of the possibility of very strong hydrogen bonding, and the broad band for the oxygen-bound proton would tend to support this. The nmr spectrum of the monoanion of DIA in D_2O gives a sharp singlet for C–H resonance at 7.92 which would support rapid exchange in a charged anti–anti form but the same spectrum would be expected from the syn–syn if exchange with solvent water were rapid enough which is entirely possible

The ultraviolet spectrum of recrystallized DIA in carbon dioxide–water shows only one broad peak centered at 250 mμ, ϵ 19,200; the dianion (pH 11.10, NaOH) shows a peak at 217 mμ, ϵ 5500, and a more intense broad peak at 322 mμ, ϵ 32,200. The infrared spectrum was studied in potassium bromide disk because of the insolubility of DIA in carbon tetrachloride or chloroform; the spectrum of DIA-d_2 was also studied. The differences of these two spectra are at 7.0 μ, between 9 and 11 μ, and 13 and 15.25 μ with the most striking differences being in the 9–11 region. The position of the broad band due to hydrogen-bonded hydroxyl is close to the 3250 cm^{-1} reported by Palm and Werbin[5] for α oximes but the C=N stretching band appears some 50 cm^{-1} to lower frequencies than reported by these authors for α oximes and some 40 cm^{-1} reported for β oximes. This latter effect is probably due to conjugation between the C=N linkages and the carbonyl group. This would also explain the low frequency of the C=O stretching mode although intramolecular hydrogen bonding would also produce a shift to lower frequencies. The spectral data are consistent with either syn–syn or anti–anti. Dilution infrared studies should permit a decision, but, as mentioned, solubility problems make this type of study impracticable with DIA.

Since intramolecular hydrogen bonding in monoanions markedly alters the K_1 to K_2 ratio for dibasic acids[6] (*e.g.*, maleic acid *vs.* fumaric acid), the ionization constants for DIA were determined by titration with 0.1 N sodium hydroxide in carbon dioxide free water. The neutralization equivalent determined to be 58.13 against 58.04 for theory indicates that the keto oxime did not hydrolyze appreciably during the 2 hr required for the determination. A titration curve showed no sharp breaks indicating that the two pK_a values lie close together: pK_1 was found to be 7.58 and pK_2, 8.85. The ratio between the two ionization constants ($K_1 = 18.2K_2$) is very close to that reported for fumaric acid[6] ($K_1 = 22K_2$) and considerably different from that for maleic[6] acid ($K_1 = 49140K_2$) indicating that the negative charge on the monoanion exerts very little effect in reducing ionization of the second proton. This would favor the syn–syn structure.

To obtain definite spectral confirmation, model compounds were studied so that appropriate assignments might be made. The syn–syn isomer of DIA should, in dilute solution, show only intermolecular hydrogen bonding while the anti–anti form should show only intramolecular hydrogen bonding. 1-Oximinoacetone can exist in syn and anti forms with the anti, in high dilution, expected to show only intramolecular hydrogen bonding. However, to make meaningful assignments in this compound it was also necessary to study the spectrum of ethyl oximinoacetoacetate; regardless of isomer, this compound involves the possibility of intramolecular bonding between the hydroxyl hydrogen and a carbonyl oxygen. Both of these compounds have sufficient solubilities in chlorinated solvents to make dilution studies convenient.

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At relative high concentrations of ethyl oximino-acetoacetate in carbon tetrachloride, two OH absorption peaks are observed: 3380 cm^{-1} (broad) and 3560 cm^{-1} (sharp). On dilution, the intensity of the 3380 band decreased and could be made to disappear while the 3560 band changed only slightly on dilution. In carbon tetrachloride solution, 1-oximinoacetone showed the same characteristics: a concentration dependent band at 3380 cm^{-1} and a concentration independent band at 3560 cm^{-1}. The 1-oximinoacetone, prepared by the nitrosation of acetone by butyl nitrite, is the anti isomer.

A comparison of the 1600–1800 cm^{-1} region of the spectra of *anti*-1-oximinoacetone and ethyl oximino-acetoacetate, Table I, indicates that the best configuration for the latter involves hydrogen bonding between the OH and the acetyl carbonyl group. This configuration had been assigned by Jovitschitsch[7] to this compound prepared by a different procedure in 1898.

TABLE I

COMPARISON OF IR SPECTRA 1600–1800 CM^{-1}
REGION ACETONITRILE SOLUTION

Functional group	*anti*-1-Oximino-acetone	Ethyl oximino-acetoacetate	DIA
C=O ester		1730	
C=O nonbonded keto	1700	1700	1695
C=O bonded keto	1675, strong	1675, strong	1650, very weak
C=N	1620, weak	1619, weak	1620,[a] very strong

[a] Concentration dependent.

anti-1-Oximinoacetone showed equal intensities at 1700 and 1675 cm^{-1} for the free and bonded carbonyl groups. A weak band in DIA at 1650 cm^{-1} might be assigned to an intramolecularly bonded carbonyl but the intensity of this band is much less than for the bonded carbonyl of *anti*-1-oximinoacetone. In addition, the C=N band in DIA is much more intense than the 1650 band while the opposite is true for the oximino-acetone. This would argue against assigning a bonded carbonyl in DIA and would support the syn–syn conformation.

Additional support for the syn–syn structure is obtained from further nmr studies. *anti*-1-Oximinoacetone in deuteriochloroform shows three bands: three protons at 2.45 (methyl group), one proton at 7.50 (aldehydic), and one proton at 9.70 ppm (hydroxyl). The aldehydic proton in DIA appears at 8.13 ppm, a much lower position. Since the oximino groups in DIA are not conjugated, the downfield position of the aldehydic proton would not be expected to arise solely from the influence of an additional oximino group on each aldehydic proton. The additional deshielding observed for the aldehydic protons of DIA relative to the oximino-acetone must arise from the deshielding influence of the oxygen atoms of the two oximino groups in DIA. Since the configuration of the oximinoacetone is known to be anti, the oximino groups in DIA must be syn. The difference in the chemical shifts of the aldehydic protons of syn and anti propionaldoxime has been shown to be 42 cps while the difference in chemical shifts of the

aldehydic protons in oximinoacetone and DIA is 36 cps.[4] The similarity of these shifts indicate that DIA must have a configuration opposite to *anti*-1-oximinoacetone. The nmr spectra for the *syn*-oximinoacetophenone shows a chemical shift for the aldehydic proton of 8.13 ppm[8] which is identical with that in DIA. The syn–syn structure of DIA would appear to be certain.

Experimental Section

Preparations of Materials.—1,3-Dioximinoacetone (DIA) was prepared according to the process of Geissman, et al.,[2] in about 60% yield. The acetonedicarboxylic acid used was prepared according to Adams, Chiles, and Rassweiler.[9] The crude DIA was recrystallized from water at 60°, with considerable loss, dried *in vacuo* over phosphoric anhydride, and stored under refrigeration in brown bottles. It is quite stable under these conditions. Melting point is a poor criterion of purity; recrystallized material showing only one spot on tlc silica gel G, unactivated, developed with chloroform–methanol (80:20) does not give a sharp phase transition but changes from transparent birefringent flakes at 125–140 into an opaque white solid which decomposes with darkening and gas evolution at 206–212°. The so-called "heat and ultraviolet stable isomer"[1] shows the same changes except that the original material is not birefringent.

Anal. Calcd for C$_3$H$_4$N$_2$O$_3$: C, 31.10; H, 4.30; N, 24.10. O, 41.30. Found: C, 31.21; H, 3.43; N, 23.98; O, 41.21.

DIA-1,3-d_2 was prepared by the Geissman method[2] using 85% D$_2$O as solvent in the nitrosation; recrystallization was from water.

Anal. Calcd for C$_3$H$_2$D$_2$N$_2$O$_3$: C, 30.51; H and D, 5.12; O, 40.63.

Anal. Calcd for 83% DIA-d_2–17% DIA: C, 30.58; H, 4.84; O, 40.77. Found: C, 30.85; H, 3.56; O, 40.68.

Deuterium content was determined by nmr analysis comparing the integrated area under the C–H peak at 7.42 ppm with the OH peak at 11.14 ppm using acetone-d_6 as solvent. The ratio was 85:7 indicating 91.7%. This is probably slightly high due to adventitious water. The C–H peak of the DIA-d_2 at 7.42 while in DIA it is at 8.13, is very small indicating high deuterium incorporation.

1-Oximinoacetone was prepared by the butyl nitrite nitrosation of acetone by the method of Slater.[10] Ethyl oximinoacetoacetate was prepared by the method of Adkins and Reeves.[11]

Nmr Studies.—All nmr spectra were recorded on a Varian Associates A-60A spectrometer, generally in dimethyl sulfoxide, with tetramethylsilane as internal standard.

Infrared and Ultraviolet Studies.—These were carried out on a Perkin-Elmer Model 221 and Model 202.

Ionization Constants.[12]—Recrystallized DIA was dissolved in CO$_2$-free water and titrated with 0.1 N sodium hydroxide with a Leeds and Northrup pH meter to follow changes. Some 60 points were recorded between pH 4.1 and 11.63. There were no sharp breaks. The pK_a values were calculated in such a way as to minimize interference from the additional ionization mode. $K_1 = [H^+][HP^-]/[H_2P]$ {where $[H^+]$ = hydrogen ion concentration (mol/l.), $[HP^-]$ = concentration of DIA monoanion (mol/l.) and $[H_2P]$ = concentration of undissociated DIA (mol/l.)} which gave $K_1 = 2.61 \times 10^{-8}$ for the first ionization and $^pJ_1 = 7.58$ Hz. The second ionization was calculated from the relationship $K_A = K_W/K_H$, where $K_W = 1.0 \times 10^{-14}$ and K_H = hydrolysis constant for DIA. To calculate K_H, it was necessary to determine the equivalence point by a plot of pH (ml *vs.* ml). Concentration of appropriate species at the pH defined by the equivalence point were then calculated and substituted into $K_H = [OH^-][HP^-]/(P^{2-})$ to give $K_H = 7.00 \times 10^{-6}$, from which K_A, which equals $K_2 = 1.43 \times 10^{-9}$, and p$K_2 = 8.85$.

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Appropriate corrections were made for increase in reactant volume due to added titrant.

Registry No.—*syn-syn*-DIA, 26309-06-8; *anti*-1-oximinoacetone, 17280-41-0.

α-Methoxy-α-trifluoromethylphenylacetic Acid.
## Configuration by Asymmetric Synthesis[1]

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(−)-α-Hydroxy-α-trifluoromethylphenylacetic acid (13) has been prepared by asymmetric synthesis involving the reaction of phenylmagnesium bromide with (−)-menthyl trifluoropyruvate [10, CF_3COCOO-(−)-menthyl]; 22% asymmetric induction was observed. Application of Prelog's generalization to this system is unambiguous and leads to the assignment of the *S* configuration to this product and to the corresponding methyl ether 1 and methyl ether–methyl ester 14, in accord with previous work. (−)-Menthyl glyoxylate [HCOCOO-(−)-menthyl] gave 19% asymmetric synthesis of the (*S*)-mandelic ester; this indicates that the nature of the achiral group (CF_3 *vs.* H) has only a minor effect upon the *extent* of asymmetric induction in this system.
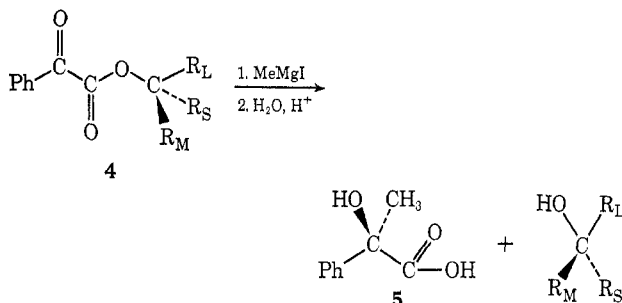
α-Methoxy-α-trifluoromethylphenylacetic acid (1, MTPA)[3] is a valuable reagent for the determination of enantiomeric purity of alcohols and amines. Circumstantial evidence for the *S* configuration for (−)-MTPA has been obtained by correlation of the nmr chemical shift of (−)-methyl α-methoxy-α-trifluoromethylphenylacetate in a chiral solvent with that of (*R*)-(−)-methyl mandelate.[4] More recently an extensive study of the circular dichroism of a series of α-substituted phenylacetic acids[5] has convincingly supported this assignment. We had hoped to establish the absolute configuration of MTPA by the conversion of *O*-methylatrolactic acid (2) of known configuration into the methyl ether of methylphenyltrifluoromethylcarbinol (3) by treatment with sulfur tetrafluoride. This intermediate, 3, should be readily accessible from MTPA 1. This approach is similar to that which we have
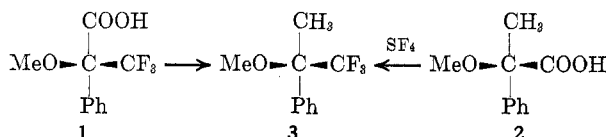

used to establish the configuration of phenyltrifluoromethylcarbinol and methyltrifluoromethylcarbinol.[6] However repeated attempts to achieve the conversion of 2 to 3 have failed to produce a detectable amount of the trifluoromethyl product 3; therefore this direct approach has been reluctantly abandoned in favor of the following alternative.

According to the Prelog generalization,[7] when the small, medium, and large groups (R_S, R_M, R_L) in the

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alcohol moiety of a chiral benzoylformate ester are as represented in 4, *R*-(−)-atrolactic acid (5) will be pro-

duced in excess upon treatment with methylmagnesium iodide. This empirical correlation has been exceedingly reliable for predicting the configuration of secondary carbinols; less use has been made of this generalization for the determination of configuration of α-hydroxy acids, even though the correlation here should be on even firmer ground. For example, the (−)-menthyl group in the keto ester 6 is responsible for the different rates of attack of the reagent on one *vs.* the other diastereotopic faces of the prochiral keto group to give 7 in excess. If R is varied while the chiral "inducing"
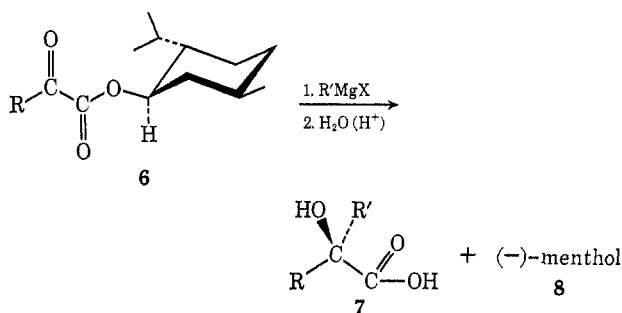
(−)-menthyl group is retained, stereoisomers of corresponding configuration should predominate regardless of the nature of the achiral R group. In such comparable reactions the asymmetric reaction is brought about by the same chiral moiety while R, which is achiral, is separated by at least three atoms from the inducing chiral centers. The proximity of R to the