6-Nitro-7-octadecanone (*p*-tolylsulfonyl)hydrazone (14): yield 95%; mp 63–65 °C; IR (KBr) ν 3260 (NH), 1600 (C=C), 1555 cm^{-1} (NO_2); ^1H NMR δ 0.72–0.92 (m, 6 H), 0.95–2.6 (m, 28 H), 2.42 (s, 3 H), 5.0 (m, 1 H), 7.57 (dd, AA'BB' pattern, 4 H, J = 8 Hz), 8.2 (s, 1 H). Anal. Calcd for $C_{25}H_{43}N_3O_4S$: C, 62.34; H, 9.00; N, 8.73; S, 6.64. Found: C, 62.45; H, 9.12; N, 8.59; S, 6.50.

2-Nitrocyclopentadecanone (*p*-tolylsulfonyl)hydrazone (17): yield 98%; mp 120–121 °C; IR (KBr) ν 3240 (NH), 1600 (C=C), 1552 cm^{-1} (NO_2); ^1H NMR δ 1.1–1.55 (m, 22 H), 2.05–2.4 (m, 4 H), 2.42 (s, 3 H), 5.0 (t, 1 H, J = 7.5 Hz), 7.57 (dd, AA'BB' pattern, 4 H, J = 8 Hz), 8.2 (s, 1 H). Anal. Calcd for $C_{22}H_{35}N_3O_4S$: C, 60.39; H, 8,06; N, 9.61; S, 7.31. Found: C, 60.50; H, 8.15; N, 9.48; S, 7.47.

Reductive Denitration–Deoxygenation of α-Nitro Ketone (*p*-Tolylsulfonyl)hydrazones to Alkanes. General Procedure. To a solution of lithium aluminum hydride (0.3 g, 7.92 mmol) was added dry THF (30 mL), the mixture was stirred and cooled to 0 °C, and, under N_2 a solution of (*p*-tolylsulfonyl)-hydrazine (2.64 mmol) in dry THF (20 mL) was added dropwise. The mixture was stirred for 10 h at 60 °C, then treated carefully with cold water (25 mL), acidified with 2 N HCl, and extacted with *n*-pentane (3 × 30 mL). The organic layer was dried with Na_2SO_4, the solvent was removed by distillation, and the crude product was purified by short chromatography, over silica gel, using *n*-pentane as eluent.

Pentylbenzene (3): yield 70%; bp_{60} 115 °C (lit.[18] bp 185–186 °C).

Dodecylbenzene (6): yield 61%; $bp_{0.2}$ 120 °C (lit.[22] bp_1 148 °C).

(4-Methylpentyl)benzene (9): yield 67%; bp_{10} 90 °C (lit.[23] bp_{767} 219 °C).

***n*-Tetradecane (12)**: yield 65%; bp_{20} 137 °C (lit.[20] $bp_{0.003}$ 60–64 °C).

***n*-Octadecane (15).** yield 68%; bp_8 168 °C (lit.[19] $bp_{0.15}$ 99–104 °C); ^1H NMR δ 0.89 (t, 6 H, J = 7 Hz), 1.1–1.35 (m, 32 H); ^{13}C NMR δ 14.107, 22.721, 29.408, 29.704, 29.746, 31.968; MS (*m/e*, relative intensity) 254 (M^+, 3), 141 (5), 127 (7), 113 (12), 112 (4), 99 (23), 98 (8), 97 (100), 85 (86), 84 (11), 83 (12).

Cyclopentadecane (18): yield 71%; mp 60–61 °C (lit.[21] mp 62–61 °C).

(*Z*)-19-Nitro-9-tricosen-18-one (21). A mixture of **19** (6.65 g, 25 mmol) and 1-nitropentane (**20**) (2.92 g, 25 mmol) was mechanically stirred for 5 min and then cooled in an ice bath. After the addition of chromatographic alumina (activity I, 5 g) and stirring at room temperature for 24 h, CH_2Cl_2 (50 mL) and tetra-*n*-butylammonium hydrogen sulfate (0.85 g, 2.5 mmol) were added. Under stirring and cooling to −10 °C, 30% H_2SO_4 (65 mL) and potassium dichromate (9.55 g, 32.5 mmol) were simultanously added. After stirring for 2 h at −10 °C, aqueous $FeSO_4$ (40 mL) was added, and the organic layers were separated. The organic phase was dried (Na_2SO_4) and passed through a bed of Florisil. The solvent was removed under reduced pressure to afford the crude α-nitro ketone **21** (8.57 g), which does not need purification. However, after chromatography (cyclohexane–ethyl acetate, 8:2) 8.1 g (85%) of the pure (*Z*)-19-nitro-9-tricosen-18-one (**21**) was obtained as an oil: IR (neat) ν 1730 (CO), 1552 (NO_2); ^1H NMR δ 0.9 (2t, 6 H, J = 6.8 Hz), 1.1–2.12 (m, 32 H), 2.55 (m, 2 H), 5.08–5.15 (m, 1 H, J = 4.7 Hz), 5.28–5.42 (m, 2 H). Anal. Calcd for $C_{23}H_{43}NO_3$: C, 72.39; H, 11.36; N, 3,67. Found: C, 72.55; H, 11.49; N, 3.50.

(*Z*)-19-Nitro-9-tricosen-18-one (*p*-Tolylsulfonyl)hydrazone (22). To a solution of compound **21** (3 g, 7.874 mmol) in methanol was added (*p*-tolylsulphonyl)hydrazine (1.54 g, 8.26 mmol). The mixture was stirred for 10 h at room temperature and then, after workup as in the general procedure, 3.96 g (92%) of the pure compound **22** was obtained: mp 53–55 °C; IR (KBr) ν 3223 (NH), 1600 (C=C), 1550 (NO_2), 1340, 1170 (SO_2); ^1H NMR δ 0.88 (2t, 6 H, J = 6.8 Hz), 1.05–1.50 (m, 26 H), 1.85–2.05 (m, 4 H), 2.05–2.22 (m, 4 H), 2.42 (s, 3 H), 4.95–5.02 (m, 1 H, J = 4.6 Hz), 5.25–5.42 (m, 2 H), 7.57 (dd, AA'BB' pattern, 4 H, J = 8 Hz), 7.9 (s, 1 H). Anal. Calcd for $C_{30}H_{51}N_3O_4S$: C, 65.54; H, 9.35; N, 7.64; S, 5.82. Found: C, 65.71; H, 9.60; N, 7.45; S, 6.01.

(*Z*)-9-Tricosene (23). A suspension of $LiAlH_4$ (0.49 g, 10.5 mmol), in dry THF (40 mL) was stirred under nitrogen and cooled to 0 °C. The tosylhydrazone **25** (1 g, 1.82 mmol) was dissolved in dry THF (20 mL) and added dropwise. The mixture was stirred for 0.5 h at 0 °C and for 10 h at 60°C; then, after workup as in the general procedure, the crude product obtained was purified by short chromatography using *n*-pentane as eluent. Kugelrohr distillation at 170 °C (0.1 min) gave 0.38 g (66%) of pure (*Z*)-9-tricosene (Muscalure) (**23**) (lit.[13a] $bp_{0.01}$ 140–142 °C): ^1H NMR δ 0.88 (2t, 6 H, J = 6.8 Hz), 1.11–1.42 (m, 34 H), 1.9–2.11 (m, 4 H), 5.28–5.41 (m, 2 H); ^{13}C NMR δ 14.11, 22.72, 27.225, 29.36, 29.41, 29.57, 29.61, 29.71, 29.74, 29.81, 31.96, 129.87; MS (*m/e*, relative intensity) 322 (M^+, 4), 125 (20), 112 (11), 111 (45), 98 (19), 97 (94), 85 (31), 84 (32), 83 (100), 82 (26), 71 (46), 70 (47), 69 (88).

Deuterium Labeling by Denitration–Deoxygenation of α-Nitro Ketone. Reduction of 8 to (4-Methyl-3,4-dideuteriopentyl)benzene (9-d_2). A suspension of $LiAlD_4$ (0.158 g, 3.96 mmol) in dry THF (15 mL) was stirred under nitrogen in a 100-mL flask fitted with a septum inlet and cooled to 0 °C. The tosylhydrazone **20** (0.513 g, 1.32 mmol) was dissolved in dry THF (10 mL) and added dropwise. The mixture was refluxed at 60 °C for 10 h, then cooled, treated carefully with cold water (10 mL), acidified with 2 N HCl, and extracted with *n*-pentane (3 × 10 mL). The organic layer was dried ($MgSO_4$), the solvent was removed by distillation, and the crude product **9**-d_2 was purified by short chromatography using *n*-pentane as eluent: yield 0.12 g (55%); ^1H NMR δ 0.88 (s, 6 H), 1.2–1.35 (m, 1 H), 1.55–1.7 (m, 2 H), 2.58–2.63 (m, 2 H), 7.15–7.35 (m, 5 H); ^{13}C NMR δ 22.45, 27.317, 29.25, 36.24, 37.87, 38.12, 38.37, 125.55, 128.23, 128.32, 128.38, 128.46, 142.98; MS (*m/e*, relative intensity) 164 (M^+, 20), 105 (5), 94 (12), 93 (37), 92 (47), 91 (100).

(4-Methyl-3,3,4-trideuteriopentyl)benzene (9-d_3). The procedure was the same as in case of the compound **9**-d_2 except that trifluoroacetic acid-*d*/deuterium oxide (1:9) was used for the quenching of the reaction in place of cold water and 2 N HCl: yield 52%; ^1H NMR δ 0.88 (s, 6 H), 1.52–1.68 (m, 2 H), 2.55–2.63 (m, 2 H), 7.13–7.25 (m, 5 H); ^{13}C NMR δ 22.425, 29.15, 36.21, 125.56, 128.22, 128.38, 142.983; MS (*m/e*, relative intensity) 165 (M^+, 82), 107 (28), 95 (31), 94 (77), 93 (90), 91 (100), 79 = 78 (32), 77 (37), 65 (64).

Acknowledgment. We thank the Ministero della Pubblica Istruzione of Italy for financial support of this work.

Supplementary Material Available: Characterization data (^1H NMR, ^{13}C NMR, and MS) of compounds **3**, **6**, **9**, **12**, **15**, and **18** (1 page). Ordering information is given on any current masthead page.

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NMR Spectroscopy of Malondialdehyde[1]

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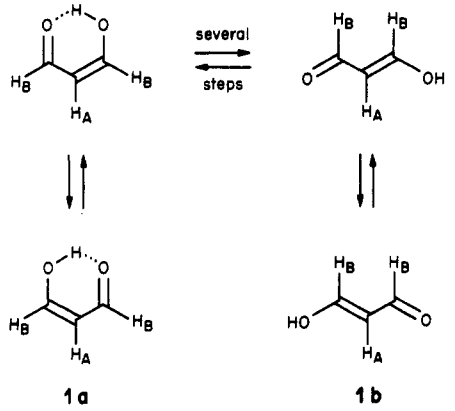
Received May 4, 1989

β-Dicarbonyl compounds tend to exist as stable enols,[2] which creates the possibility of cis–trans isomerism about

(1) Part 8 in the series Chemistry under Physiological Conditions. Part 7 is ref 7 below.

0022-3263/90/1955-5161$02.50/0

the enolic double bond. Open-chain derivatives generally adopt the cis conformation (e.g., see **1a**);[2a] nevertheless, trans enols (e.g., **1b**) have been observed,[2b,3] and in some cases mixtures of cis and trans enols have been found.[2c]



Malondialdehyde (1) has been reported to be a trans enol in water,[4] ethanol,[5] or diethyl ether,[6] and a cis enol in hexane,[6] carbon tetrachloride,[4] dichloromethane,[4,6] or dichloromethane–fluorotrichloromethane.[5] The situation in chloroform appears to be more complicated. Bothner-By and Harris[3] reported that 1 exists in the "s-trans conformation", whereas George and Mansell[4] reported the "s-cis conformation" in chloroform. Both groups based their conclusions on the magnitudes of the coupling constants in the ^{1}H NMR spectra. We became interested in the structure of 1 when we used it as a starting material in our preparation of the bicyclo[3.3.1] system via the Weiss reaction.[7] We have found that the coupling constant in chloroform-*d* depends upon the concentrations of methoxy-containing species present in the solution. Understanding the behavior of 1 is important because it is the simplest β-dicarbonyl compound and, in addition, it is of considerable biological interest.[8]

Results

In their experimental section Bothner-By and Harris[3] state, "Solutions of II [malondialdehyde] and III [acetylacetaldehyde] were obtained by hydrolysis of the acetals, $(EtO)_2CH{\cdot}CH_2CH(OEt)_2$ and $CH_3COCH(OMe)_2$, respectively, with an equal volume of dilute aqueous hydrochloric acid, followed by extraction with $CDCl_3$". When we used the more detailed hydrolysis procedure of Protopopova and Skoldinov[9a] (but substituted 1,1,3,3-tetramethoxypropane, **2**, for the tetraethoxy derivative) and extracted with an equal volume of $CDCl_3$, we obtained a solution of 1 with a coupling constant of J = 8.2 Hz in its ^{1}H NMR spectrum. Considering the range of J values that has been observed (vide infra), this is in qualitative agreement with the value of 9.69 Hz reported by Bothner-By and Harris.[3] The average chemical shifts we measure in $CDCl_3$, δ_A = 5.63 ± 0.02 and δ_B = 8.36 ± 0.02 ppm (see Table I), are somewhat different from the values they reported (δ_A = 5.04 and δ_B = 8.40 ppm). In particular, the discrepancy in the chemical shift of H_A is well outside experimental error. Our values are in complete accord with those of George and Mansell: δ_A = 5.63 and δ_B = 8.37 ppm.[4] When the NMR sample (~0.5 mL) with J = 8.2 Hz was shaken with 1 M HCl (~0.1 mL), the chemical shifts δ_A and δ_B were not changed significantly, but the coupling constant was decreased to J = 6.6 Hz. When we followed our earlier procedure,[7] which used an equimolar amount of 1 M HCl, and extracted with an equal volume of $CDCl_3$, we obtained a solution of 1 with essentially the same values of δ_A and δ_B and J = 4.9 Hz. George and Mansell[4] prepared solutions of 1 from "the impure sodium salt" and observed J = 3.7 Hz in $CHCl_3$. When we prepared 1 from sodio-1 we obtained $CDCl_3$ solutions with J = 3.5 Hz.

Table I. ^{1}H NMR Data for Malondialdehyde

entry	solvent	δ_A[a]	δ_B[a]	J_{AB}
1	0.3 M HCl (0.08 equiv)/H_2O[b]	5.66	8.48	10.4
2	1.0 M HCl (1 equiv)/H_2O[c]	5.68	8.48	10.4
3	entry 2 + NaOH (pH 8 or 9)	5.30	8.64	10.2
4	sodium salt (pH 9.6)	5.30	8.64	10.1
5	entry 4 + HCl (pH 7.4)	5.30	8.64	10.1
6	entry 4 + HCl (pH 6.7)	5.30	8.64	10.2
7	entry 4 + HCl (pH 6.0)	5.31	8.64	10.2
8	entry 4 + HCl (pH 5.2)	5.34	8.63	10.2
9	entry 4 + HCl (pH 4.0)	5.53	8.55	10.2
10	entry 4 + HCl (pH 3.0)	5.67	8.49	10.4
11	entry 4 + HCl (pH 2.0)	5.69	8.48	10.2
12	entry 4 + HCl (pH 1.0)	5.70	8.50	10.4
13	$CDCl_3$ extract of entry 1[d]	5.64	8.38	8.2
14	entry 13 + HCl/H_2O[e]	5.65	8.37	6.6
15	$CDCl_3$ extract of entry 2[d]	5.62	8.34	4.9
16	$CDCl_3$ extract of entry 12[d]	5.63	8.35	3.5
17	entry 16 + Na_2SO_4[f]	5.63	8.35	3.5

[a] Chemical shifts are 0.00 for DSS in H_2O and for TMS in $CDCl_3$. [b] Procedure of ref 9a. [c] Procedure of ref 7. [d] A volume of $CDCl_3$ equal to that of the H_2O was used. [e] 0.1 mL of 1 M HCl. [f] Anhydrous powder.

In addition to 1 we identified β-methoxyacrolein (**3**) and 3,3-dimethoxypropanal (**4**) by ^{1}H NMR and GC–MS analyses.[8] Our assignments of coupled H's in all products were confirmed by 2D NMR (COSY). In fact, **3** and **4** were preferentially extracted into chloroform (see Table III), while most of the 1 remained in the aqueous phase. Also present were a number of minor products, detected by ^{1}H NMR and GC–MS analyses. Upon the addition of base, high yields (ca. 90%) of sodium malondialdehyde were measured. Protopopova and Skoldinov[9a] reported a good yield of sodio-1 (71% isolated) upon the addition of NaOH.[9b] We measured a 35% yield of 1 before the addition of base; 25% has been reported by other investigators.[8]

The amounts of **3**, **4**, and MeOH in the various solutions were measured (see Table III). The observed coupling constants correlate linearly with the quantity R = ([MeOH] + 2[4])/[1], viz. J = 3.5 + 0.156R. The corre-

(2) (a) Emsley, J. *Structure Bonding* **1984**, *57*, 147. Following this author, when we refer to the cis enol, we mean the conformer with an intramolecular H-bond. Only planar conformers are considered, see also ref 18. (b) Yoffe, S. T.; Petrovsky, P. V.; Goryunov, Y. I.; Yershova, T. V.; Kabachnik, M. I. *Tetrahedron* **1972**, *28*, 2783. (c) Noy, R. S.; Gindin, V. A.; Ershov, B. A.; Kol'tsov, A. I.; Zubkov, V. A. *Org. Magn. Reson.* **1975**, *7*, 109.

(3) Bothner-By, A. A.; Harris, R. K. *J. Org. Chem.* **1965**, *30*, 254.

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(8) Marnett, L. J.; Tuttle, M. A. *Cancer Res.* **1980**, *40*, 276. See also ref 19.

(9) (a) Protopopova, T. V.; Skoldinov, A. P. *Zh. Ob. Khim.* **1958**, *28* (Eng. edition p 241). (b) Presumably, NaOH converts **3** and **4** and perhaps other minor products to 1; see also ref 20. (c) Martinez, A. M.; Cushmac, G. E.; Roček, J. *J. Am. Chem. Soc.* **1975**, *97*, 6502. Martinez, A. M. Ph.D. Thesis, University of Illinois—Chicago, 1972. The formula used for the UV calculations was adapted for the NMR data:

$$pK_a = pH - \log \frac{(\delta - \delta_{AH})}{(\delta_{A^-} - \delta)}$$

(d) Golding, B. T.; Patel, N.; Watson, W. P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 668.

Table II. ^{1}H NMR Chemical Shifts of Malondialdehyde in Various Solvents[a]

solvent	δ_A	δ_B	J_{AB}	ref	cis:trans[b]
hexane	5.5	8.28	3.7	6	96:4
CCl_4	5.49	8.31	3.4	4	100:0
CH_2Cl_2	–	8.35	3.8	4	94:6
$CD_2Cl_2/CFCl_3$	5.68	8.37	3.5	5	99:1
$CDCl_3$	5.044	8.397	9.69	3	10:90
	5.63	8.35	3.5	this work	99:1
$CHCl_3$	5.63	8.37	3.7	4	96:4
$(CH_3CH_2)_2O$	5.55	8.39	7.4	6	43:57
			10.2[c]	6	3:97
CD_3CD_2OD	–	8.52[d]	–	5	–
H_2O	5.65	8.49	10.3	4	1:99
	5.68	8.48	10.4	this work	0:100

[a] Spectra were measured at ambient temperature unless otherwise noted. [b] Calculated assuming a linear relationship between J_{AB} and this ratio. [c] –60 °C. [d] Solution contains 1-d_2.

Table III. Concentrations of Products from 2 in $CDCl_3$

entry	procedure	J_{AB}	10^2[1]	10^2[MeOH]	10^2[3]	10^2[4]
1	acidify sodio-1	3.5	3.24	<0.1	<0.1	<0.1
2	Bertz[7]	4.9	3.36	21.0	24.6	5.10
3	entry 4 shaken with 0.1 mL of 1 M HCl	6.6	3.06	22.1	19.4	18.4
4	Protopopova-Skoldinov[9a]	8.2	3.49	80.9	29.7	12.5

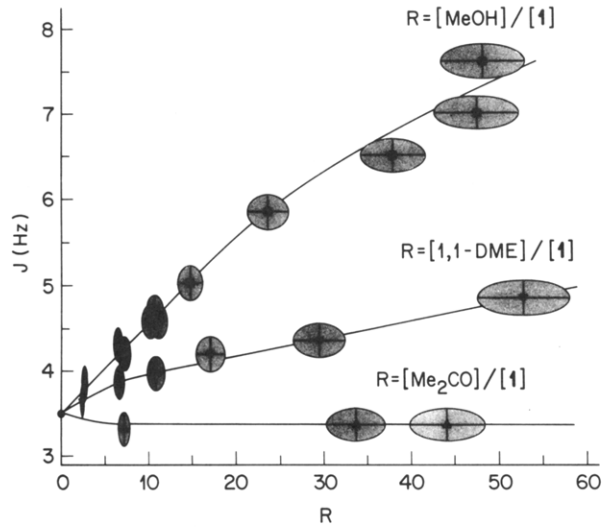

Figure 1. Plots of J vs R for R = [MeOH]/[1] (■), [1,1-DME]/[1] (▼), and [Me_2CO]/[1] (▲). Open squares are for solutions also containing 3.5 equiv of dioxane. The circle represents the value for the initial solutions. Error bars are ±10% for R and ±0.2 Hz for J.

lations with [MeOH]/[1], [3]/[1], [4]/[1], ([3] + [4])/[1], ([MeOH] + [3])/[1], ([MeOH] + [4])/[1], ([MeOH] + [3] + [4])/[1], or ([MeOH] + 3[4])/[1] are not as good. A caveat here: although the correlation coefficient is good (>0.999) the line is based on but four points.

Solutions of **1** with low levels of impurities were generated via protonation of sodio-**1**. Incremental addition of MeOH, 1,1-dimethoxyethane (DME), or acetone gave the results included in Figure 1. Acetone, a typical carbonyl compound, did not increase the coupling constant; in fact, it decreased it a bit to a constant value J = 3.4 Hz. Since **4** tends to decompose to **3**, it was modeled by 1,1-DME, which has approximately the same steric requirements. After a small nonlinear regime, J is a linear function of [1,1-DME]/[1]; J(DME) = 3.8 + 0.021[1,1-DME]/[1] (correlation coefficient = 0.997 for five points). This slope is about half of the initial slope (~0.042). The MeOH data is well-described by the line J(MeOH) = 3.6 + 0.099[MeOH]/[1] (correlation coefficient = 0.995 for nine points) up to an abscissa of ~20, where a saturation effect appears to cause the plot to level off. The coupling constants for the 1,1-DME and MeOH runs are the averages of the two values measured at the olefinic triplet of **1**. The formyl doublet is broader, especially in the presence of large excesses of 1,1-DME or MeOH, and measurement is not as accurate (for raw data, see Table IV, Supplementary Material).

In one run with MeOH, the reaction mixture also contained a constant amount (3.5 equiv) of 1,4-dioxane, which had been used as an internal standard in the aqueous solution. Within experimental error this level of 1,4-dioxane does not appear to affect the coupling constant. A solution of **1** in wet or dry deuteriochloroform had J = 3.5 Hz, as did a dry deuteriochloroform solution that also contained 3.5 equiv of 1,4-dioxane.

Table I also contains NMR data for 1 M aqueous solutions of **1** as a function of pH. From the data in Table I for pH 4.04, 9.6, and 1.0, pK_a = 4.2 ± 0.2. The uncertainty was due to drift in the pH measurements. The pK_a determined by using UV measurements on a much more dilute solution (~10^{-4} M) was 4.57.[9c] We repeated the UV experiment and obtained the same result. When we repeated the NMR titration of sodio-**1** with more data points (Figure 2), we got pK_a = 4.0 ± 0.2. By starting with a 1 M solution of **1** and adding base to get pH 4.38, we obtained a value of δ_A = 5.55 ppm, which corresponds to pK_a = 4.6 ± 0.1. **1** has been reported to form dimer and trimer at pH ~4.[9d]

The ^{13}C NMR spectrum of **1** (from sodio-**1**) in deuteriochloroform (see the Experimental Section) consists of a single pair of lines for the cis enol. In water (pH 1) the ^{13}C NMR spectrum of **1** is also a single pair of lines, which is consistent with the presence of the trans enol in water.[4] From the number of lines in its ^{13}C NMR spectrum, sodio-**1** in water (pH 9.6) contains at least four major species, which is not apparent from its ^{1}H NMR spectrum (Table I).

Discussion

Because it is the simplest β-dicarbonyl compound, **1** has been the subject of numerous spectroscopic investigations. For **1** in the gas phase, X-ray photoelectron,[5] infrared,[10] and microwave[11] spectroscopy establish "a planar, intramolecularly hydrogen-bonded form with two equivalent, individually asymmetric equilibrium configurations between which tunneling occurs".[11] In the solid state, "the

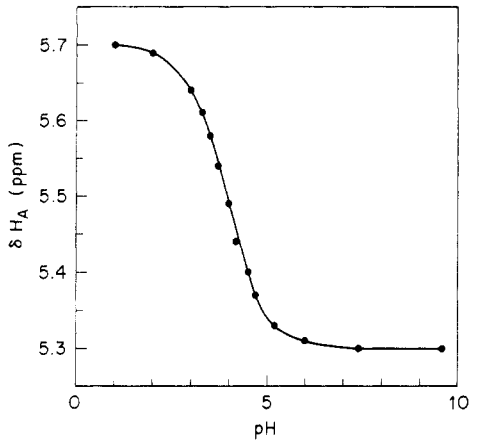

Figure 2. Plot of δH_A vs pH.

open-chain s-trans conformation is stabilized by the formation of a strong intermolecular H-bond", according to an analysis of low temperature infrared spectra of solid **1**.[12]

In solution both cis and trans isomers of **1** have been observed by NMR spectroscopy.[3-6] The ^{1}H NMR spectrum of **1** is an AB_2 system in all solvents that have been studied. In the cis enol the apparent symmetry is attributable to tunneling between equivalent ABM systems (see preceding paragraph). At first glance it might be predicted that the trans enol would give rise to an ABM pattern,[13] similar to that of β-methoxyacrolein;[8,14] however, it is also an AB_2 system in all solvents where it has been found to exist. Apparently, intermolecular H-exchange is rapid vis-à-vis the NMR timescale; equilibration via the dicarbonyl tautomer has been ruled out.[5] Moreover, the chemical shifts of H_A in the cis and trans forms are nearly the same, which is also the case for H_B (see Tables I and II).[3-6] Consequently, the only parameter which appears to change significantly with the cis:trans ratio is the coupling constant J_{AB} (simply referred to as J in the rest of this paper).[15] While the value of J estimated for **1a** was 4.1 Hz,[3] the lowest value observed to date is 3.4 Hz (Table II).[4] We also observe $J = 3.4 \pm 0.1$ Hz in the presence of acetone (7–44 equiv), which may be a "scavenger" for traces of MeOH. The highest J observed before our work was 10.3.[4] Our highest value is 10.4 Hz, which is the number that was estimated for **1b**.[3] Assuming that these lowest and highest values correspond to pure cis and trans isomers, respectively, we can calculate the ratio of these forms for solutions with intermediate values, assuming a linear relationship (Table II).

George and Mansell attributed the difference between their results and those of Bothner-By and Harris to "polar impurities" in solutions of **1** prepared by the latter authors.[4] In fact, carbonyl compounds appear not to be effective, as judged by our results with acetone. Dioxane is also ineffective. The values of J in Table III do correlate with the ratio of CH_3O compounds to **1**, provided that **3** is excluded. The exclusion of **3** can be rationalized by the fact that an electron pair of the MeO group in **3** is delocalized into the π-system by resonance; consequently, the methoxy group of **3** is not available for H-bonding. The factor of 2 in the expression for J can be understood if **4** is about half as effective as MeOH at changing J, which is consistent with the data for MeOH and 1,1-DME in Figure 1. The acetone results suggest that the carbonyl group of **4** does not play an important role; however, this may be an over-simplification if a cooperative effect operates between the carbonyl and methoxy groups.

Apparently, intermolecular H-bonding of the enolic H of **1** with the methoxy oxygens of MeOH or **4** effectively competes with intramolecular H-bonding. Bertz, Rihs, and Woodward[16] have published an X-ray crystal structure of a phenolic H which is H-bonded to the O of a MeOH molecule rather than the O of a keto group in the ortho position. This complex may serve as a model for the 1–MeOR H-bond. Bothner-By and Harris studied **1** prepared from 1,1,3,3-tetraethoxypropane. Presumably, H-bonding to ethoxy groups (especially in ethanol) stabilized the trans enol in this case.

The intramolecularly H-bonded cis enol structure (**1a**) is predicted to be the most stable conformer based on ab initio calculations with full geometry optimization (4-21G basis sets).[18] Conformer **1b** is not predicted to be the most stable trans enol; however, these calculations do not include *intermolecular* H-bonding.

Intramolecular H-bonding has often been cited as the reason that the cis enols of β-dicarbonyl compounds are generally more stable than the trans. Considering the coexistence of both forms in the case of **1** at room temperature in ether[6] or in chloroform also containing methanol, intermolecular and intramolecular H-bonding must provide comparable stabilization. Other factors must also be important in cases such as formylacetone and 2,4-pentanedione, which exist primarily or exclusively in the cis form in organic solvents. (Formylacetone contains small amounts of trans enol in acetone[2c] and is predominantly trans in water.[4]) According to Yoffe et al.,[2b] "no reliable evidence of trans-enolization has been found for open chain β-diketones..."[17] The crucial difference may be attributed to steric effects (e.g., 1,3-allylic strain) in the intermolecularly H-bonded trans conformers.

As a side product of prostaglandin and thromboxane biosynthesis[19a] and an end product of lipid peroxidation,[19b]

(10) Seliskar, C. J.; Hoffmann, R. E. *J. Mol. Spect.* **1982**, *96*, 146.
(11) Baughcum, S. L.; Duerst, R. W.; Rowe, W. F.; Smith, Z.; Wilson, E. B. *J. Am. Chem. Soc.* **1981**, *103*, 6296.
(12) Piaggio, P.; Rui, M.; Dellepiane, G. *J. Mol. Struct.* **1981**, *75*, 171.
(13) One of us (ref 7) had previously reported that **1** prepared from **2** was a mixture of cis and trans enols. While this conclusion was correct, it was for the wrong reason. The spectrum in question contained the peaks for cis enol **1a** and also peaks consistent with 3-hydroxyacrolein, which were incorrectly assigned to trans enol **1b**. They are correctly assigned to 3-methoxyacrolein, **3**. The methoxy peak of **3** was not recognized due to its proximity to other OMe signals (e.g., MeOH, 3,3-dimethoxypropanal, and unreacted **2**).
(14) Maddaluno, J.; d'Angelo, J. *Tetrahedron Lett.* **1983**, *24*, 895.
(15) Spin-spin coupling between the "formyl" H's and the enolic H has been observed at low temperatures (see ref 6).
(16) Bertz, S. H.; Rihs, G.; Woodward, R. B. *Tetrahedron* **1982**, *38*, 63.
(17) The UV spectra of **1** in organic solvents have been interpreted in a manner opposite to our interpretation of the ^{1}H NMR spectra: Kwon, T.-W.; Van der Veen, J. *J. Agric. Food Chem.* **1968**, *16*, 639. The absorption band observed in chloroform, dichloromethane, and with increasing cyclohexane content in cyclohexane–ether mixtures was assigned to the s-trans enol of **1**. The **1** used for these studies was prepared by the acid-catalyzed hydrolysis of 1,1,3,3-tetraethoxypropane, and undoubtedly contained β-ethoxyacrolein and other impurities,[3,8,9a] which may have been responsible for the UV results. The presence of substantial amounts of the dicarbonyl form of **1** in nonpolar solvents was proposed to account for some of the UV results; however, the dicarbonyl form of **1** has not been observed by NMR.[3-6]
(18) George, P.; Bock, C. W.; Trachtman, M. *J. Comput. Chem.* **1980**, *1*, 373.
(19) (a) Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 899; *J. Biol. Chem.* **1967**, *242*, 5344. (b) Bernheim, F.; Bernheim, M. L. C., Wilbur, K. M. *J. Biol. Chem.* **1948**, *174*, 257. (c) Nair, V.; Turner, G. A.; Offerman, R. J. *J. Am. Chem. Soc.* **1984**, *106*, 3370. Marnett, L. J.; Basu, A. K.; O'Hara, S. M.; Weller, P. E.; Rahman, A. F. M. M.; Oliver, J. P. *Ibid.* **1986**, *108*, 1348. (d) Haberland, M. E.; Fong, D.; Cheng, L. *Science* **1988**, *241*, 215.
(20) Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 2833.

1 is a compound with considerable biological interest, which is further heightened by the observation that it is mutagenic.[8] The reactions of 1 with nucleophiles such as the nucleic acid bases[19c] and proteins[19d] have been reported. Our NMR observations suggest that at pH 7.4 ("physiological pH") 1 exists completely in the form of its sodium salt (see Table I and Figure 2). This conclusion is supported by UV studies, which show spectral changes from pH 2.8 to 6.5 but none above pH 6.5.[17] We believe these conclusions should also hold in biological systems and may be relevant to the reactivity of 1 in such systems.

Summary

The intramolecularly H-bonded cis enolic form of malondialdehyde in chloroform is converted to an intermolecularly H-bonded trans enol by methoxy compounds such as methanol and 3,3-dimethoxypropanal. "Polar impurities" such as acetone and dioxane do not induce this effect. In aqueous solution sodio-1 predominates at pH >6. Based upon ^{1}H NMR coupling constants, both 1 and sodio-1 have the trans configuration in aqueous solution.

Experimental Section

Caution. Malondialdehyde, 3,3-dimethoxypropanal, and especially β-methoxyacrolein have been reported to be mutagenic[8] and should be handled with utmost care.

Malondialdehyde (1) was prepared by either the acid-catalyzed hydrolysis of 1,1,3,3-tetramethoxypropane (2) or the protonation of sodio-1. The hydrolysis of 2 was carried out by using the procedures of Protopopova and Skoldinov (12 mmol of 2, 1 mmol of HCl/3.5 mL of water)[9a] or Bertz (10 mmol of 2, 10 mmol of HCl/10 mL of water)[7] and was followed by ^{1}H NMR spectroscopy with solvent suppression. The former procedure required 75 min at 25 °C followed by 10 min at 55 ± 5 °C. The latter was followed for 75 min at 25 °C; the amount of 1 became constant after 45 min. The aqueous solutions were extracted with equal volumes of deuteriochloroform, which were used for the NMR studies summarized in Tables I and III. To obtain NMR spectra in pure water, an internal capillary of acetone-d_6 was used for locking the spectrometer.

For the studies in which MeOH, 1,1-DME, or acetone was added, 1 was obtained by acidification (pH 1) of 1 M aqueous solutions of sodio-1.[9a,19] The solid sodio-1 had been dried for 6 days at 100 °C/0.1 mTorr. ^{13}C NMR (H_2O, pH 9.6): δ 193.9, 193.04 (shoulder), 193.0, 192.5, 109.5, 109.3 ppm. Minor peaks at δ 193.8, 193.7, 193.2, 192.8, 192.7, 192.5 (shoulder), 192.3, 191.9, 191.8, 191.7, 191.6 ppm. ^{13}C NMR (H_2O, pH 1): δ 186.1, 111.5 ppm. ^{13}C NMR ($CDCl_3$): δ 181.5, 103.5 ppm. Extraction with an equal volume of deuteriochloroform and drying over anhydrous sodium sulfate gave the material used for the addition of MeOH (Mallinckrodt anhydrous, 0.01% water actual lot analysis), 1,1-DME (stored over 5A molecular sieves), or acetone (dried over 5A molecular sieves). In one of the MeOH runs 1,4-dioxane (4 equiv), which had been added to the aqueous solution of sodio-1 as an internal standard, was also present (see text). Benzene (100 μL) was added to the deuteriochloroform solutions as an internal standard, or the residual $CHCl_3$ peak was used. Deuteriochloroform solutions were referenced with TMS; aqueous solutions with sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS), which was also used as an internal standard for integration. NMR spectra were obtained with a Bruker AM 360; parameters were used that gave 0.1-Hz digital resolution.

Acknowledgment. S.H.B. wishes to thank Prof. H. Quast (Würzburg) for suggesting that we reinvestigate this problem, and we thank A. M. Mujsce (AT&T Bell Laboratories) for GC–MS analyses.

Supplementary Material Available: Table of data for the addition of acetone, 1,1-DME, or MeOH to 1 (1 page). Ordering information is given on any current masthead page.

Diaryl-Substituted Maleic Anhydrides

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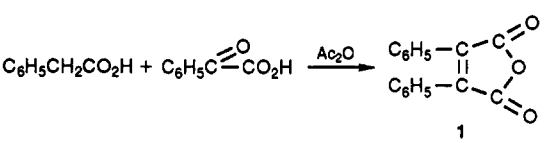
Received November 30, 1989

In previous work we have described the photodimerization of 1-cyclohexene-1,2-dicarboxylic anhydride[1] and the preparation and properties of polyimides derived from the photodimer as well as from the photodimer of dimethyl maleic anhydride.[2] Although these polyimides exhibited good thermal and hydrolytic stability, we wished to prepare fully aromatic analogues of dimethylmaleic anhydride and especially its photodimer for optimum physical and chemical properties.

A report by Fager that diphenylmaleic anhydride gave a photodimer[3] led us to investigate the aryl-substituted maleic anhydrides. Various routes to diphenylmaleic anhydride (1) were surveyed by Koelsch and Wawzonek[4] who concluded that the best synthesis by far was a Perkin condensation of benzoylformic acid as the mixed K–Na salt with phenylacetic acid by acetic anhydride. We prepared



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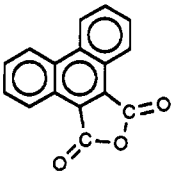
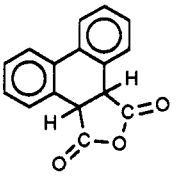
several hundred grams of diphenylmaleic anhydride this way and tried to duplicate Fager's photodimerization. Both NMR and mass spectrometry showed that the product of UV irradiation was a mixture of the phenanthrene dicarboxylic anhydride and its dihydro derivative.





When diphenyl anhydride was irradiated in solution with iodine and O_2, only the phenanthrene anhydride formed. Its physical properties were identical with the putative photodimer. A scale model shows that diphenylmaleic anhydride is crowded, and that explains its ready cyclization by loss of H_2 from the excited state.

Under electron impact diphenylmaleic anhydride shows a large peak for loss of CO, but only a small peak for loss of CO_2. This pattern constitutes a reversal of that characteristic of maleic and phthalic anhydrides and their derivatives generally.[5–9] The difference in behavior must be attributed to the phenyl substituents, presumably by

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0022-3263/90/1955-5165$02.50/0