

Tautomerism in Malonic Ester Derivatives of *s*-Triazine

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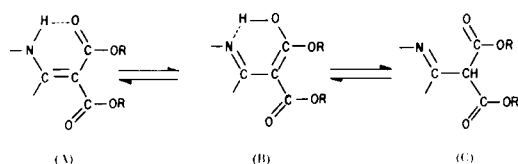
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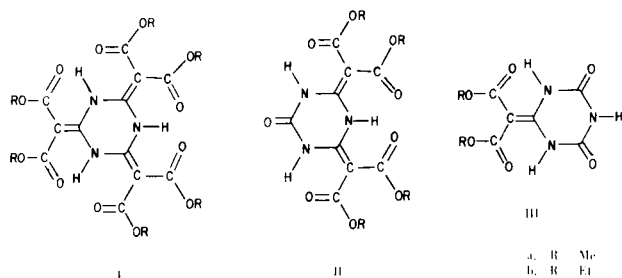
Received December 19, 1974

Pmr and uv spectra of tris-, bis- and monomalonic ester derivatives of *s*-triazine were studied in chloroform, dioxane, methanol, water, acetonitrile, dimethylsulfoxide, dimethylformamide, and cyclohexylamine. The results indicate that the enaminic structures (I, II and III) predominate in chloroform, dioxane, methanol and water. A small amount of enolate is present in acetonitrile and a larger amount of enolate is present in dimethylsulfoxide, dimethylformamide and cyclohexylamine in the case of the tris- and bismalonic ester derivatives of *s*-triazine. The conclusion is reached that for these latter compounds in basic solvent, a tautomeric equilibrium exists between the enaminic form and resonance-stabilized enolate ions.

The malonic ester derivatives of *s*-triazine have the possibility of exhibiting the tautomeric equilibria shown; hereafter referred to as the enamine (A), enol (B) and keto (C) forms.



In a previous paper (2), we reported that the tris-, bis- and mono(diethyl malonate) derivatives of *s*-triazine in the solid state and in chloroform solution exist predominantly as the enaminic structures Ib, IIb and IIIb.



Marked shifts of the infrared C=O stretching bands to lower frequency and of the NH proton nmr absorptions to low field pointed to the existence of strong NH \cdots O hydrogen bonds. An extensive investigation of tautomerism in side-chain derivatives of *N*-heterocycles by Mondelli and Merlini (3) has shown that tautomeric equilibrium depends on solvent and the nature of the heterocycle with noticeable contribution of enaminic structures. In the case of β -oxo side-chain derivatives of *s*-triazine, the predominate tautomer was determined to be the enol form (4).

For this pmr and uv study we prepared three new dimethyl malonate derivatives of *s*-triazine by reaction of stoichiometric amounts of sodium dimethyl malonate with cyanuric chloride in dioxane, yielding the tris-(dimethyl malonate) derivative (Ia), 2,4,6-tris(dimethoxycarbonylmethylene)hexahydro-*s*-triazine, the bis-(dimethyl malonate) derivative (IIa), 2,4-bis(dimethoxycarbonylmethylene)-6-oxohexahydro-*s*-triazine, and the mono-(dimethyl malonate) derivative (IIIa), 2-dimethoxycarbonylmethylene-4,6-dioxohexahydro-*s*-triazine. The prominent infrared absorptions were analogous to those reported previously for the diethyl malonate derivatives (2). The pmr spectral data for the tris-, bis- and mono-(dimethyl malonate) derivatives of *s*-triazine in deuteriochloroform and deuteriodimethylsulfoxide are given in Table I.

Table I

Pmr Chemical Shifts (δ) and Integrated Areas for Dimethyl Malonate Derivatives of *s*-Triazine

Malonate Derivative	Solvent	CH ₃	NH
Mono(dimethyl)	deuteriochloroform	3.82 (6H, singlet)	12.4 (2H, broad singlet) 8.4 (1H, broad singlet)
Bis(dimethyl)	deuteriochloroform	3.88 (6H, singlet) 3.82 (6H, singlet)	14.2 (1H, broad singlet) 12.4 (2H, broad singlet)
Tris(dimethyl)	deuteriochloroform	3.88 (18H, singlet)	14.1 (3H, broad singlet)
Mono(dimethyl)	DMSO-d ₆	3.72 (6H, singlet)	11.8 (< 2H, broad singlet) (a)
Bis(dimethyl)	DMSO-d ₆	3.73 (singlet)	(b)
Tris(dimethyl)	DMSO-d ₆	3.76 (singlet)	(c)

Concentrations are in the range 40-50 mg. in 0.4-0.5 ml. of solution; (a) Additional broad absorption expected not detectable. (b) NH Absorption not detectable; (c) NH Absorption not detectable, this ester only slightly soluble in DMSO.

The pmr data in deuteriochloroform are in accord with the enaminic forms Ia, IIa and IIIa. Thus the NH absorptions at 14.1 and 14.2 δ for the tris- and bis-(dimethyl malonate) derivatives are associated with chelation involving two methoxycarbonyl groups, and the NH absorptions at 12.4 δ for the bis- and mono(dimethyl malonate) derivatives are associated with chelation involving one methoxycarbonyl group. The absorption at 8.4 δ for the mono(dimethyl malonate) derivative is associated with the NH proton which is not adjacent to a malonate group, since only this absorption shifts upfield upon

dilution, indicative of intermolecular rather than intramolecular hydrogen bonding (5). In the case of the bis(dimethyl malonate) derivative in deuteriochloroform, the non-equivalence of the methyl protons is evident as is expected for structure IIa in which there are two sets of methyl groups in different magnetic environments. In contrast, the pmr spectrum of the bis(dimethyl malonate) derivative in DMSO-d₆ shows apparent magnetic equivalence of the methyl groups as evidenced by only one methyl resonance. Figure 1 shows the effect on the methyl resonances of the bis(dimethyl malonate) derivative

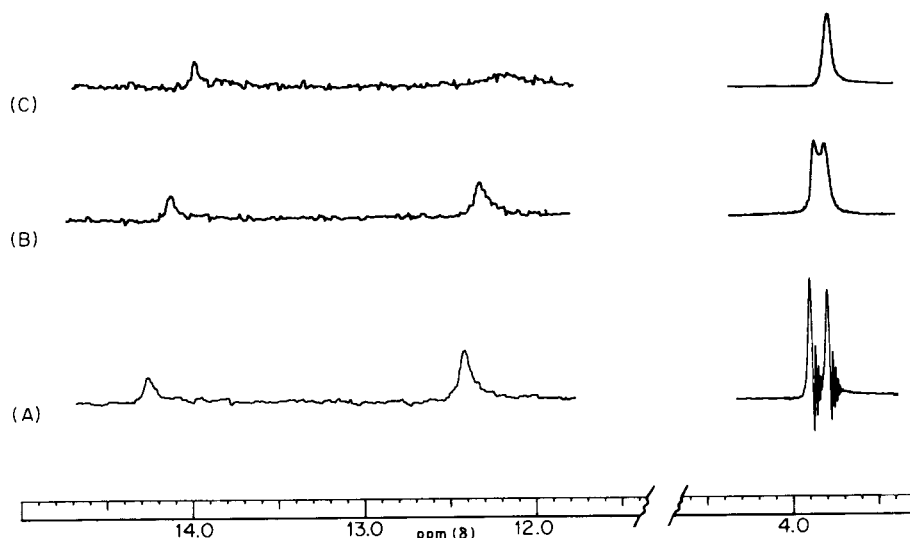


Figure 1. Pmr spectra of the bis(dimethyl malonate) derivative of *s*-triazine (11-15 ppm region has been amplified). A: 100% deuteriochloroform; B: 90% deuteriochloroform, 10% DMSO-d₆; C: 75% deuteriochloroform, 25% DMSO-d₆. Note: For the deuteriochloroform-DMSO-d₆ mixtures, the water impurity peak (not shown) increases as the bis(dimethyl malonate) derivative is added, indicating that the water is exchanging with the OH protons of the enolate tautomer.

when DMSO- d_6 is added to a deuteriochloroform solution. The broadening and eventual merging of the methyl peaks is indicative of a dynamic exchange process such as would occur if some enol tautomer were being formed as the DMSO- d_6 is added. A pmr spectrum of the bis(dimethyl malonate) derivative in 1/1 deuteriochloroform/DMSO- d_6 at 0° was particularly revealing. At this temperature the NH protons exchange more slowly and absorptions at 14.0 and 12.0 δ in the integral ratio of 1 to 2 were clearly visible. However, the total NH integral was only two-thirds of that expected for the three enaminic protons. Thus under these conditions, approximately 33% enol tautomer must be present. The formation of a keto tautomer would have been indicated by the presence of a methine CH pmr peak; however, in no instance was such a peak observed.

In order to verify the existence of a tautomeric equilibrium, the uv-visible spectrum of the bis(dimethyl malonate) derivative of *s*-triazine was observed in chloroform and DMSO. The prominent absorption for this

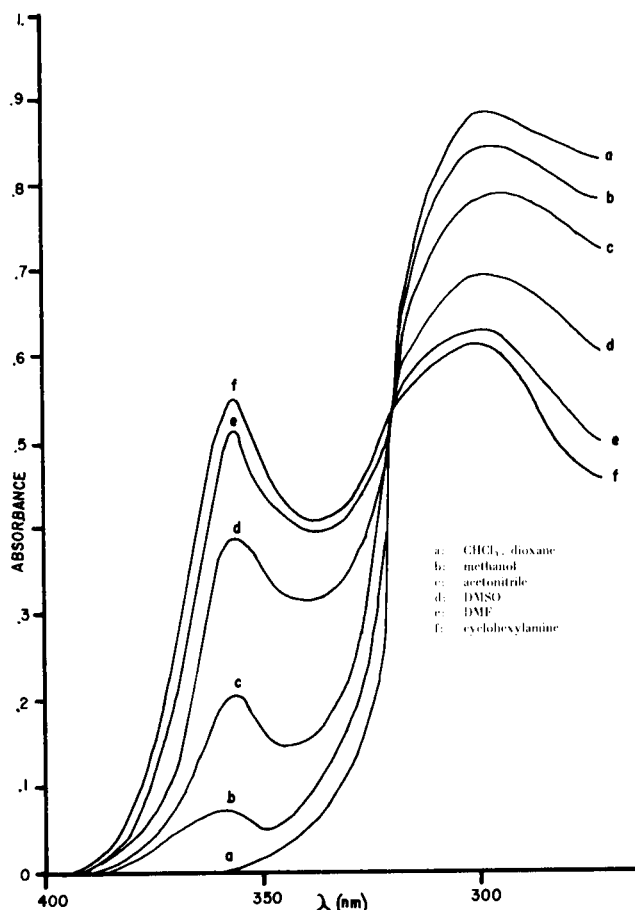
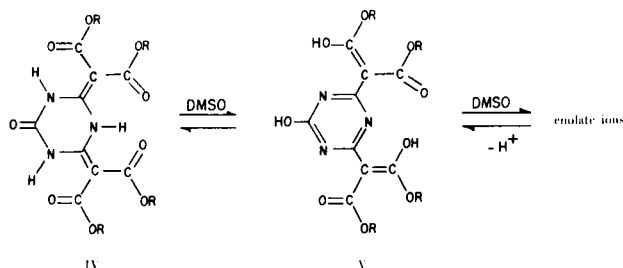


Figure II. Uv-visible spectra of the bis(dimethyl malonate) derivative of *s*-triazine in DMSO-chloroform mixtures. Concentrations are 2.74×10^{-5} molar.

compound in both chloroform and in non-polar carbon tetrachloride is a band with $\lambda_{\max} = 318$ nm and $\epsilon = 34,000$. When solutions are prepared in DMSO, the 318 nm band diminishes and a new band appears having $\lambda_{\max} = 357$ nm and ϵ about 50,000. The 357 nm band can be enhanced by the addition of a base such as ammonia, the 318 nm band diminishing, while the reverse effect is caused by adding acid. Figure II shows the uv-visible spectra for the bis(dimethyl malonate) derivative in chloroform and DMSO, plus mixtures of the two solutions. An isobestic point is evident at about 330 nm indicating the wavelength at which the equilibrating species have equal absorptivities. The chloroform uv-visible spectrum is always reproducible; however, the uv-visible spectrum in DMSO as well as DMF is not. The band at 357 nm can vary from small to as large as the 318 nm band, and this is probably due to minute amounts of basic impurities present in these two solvents which were not removed on distillation or were formed on standing. An extension of the uv and pmr study to the bis(diethyl malonate) derivative of *s*-triazine gave results analogous to those of the bis(dimethyl malonate) derivative. Thus the spectroscopic data indicate that in the proton accepting solvents such as DMSO a tautomeric equilibrium exists as shown.



The formation of the enolate is accompanied by a uv-visible shift to the red in the manner expected for a conjugated enolate ion. In the pmr spectrum of the enolate, free rotation of both malonate groups of the enolate would permit chemical shift averaging of the methyl pmr absorptions. Mixed enamine/enolate structures such as VI are also possible, although lacking the aromaticity of the completely enol form V. They are difficult to exclude based on pmr spectroscopy, since rapid interconversion of tautomeric forms would also result in chemical shift averaging of the methyl resonances.

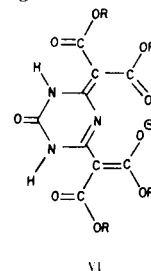


Table II
Effect of Solvent on Uv and Pmr Spectra of Bis(dimethyl malonate) Derivative

Solvent	Effect on 357 nm Uv Band (a)	Effect on Pmr Me Peak (b)
Water, pH = 7	357 band very weak	(insufficient solubility)
Water, pH = 6	357 band absent	(insufficient solubility)
Water, pH = 8	357 band present	(insufficient solubility)
Chloroform	357 band absent	doublet
<i>p</i> -Dioxane	357 band absent	doublet
Chloroform-acetonitrile	257 band very weak	broadened doublet
Acetonitrile	357 band weak	broadened singlet
DMF	357 band present	singlet
DMSO	357 band present	singlet

(a) Concentrations approximately 2.5×10^{-5} molar. (b) The deuterated forms of chloroform, *p*-dioxane, water, acetonitrile and dimethylsulfoxide were used for the pmr measurements.

The effect of various solvents on the pmr and uv-visible spectra of the bis(dimethyl malonate) derivative of *s*-triazine is shown in Table II. These data demonstrate

that whenever the presence of an enolate ion is indicated in the uv-visible spectrum of the bis(dimethyl malonate) derivative, the pmr spectrum shows chemical shift averaging of the methyl resonances. It is also evident that the acetonitrile solution is more weakly basic than the DMSO or DMF solutions as expected.

The uv-visible spectra of the tris(dimethyl malonate) derivative of *s*-triazine in various solvents are shown in Figure III. Here also two bands are present in basic or proton-accepting solvents, one having λ max near 312 nm with $\epsilon = 44,000$ and one having λ max near 360 nm with ϵ about 90,000. When 1 *N* sodium or potassium hydroxide is added to the slightly soluble tris(dimethyl malonate) derivative in DMSO, an acid-base reaction occurs to give a soluble salt. This reaction was carried out in a nuclear magnetic resonance tube by adding the base dropwise until the tris(dimethyl malonate) derivative just dissolved, and the pmr spectrum of the product showed two non-equivalent methyl resonances in the integral ratio of 2 to 1 as expected for the mono sodium or potassium salt. Solid salts were obtained by evaporation of the DMSO, and the uv-visible spectra of these salts in solution showed predominantly the 360 nm band, until a small amount of acid was added, whereupon the 312 nm band appears at the expense of the 360 band. The pmr spectra of the salts in deuteriochloroform also show non-equivalent methyl resonances until a small amount of acid is added, and then the spectra revert to that of the enaminic tautomer Ia. Thus, the spectroscopic evidence for the tris(dimethyl malonate) derivative is consistent with a tautomeric equilibrium in proton accepting solvents between enaminic and resonance-stabilized enolate structures in the manner previously indicated for the bis(dimethyl malonate) derivative, with the possible involvement of a mixed enamine/enolate form analogous to VI. Using cyclohexylamine as a solvent for comparison and the measured extinction coefficients of the uv-visible

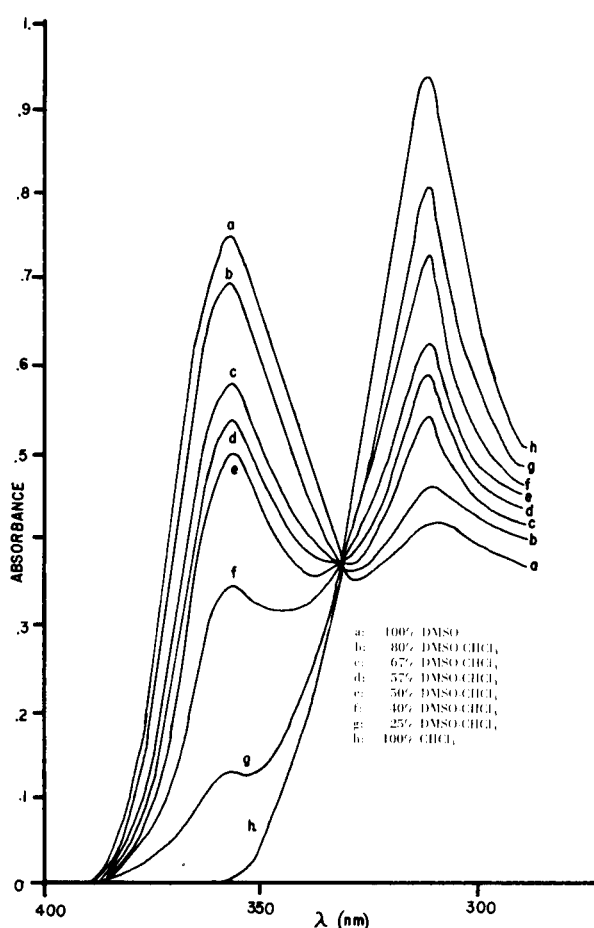


Figure III. The Uv-visible spectra of the tris(dimethyl malonate) derivative of *s*-triazine in various solvents. Concentrations are 2.0×10^{-5} molar.

bands for the tris- and bis(dimethyl malonate) derivatives, the ratio of enolate to enamine can be calculated for concentrations of both compounds about 2×10^{-5} molar. For the former compound the ratio is 1 to 2.3, while for the latter it is 1 to 6.7, thus indicating an increase in acidity of the triazine when three malonate groups are attached to the ring.

The existence of an enamine/enolate equilibrium for the mono(dimethyl malonate) derivative of *s*-triazine in basic solvent is not as apparent as for the bis- and tris-(dimethyl malonate) derivatives. Since conjugation between two malonate groups in the enolate ion cannot occur in this case, no uv-visible band above 350 nm is expected. The uv-visible spectrum of this compound in chloroform exhibits a λ max at 278 nm. As DMSO or other proton accepting solvent is added, a shoulder appears near 300 nm. Addition of small amounts of base increases this shoulder, and conversely, addition of small amounts of acid causes this shoulder to disappear. Also, a measurement of the conductance of all three malonate derivatives in freshly distilled DMSO showed that the non-conducting DMSO became conducting upon the addition of each of the three compounds. Thus, the evidence indicates that a tautomeric equilibrium also exists for the mono(dimethyl malonate) derivative of *s*-triazine in basic or proton-accepting solvents.

EXPERIMENTAL

The pmr spectra were recorded on a Varian HA-100 spectrometer using TMS as the internal reference in all cases. The probe temperature was 28°. The uv-visible spectra were obtained using Beckman DB and DB-G spectrophotometers employing a hydrogen lamp for the 240-330 nm range. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Reagent grade acetonitrile, *p*-dioxane, dimethylsulfoxide, dimethylformamide and cyclohexylamine were dried and distilled before use. Reagent grade chloroform and absolute methanol were used without additional purification. Deuterated water, chloroform, *p*-dioxane, acetonitrile and

dimethylsulfoxide were obtained from Stohler Chemical Co. and used as received.

The syntheses of the tris-, bis- and mono(dimethyl malonate) derivatives of *s*-triazine were identical to those for the corresponding diethyl malonate derivatives reported previously (2) with sodium dimethyl malonate being substituted for sodium diethyl malonate. The purified compounds were white crystalline solids.

2,4,6-Tris(dimethoxycarbonylmethylene)hexahydro-*s*-triazine (Ia).

This compound had m.p. 265° dec.

Anal. Calcd. for $C_{18}H_{21}N_3O_{12}$: C, 45.86; H, 4.46; N, 8.92. Found: C, 45.95; H, 4.52; N, 8.94.

2,4-Bis(dimethoxycarbonylmethylene)-6-oxohexahydro-*s*-triazine (IIa).

This compound had m.p. 215-216°.

Anal. Calcd. for $C_{13}H_{15}N_3O_9$: C, 43.70; H, 4.20; N, 11.76. Found: C, 43.79; H, 4.30; N, 11.80.

2-Dimethoxycarbonylmethylene)-4,6-dioxohexahydro-*s*-triazine (IIIa).

This compound had m.p. 218-219°.

Anal. Calcd. for $C_8H_9N_3O_6$: C, 39.51; H, 3.70; N, 17.28. Found: C, 39.59; H, 3.61; N, 17.30.

Acknowledgment.

The authors wish to express their appreciation to Mr. Kurt Markkola for his assistance in some of this work under the H.E.W. College Work-Study Program.

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