Journal of Chemical Crystallography, Vol. 30, No. 3, 2000

Synthesis, crystal structure and molecular modeling (AM1) of two 5-arylidene derivatives of Meldrum's acid

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Received March 7, 2000

The synthesis and structural characterization of two 5-Arylidene derivatives of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) are described: 5-(4-Nitrobenciliden)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**), and 5-(4-Methoxybenciliden)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3b**). The structure of **3a** was refined to $R_1 = 0.0421$ for 2148 reflections (with $I > 2\sigma$ (I)). Crystal data for **3a**: $C_{13}H_{11}NO_6$, orthorhombic, space group *Pbca*, a = 16.008(3), b = 6.137(1), c = 25.281(5) Å, V = 2483.6(8) Å^3, Z = 8. The structure of **3b** was refined to $R_1 = 0.0496$ for 4681 reflections (with $I > 2\sigma(I)$). Crystal data for **3b**: $C_{14}H_{14}O_5$, triclinic, space group P1, a = 9.131(2), b = 9.922(2), c = 14.490(3)Å, α = 85.076(6), β = 84.80(3), γ = 89.37(2)°, V = 1302.4(5) Å^3, Z = 4. The results of crystallographic and molecular modeling (AM1) were compared. The molecules in the crystal are held together, in both compounds, by van der Waals forces and C—H···O hydrogen bond interactions.

KEY WORDS: Crystal structure; AM1; X-ray diffraction; Meldrum's acid.

Introduction

Isopropylidene alkylidenemalonates[1] obtained from Meldrum's acid, have achieved considerable interest as highly reactive Michael acceptors,[2] electron-deficient dienophiles,[3] strongly polarized heterodynes,[4] and precursors of the corresponding saturated compounds[5] as well as of methylene ketenes.[6] Our own interest in these structures stems from their use as a Knovenagel product in the synthesis of different 2(1H)pyridones derivatives in a Hantzsch-like reaction as Michael acceptor. In several papers we have reported the use of 5-arylidene-2,2-dimethyl-1,3-dioxan-4,6-diones (**3**) as a key intermediate in the synthesis of pyrido[2,3-d]pyrimidines.[7, 8] Recently, we have reported the structural study of 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines[9] as potential calcium channel modulators, synthesized from the appropriate 5-arylidene substituted Meldrum's acid (**3**), dimedone and ammonium acetate.

Experimental

*Synthesis of 5-Arylidene-2,2-dimethyl-1,3-dioxan-4,6-diones (**3**)*

A mixture of Meldrum's acid (20 mmol) and the corresponding aromatic aldehyde (20 mmol) was dissolved in acetonitrile 20 mL, and piperidine (0.1 mL) was added. The resulting solution was stirred at room temperature for 10 h. Afterwards, it was poured into ice-water, and the precipitate was collected by filtration. Further purification was accomplished by recrystallization from ethanol.

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Table 1. Crystal Data and Structure Refinement

Compound	$C_{13}H_{11}NO_6$	$C_{14}H_{14}O_5$
CCDC deposit no.	CCDC-1003/5758	CCDC-1003/5759
Color/shape	Colorless/plate	Yellow/prism
Chemical formula	$C_{13}H_{11}NO_6$	$C_{14}H_{14}O_5$
Formula weight	277.23	265.25
Temperature	293(2)	293(2)
Crystal system	Orthorhombic	Triclinic
Space group	*Pbca*	$P\bar{1}$
Unit cell dimensions		
$a = 16.008(3)$ Å	$a = 9.131(2)$ Å	$\alpha = 85.076(6)°$
$b = 6.137(1)$ Å	$b = 9.922(2)$ Å	$\beta = 84.80(3)°$
$c = 25.281(5)$ Å,	$c = 14.490(3)$ Å	$\gamma = 89.38(2)°$
(From 27 reflections, $10.2 < \theta < 53.1$)	(From 38 reflections, $12.56 < \theta < 36.90$)	
Volume	2483.6(8) Å^3	1302.4(5) Å^3
Z	8	4
Density (calculated)	1.483 mg m^{-3}	1.337 mg m^{-3}
Absorption coefficient	1.020 mm^{-1}	0.860 mm^{-1}
Diffractometer/scan	Siemens P4/ω/2θ	Siemens P4/ω/2θ
Radiation/wave length	1.54184 Å	1.54184 Å
$F(000)$	1152	552
Crystal size	0.40 × 0.25 × 0.06 mm	0.76 × 0.68 × 0.38 mm
θ range for data collection, deg	1 to 69.21	1 to 69.04
Index ranges	$-1 \le h \le 19$, $-1 \le k \le 6$, $-30 \le l \le 1$	$-10 \le h \le 1$, $-11 \le k \le 11$, $-17 \le l \le 17$
Reflections measured	3367	5656
Independent/observed reflections	2148 ($R_{int} = 0.031$)/1755[$I > 2\sigma(I)$]	4681 ($R_{int} = 0.039$)/4401[$I > 2\sigma(I)$]
Absorption correction	Semi-empirical from ψ-scans[23]	Semi-empirical from ψ-scans[23]
Range of rel. transm. factors	0.547/0.941	0.499/0.721
Data/restraints/parameters	2148/0/184	4681/0/350
Goodness-of-fit on F^2	1.055	1.092
SHELXL97 weight parameters	0.0615, 0.9104	0.0627, 0.2666
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0421$, $wR_2 = 0.1220$	$R_1 = 0.0476$, $wR_2 = 0.1295$
R indices (all data)	$R_1 = 0.0526$, $wR_2 = 0.1220$	$R_1 = 0.0496$, $wR_2 = 0.1314$
Largest diff. Peak/hole	0.20/−0.20	0.22/−0.25

Spectroscopy

Melting points were determined in a capillary tube in an Electrothermal C14500 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker DPX300 spectrometer (300 MHz-^{1}H and 75.47 MHz-^{13}C). Chemical shifts are given as δ values against tetramethylsilane as the internal standard, and J values are given in Hz. The IR spectra were measured with a Shimadzu FTIR 8300 instrument as potassium bromide pellets. Mass spectra were obtained with a Hewlett Packard 5989 A machine. Microanalyses were performed in a Perkin Elmer 2400 CHN by the *Servicio de Microanálisis of Universidad Complutense de Madrid*. The reactions were monitored by TLC and performed on silica-gel plates (Merck 60F$_{250}$) using hexane:ethyl acetate (8:2) as the eluent. Commercially available starting materials and reagents were purchased from commercial sources (BDH and Fluka) and were used without further purification. Aromatic aldehydes were distilled before use.

*5-(4-Nitrobenciliden)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3a**)*

Following the general procedure gave **3a**, 88% yield, m.p. 142-143°C, ν_{max}/cm^{-1} 1759 (C=O), 1730 (C=O), 1629 (C=C), 1527 and 1350 (NO_2); ^{1}H NMR (DMSO-d_6) δ 8.49 (1H, s, CH-7), 8.28 (2H, d, H3′, H5′, J = 8.7 Hz), 8.05 (2H, d, H2′, H6′, J = 8.7 Hz), 1.77 (6H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 164.1 (CO), 163.2 (CO), 153.6 (C7), 147.8 (C1′), 138.2 (C4′), 132.2 (C2′, C6′), 122.8 (C3′, C5′), 118.8 (C5), 104.9 (C2), 26.9 (CH_3); m/z: 277 (M$^+$, 5%), 219 (100), 202 (98), 172 (46) and 101 (52). Anal Calc. for

Table 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters (Å^2 $\times$ 10^3) for Compound **3a**

	x	y	z	U(eq)^a
O(1)	4138(1)	3974(2)	6877(1)	45(1)
O(3)	2995(1)	1613(2)	6764(1)	40(1)
O(4)	2518(1)	772(2)	5975(1)	41(1)
O(6)	4764(1)	5469(3)	6194(1)	60(1)
O(11)	3632(1)	−2501(3)	3319(1)	72(1)
O(12)	3060(1)	−4913(3)	3822(1)	69(1)
N(1)	3412(1)	−3177(3)	3753(1)	48(1)
C(2)	3717(1)	2082(3)	7084(1)	40(1)
C(4)	3081(1)	1498(3)	6234(1)	32(1)
C(5)	3858(1)	2471(3)	6017(1)	33(1)
C(6)	4297(1)	4090(3)	6355(1)	39(1)
C(7)	4159(1)	2188(3)	5525(1)	36(1)
C(21)	4295(2)	150(4)	7096(1)	59(1)
C(22)	3395(2)	2753(4)	7618(1)	60(1)
C(1′)	3923(1)	741(3)	5090(1)	35(1)
C(2′)	3562(1)	−1314(3)	5151(1)	41(1)
C(3′)	3391(1)	−2595(4)	4716(1)	43(1)
C(4′)	3588(1)	−1810(3)	4218(1)	38(1)
C(5′)	3948(1)	201(4)	4141(1)	42(1)
C(6′)	4122(1)	1457(3)	4580(1)	39(1)

[a] $U_{(eq)}$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

$C_{13}H_{11}NO_6$(277.23) C, 56.32; H, 4.00; N, 5.05. Found: C, 56.47; H, 4.27; N, 5.34.

*5-(4-Methoxybenciliden)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3b**)*

Following the general procedure gave **3b**, 80% yield, m.p. 127-128°C, ν_{max}/cm^{-1} 3210 (NH), 1690 (C=O), 1660 (C=O), 1600 (C=C); ^{1}H NMR (DMSO-d_6) δ 8.30 (1H, s, CH-7), 8.22 (2H, d, H3′, H5′, J = 8.9 Hz), 7.07 (2H, d, H2′, H6′, J = 8.9 Hz), 3.89 (3H, s, OCH_3), 1.72 (6H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 164.1 (CO), 163.2 (CO), 160.2 (C4′), 156.6 (C7), 137.1 (C2′, C6′), 124.5 (C1′), 114.3 (C3′, C5′), 111.5 (C5), 104.2 (C2), 55.8 (OCH_3), 27.0 (CH_3); m/z: 262 (M$^+$, 32%), 204 (72), 176 (48), 160 (100), 145 (63), 117 (52), 89 (56). Anal Calc. for $C_{14}H_{14}O_5$ (262.26) C, 64.12; H, 5.38. Found: C, 64.43; H, 5.61.

Crystallography

Suitable crystals were obtained from slow evaporation in ethanol at room temperature. The structures were solved by direct methods and Fourier synthesis using the program SHELXS97[10] and refined on F^2 with SHELXTL97[11] with scattering factors from International Tables.[12] Other programs used include XSCANS[13] for computing data collection, cell refinement and data reduction; DIAMOND[14] for computing molecular graphics; PLATON[15] for computing publication material. Non-H atoms were refined anisotropically by full-matrix least-squares techniques. H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms. The isotropic displacement parameters

Table 3. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters (Å^2 $\times$ 10^3) for Compound **3b**

	x	y	z	U(eq)^a
O(1A)	6809(1)	−208(1)	1908(1)	66(1)
O(3A)	8868(2)	715(1)	997(1)	71(1)
O(4A)	6095(1)	541(2)	3251(1)	73(1)
O(6A)	10350(2)	2137(2)	1523(1)	85(1)
O(11A)	8058(2)	1287(1)	7237(1)	70(1)
C(2A)	7984(2)	−472(2)	1218(1)	63(1)
C(4A)	7088(2)	441(2)	2652(1)	56(1)
C(5A)	8555(2)	1050(2)	2632(1)	54(1)
C(6A)	9355(2)	1355(2)	1702(1)	62(1)
C(7A)	9184(2)	1481(2)	3366(1)	56(1)
C(8A)	7099(3)	307(2)	7740(1)	78(1)
C(21A)	7251(3)	−699(3)	353(2)	97(1)
C(22A)	8902(3)	−1640(2)	1559(2)	87(1)
C(1′ A)	8809(2)	1357(2)	4362(1)	51(1)
C(2′ A)	7815(2)	440(2)	4849(1)	57(1)
C(3′ A)	7540(2)	385(2)	5799(1)	57(1)
C(4′ A)	8266(2)	1263(2)	6301(1)	53(1)
C(5′ A)	9285(2)	2172(2)	5839(1)	60(1)
C(6′ A)	9562(2)	2202(2)	4890(1)	58(1)
O(1B)	1501(1)	5325(2)	1591(1)	72(1)
O(3B)	3378(2)	4187(1)	760(1)	70(1)
O(4B)	775(1)	4683(2)	3044(1)	71(1)
O(6B)	4586(2)	2495(2)	1411(1)	93(1)
O(11B)	3591(2)	4064(2)	6989(1)	80(1)
C(2B)	2709(2)	5480(2)	882(1)	71(1)
C(4B)	1721(2)	4639(2)	2411(1)	58(1)
C(5B)	3064(2)	3806(2)	2430(1)	57(1)
C(6B)	3748(2)	3424(2)	1521(1)	65(1)
C(7B)	3710(2)	3309(2)	3196(1)	58(1)
C(8B)	2799(2)	5148(3)	7388(2)	90(1)
C(21B)	2058(3)	5908(3)	−10(2)	108(1)
C(22B)	3828(3)	6451(2)	1137(2)	91(1)
C(1′ B)	3546(2)	3542(2)	4173(1)	55(1)
C(2′ B)	2722(2)	4582(2)	4566(1)	67(1)
C(3′ B)	2702(2)	4770(2)	5496(1)	68(1)
C(4′ B)	3512(2)	3929(2)	6069(1)	61(1)
C(5′ B)	4331(2)	2884(2)	5702(1)	69(1)
C(6′ B)	4354(2)	2708(2)	4771(1)	64(1)

[a] $U_{(eq)}$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 4. More Relevant Bond Distances [Å], Valence Angles [°] and Torsion Angles [°] for the More Stable Conformation of Compounds **3a** and **3b**

	3a AM1	**3a** X-ray	**3b** AM1	**3b X-ray** Molecule A	**3b X-ray** Molecule B
Bond distances					
O1—C2	1.430	1.440(2)	1.429	1.437(2)	1.437(2)
C2—O3	1.428	1.438(2)	1.426	1.431(2)	1.433(2)
O3—C4	1.377	1.350(2)	1.380	1.358(2)	1.350(2)
C4—O4	1.229	1.199(2)	1.230	1.206(2)	1.204(2)
C4—C5	1.470	1.485(2)	1.465	1.483(2)	1.483(2)
C5—C6	1.479	1.487(3)	1.476	1.472(2)	1.473(2)
C6—O6	1.229	1.201(2)	1.230	1.206(2)	1.204(2)
C6—O1	1.373	1.346(2)	1.375	1.347(2)	1.349(2)
C5—C7	1.349	1.345(3)	1.353	1.356(2)	1.356(3)
C7—C1′	1.452	1.464(3)	1.443	1.448(2)	1.448(2)
Bond angles					
O1—C2—O3	107.5	109.48(15)	107.5	109.64(14)	109.27(15)
C2—O3—C4	118.4	119.13(14)	118.4	118.87(13)	118.34(14)
O3—C4—C5	118.1	115.51(15)	118.1	116.11(15)	116.38(15)
C4—C5—C6	113.8	116.86(16)	113.6	116.50(14)	116.66(16)
C5—C6—O1	118.6	116.03(16)	118.6	116.80(14)	116.18(14)
C6—O1—C2	117.6	119.12(15)	117.4	119.90(13)	118.90(14)
C5—C7—C1′	129.4	132.93(18)	130.9	134.14(16)	135.17(16)
C7—C1′—C2′	122.8	124.87(17)	123.6	125.95(15)	125.78(16)
C7—C1′—C6′	117.8	116.34(18)	117.6	116.95(15)	117.27(15)
Torsion angles					
O1—C6—C5—C7	−166.3	−163.68(17)	−164.8	−164.56(16)	162.31(17)
O3—C4—C5—C7	166.3	166.10(18)	164.1	168.41(15)	−162.55(16)
O4—C4—C5—C6	157.5	154.22(18)	154.7	159.80(18)	−159.54(19)
O6—C6—C5—C4	−159.7	−156.68(19)	−158.4	−153.07(18)	154.53(18)
C4—C5—C7—C1′	−4.3	−8.9(4)	−6.7	9.6(3)	−11.9(3)
C6—C5—C7—C1′	180.0	177.89(19)	177.9	−177.43(17)	170.7(3)
C5—C7—C1′—C2′	−34.5	−29.3(3)	−24.4	16.6(3)	−10.2(3)

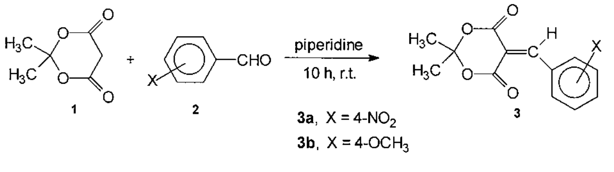
of the H atoms were fixed to 1.3 times U_{eq} of their parent atoms. Final *R* and weighted *R* values and data collection parameters for both compounds are given in Table 1, and the final geometrical parameters are given in Table 2 (compound 3a) and Table 3 (compound 3b).

Molecular modeling

Full energy minimization *in vacuo* was carried out using semiempirical AM1 calculations[16] with the aid of the MOPAC[17] molecular orbitals set. Previously, the molecular geometry was optimized using Allinger's Molecular Mechanics[18] with PCMODEL program.[19] The structures with lowest energies following the AM1 optimization were used for comparison with the X-ray structures. Calculations were performed on an IBM-RS6000 workstation.

Discussion

Compounds **3a** and **3b** were obtained as crystalline solids from Meldrum's acid (**1**) and the corresponding aromatic aldehyde **2** in the presence of catalytical amounts of piperidine in 88 and 80% yield respectively (see Scheme 1).



Scheme 1

The semiempirical (AM1) optimized geometries for lowest energy conformers for compounds **3a** ($\Delta H = -110.1$ kcal/mol) and **3b** ($\Delta H = -154.7$ kcal/mol) are presented in Figs. 1 and 2, respectively. The crystal structures within the atomic numbering

Fig. 1. Plot showing the lowest energy conformer for compound **3a** obtained by semiempirical calculations (AM1), ΔH = −110.1 kcal/mol.

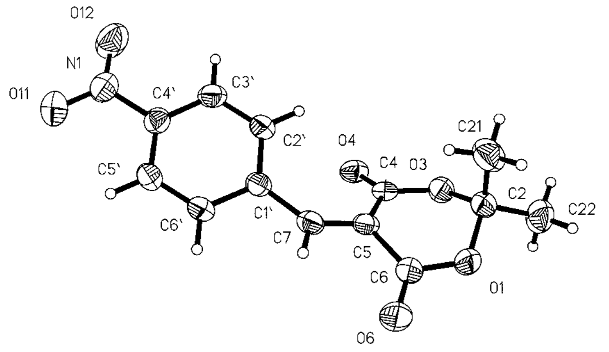


Fig. 3. A view of **3a** with the atomic numbering scheme. Displacement ellipsoids are drawn at 50% probability level for non-H atoms.

scheme for **3a** and the two crystallographic independent molecules of **3b** are shown in Figs. 3 and 4, respectively. Most relevant structural features are given in Table 4, along with those predicted by AM1 calculations for comparison purposes. Theoretical calculations are in agreement with the structural parameters derived from X-ray crystallography. Quantum chemical calculations showed that the six-member alkyl moiety adopts a flattened boat conformation with the C2 and C5 atoms out of the main boat plane.

X-ray crystallography data shows that the dioxane-dione ring system in both compounds can be described as being mainly in a boat conformation with puckering parameters[20] Q = 0.485(2) Å, θ = 104.1(2)° and φ = 117.8(2)°. This ring in compound **3a** represents 81% of puckering in an ideal cyclohexane chair (16% chair with O3 pointing down, 6% twist boat with axis through O1 and C6 pointing down 78% boat with bowsprit at C2 pointing up).[21] In compound **3b**, molecule A (puckering parameters: Q = 0.466(2) Å, θ = 75.4(2)°, φ = 66.1(2)°), the dioxane–dione ring presents 78% of puckering in an ideal cyclohexane chair (16% chair with O3A pointing down 17% twist boat with axis through O1A and C6A pointing down 67% boat with bowsprit at C2A pointing up). Similarly, molecule B (puckering parameters: Q = 0.485(2) Å, θ = 74.4(2)°, φ = 59.2(2)°) represents 82% of puckering in an ideal cyclohexane chair (17% chair with O3B pointing up 2% twist boat with axis through O1B and C6B pointing up 81% boat with bowsprit at C2B pointing down).

The bond lengths and angles are in good agreement with values retrieved from the Cambridge Structural Database.[22] There appears to be a more single-bond character in the C5—C7 bonds of **3b** molecules [mean value: 1.356(2) Å] than in 3a [1.345(3) Å]. In **3a** the dioxane-dione has local mirror symmetry to within experimental error, but in **3b** molecules, C4—C5 is longer [1.483(2) Å] than C5—C6 [1.472(2) Å]. (Further geometrical calculations with PLATON[14] revealed no higher symmetry

Fig. 2. Plot showing the lowest energy conformer for compound **3b** obtained by semiempirical calculations (AM1), ΔH = −154.7 kcal/mol.

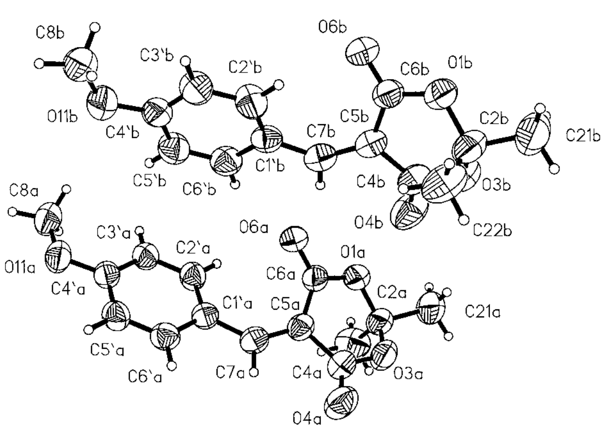


Fig. 4. A view of the two independent molecules of **3b** and their atomic numbering scheme. Displacement ellipsoids are drawn at 50% probability level for non-H-atoms.

and no solvent accessible areas.) The molecules in the crystal, in both compounds, are packed at normal van der Waals distances. There is only one C-H⋯O intermolecular interaction in **3a** [C6⋯O6: 3.250(3), H6⋯O6: 2.53 and C6−H6⋯O6: 134 ($-x + 1$, $-y + 1$, $-z + 1$)], which stabilizes the molecules in the crystal. In compound **3b** [C8B⋯O6B: 3.378(3), H14C⋯O6B: 2.45 and C8B-H14C⋯O6B: 162 ($-x$, $-y + 1$, $-z + 1$)].

Acknowledgment

This work was supported in part by the K.U. Leuven (Belgium) through an IRO scholarship for H. Novoa and *Proyectos Alma Mater* (Universidad de La Habana, Cuba).

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