

Structures of Aromatic Esters of 2,2-Dimethylpropanoic Acid: 4,6-Dimethoxy-1,3,5-triazin-2-yl 2,2-Dimethylpropanoate (1) and 4-Nitrophenyl 2,2-Dimethylpropanoate (2)

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Abstract. (1), $C_{10}H_{15}N_3O_4$, $M_r = 241.25$, monoclinic, $P2_1/n$, $a = 10.317$ (3), $b = 8.665$ (4), $c = 13.639$ (5) Å, $\beta = 100.45$ (2)°, $V = 1199.1$ Å³, $Z = 4$, $D_x = 1.336$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.54178$ Å, Ni filter, $\mu = 8.9$ cm⁻¹, $F(000) = 512$, $T = 223$ (5) K, $R = 0.046$, $wR = 0.064$ for 2277 observed reflections. (2), $C_{11}H_{13}NO_4$, $M_r = 223.23$, triclinic, $P\bar{1}$, $a = 10.308$ (1), $b = 10.857$ (1), $c = 12.121$ (2) Å, $\alpha = 71.22$ (1), $\beta = 65.70$ (1), $\gamma = 70.21$ (1)°, $V = 1136.7$ Å³, $Z = 4$, $D_x = 1.304$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.54178$ Å, Ni filter, $\mu = 8.0$ cm⁻¹, $F(000) = 472$, $T = 293$ K, $R = 0.052$, $wR = 0.074$ for 4259 observed reflections. Enhanced conjugation of aromatic π electrons with lone pairs on the adjacent O atom and simultaneous lengthening of the O—C(carbonyl) bond of the ester group of the *s*-triazine derivative compared with the 4-nitrophenyl ester explains the higher reactivity of compound (1) in acylation reactions. Also, the presence of lone-pair electrons at the *ortho* positions (N atoms) in the *s*-triazine ester, instead of H atoms as in the phenyl esters, may stabilize the cyclic intermediate in the acylation reaction.

Introduction. Active esters have been the most frequently used coupling reagents in peptide synthesis because they give high yields under mild conditions. However, they have been found to be less efficient or even totally ineffective in the synthesis of sterically hindered amino acids (Hardy, Goldsmith & Cotton, 1984; Leplawy, Kaczmarek & Redliński, 1988; Rich & Singh, 1979; Wipf & Heimgarten, 1987). The introduction of 2-chloro-4,6-disubstituted-1,3,5-triazines as a very efficient activator of carboxylic groups enables the high yield synthesis of esters, amides, carboxylic acid anhydrides and peptides even in the case of sterically hindered substrates (Kamiński, 1985, 1987). Preliminary studies based on spectroscopic data suggest that activation of carboxylic acids by means of 2-chloro-4,6-di-

methoxy-1,3,5-triazine proceeds *via* a hitherto unknown pathway, leading probably to highly reactive esters. For example, the 4-nitrophenyl ester of 2,2-dimethylpropanoic acid is unreactive towards aniline, while its *s*-triazine analogue easily affords the appropriate anilide (Kamiński, 1990). Unfortunately, very little is known about the structures and properties of triazine esters. We have therefore carried out crystal structure determinations of two aromatic esters of 2,2-dimethylpropanoic acid in the hope of explaining the higher reactivity of the *s*-triazine ester, compared with its 4-nitrophenyl analogue, in the acylation reaction.

Experimental. (1). Transparent, prismatic crystals of (1) were grown by slow cooling of a cyclohexane solution. A single crystal of dimensions $0.43 \times 0.35 \times 0.30$ mm, mounted in a capillary owing to its air sensitivity, was used for data collection on an Enraf-Nonius CAD-4F automated diffractometer. The data were collected to a maximum θ of 75° with the $\omega/2\theta$ scan technique ($0 \leq h \leq 6$, $0 \leq k \leq 10$, $-17 \leq l \leq 17$). The θ range for the 25 reflections used to define the cell constants and orientation matrix was 31.0–45.0°. Data were collected at 223 K by cooling the crystal with a stream of cold N₂ gas. The scan width was defined as $\Delta\omega = 1.5(0.50 + 1.4\tan\theta)$ °. Three standard reflections measured every 2000 s did not show any significant variation in intensity. Of 2523 unique reflections measured, 2277 had $I \geq 2\sigma(I)$ and were taken as observed. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. The structure was solved by direct methods (*MULTAN*78; Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) and refined by full-matrix least-squares calculations (*XRAY*76; Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976) on an IBM 370/145 computer. The largest Δ/σ ratio in the final cycle was 0.02. The function minimized was $\sum w(|F_o| - |F_c|)^2$ where w^{-1}

Table 1. Final positional and equivalent isotropic thermal parameters for non-H atoms with their *e.s.d.*'s in parentheses for structure (1)

$$B_{eq} = (8\pi^2/3)\sum_i U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	B _{eq} (Å ²)
O(1)	0.88004 (10)	0.60814 (14)	0.14220 (10)	3.38 (5)
O(2)	0.88303 (9)	0.36516 (13)	0.19836 (9)	2.92 (5)
O(4)	0.56333 (10)	0.48304 (15)	0.37859 (8)	3.05 (5)
O(6)	0.44375 (11)	0.32763 (17)	0.06387 (9)	3.59 (6)
N(1)	0.66628 (12)	0.34160 (17)	0.12562 (10)	2.73 (6)
N(3)	0.72996 (11)	0.43201 (16)	0.29178 (10)	2.55 (5)
N(5)	0.50173 (12)	0.40942 (18)	0.22016 (10)	2.88 (6)
C(1)	0.94256 (13)	0.49500 (18)	0.16841 (11)	2.21 (6)
C(2)	0.75155 (13)	0.38236 (18)	0.20518 (12)	2.46 (6)
C(4)	0.60040 (13)	0.44046 (19)	0.29482 (11)	2.46 (6)
C(6)	0.54136 (14)	0.35995 (20)	0.13882 (12)	2.67 (6)
C(10)	1.09016 (13)	0.47217 (19)	0.17805 (11)	2.31 (6)
C(11)	1.14827 (17)	0.47465 (26)	0.29002 (13)	3.35 (8)
C(12)	1.12149 (16)	0.31838 (24)	0.13268 (16)	3.41 (8)
C(13)	1.14720 (17)	0.60565 (26)	0.12630 (16)	3.60 (8)
C(40)	0.66552 (18)	0.51692 (27)	0.46356 (13)	3.54 (8)
C(60)	0.47740 (23)	0.26970 (33)	-0.02771 (15)	4.30 (10)

Table 2. Final positional and equivalent isotropic thermal parameters for non-H atoms with their *e.s.d.*'s in parentheses for structure (2)

$$B_{eq} = (8\pi^2/3)\sum_i U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	B _{eq} (Å ²)
C(101)	0.2114 (2)	0.7867 (2)	1.0746 (1)	4.72 (5)
C(102)	0.2028 (2)	0.6630 (2)	1.1513 (2)	4.87 (6)
C(103)	0.0969 (2)	0.6525 (2)	1.2671 (2)	4.37 (5)
C(104)	0.0024 (2)	0.7689 (1)	1.3022 (1)	3.73 (5)
N(104)	-0.1102 (2)	0.7594 (2)	1.4260 (1)	4.94 (5)
C(105)	0.0094 (2)	0.8936 (2)	1.2268 (2)	4.73 (5)
C(106)	0.1151 (2)	0.9024 (2)	1.1107 (2)	5.15 (7)
O(107)	0.3264 (1)	0.7949 (2)	0.9627 (1)	6.61 (6)
C(108)	0.3032 (2)	0.7987 (1)	0.8590 (1)	3.81 (5)
O(108)	0.1869 (1)	0.7993 (2)	0.8622 (1)	5.75 (5)
C(109)	0.4426 (2)	0.8025 (1)	0.7469 (1)	3.94 (4)
C(110)	0.4138 (3)	0.7973 (3)	0.6351 (2)	5.90 (9)
C(111)	0.4882 (3)	0.9305 (2)	0.7241 (2)	6.22 (8)
C(112)	0.5637 (2)	0.6803 (2)	0.7729 (2)	5.41 (7)
O(142)	-0.1229 (2)	0.6498 (2)	1.4890 (1)	7.17 (6)
O(141)	-0.1851 (2)	0.8626 (2)	1.4595 (2)	8.43 (7)
C(201)	0.6363 (2)	0.3093 (2)	0.6330 (2)	4.73 (6)
C(202)	0.6743 (2)	0.4205 (2)	0.5451 (2)	5.08 (6)
C(203)	0.7954 (2)	0.4034 (2)	0.4407 (2)	4.62 (5)
C(204)	0.8736 (2)	0.2749 (2)	0.4257 (1)	4.13 (5)
N(204)	1.0031 (2)	0.2571 (2)	0.3153 (1)	5.32 (5)
C(205)	0.8341 (2)	0.1636 (2)	0.5134 (2)	4.84 (6)
C(206)	0.7144 (2)	0.1813 (2)	0.6179 (2)	5.24 (7)
O(207)	0.5214 (1)	0.3280 (2)	0.7433 (1)	6.29 (6)
C(208)	0.3913 (2)	0.3052 (1)	0.7615 (1)	3.86 (4)
O(208)	0.3680 (1)	0.2874 (1)	0.6807 (1)	5.19 (5)
C(209)	0.2904 (2)	0.3051 (2)	0.8944 (1)	4.02 (5)
C(210)	0.1408 (2)	0.2953 (3)	0.9074 (2)	5.95 (7)
C(211)	0.3567 (2)	0.1817 (2)	0.9774 (2)	5.64 (7)
C(212)	0.2767 (3)	0.4323 (2)	0.9296 (2)	6.35 (9)
O(241)	1.0697 (2)	0.1440 (2)	0.3014 (2)	7.94 (6)
O(242)	1.0385 (2)	0.3558 (2)	0.2404 (1)	8.37 (7)

$= \sigma^2(F_o) + 0.002F_o^2$. H atoms were located from a difference synthesis and refined with isotropic temperature factors. The final difference synthesis showed $\rho_{max} = 0.20$ and $\rho_{min} = -0.14 \text{ e } \text{Å}^{-3}$. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV, pp. 71-73). $R = 0.046$, $wR = 0.064$.

(2). The compound was crystallized from isobutanol solution by slow evaporation of the solvent. A single crystal of dimensions $0.42 \times 0.28 \times 0.23 \text{ mm}$ was used for data collection and accurate cell determination on a CAD-4 diffractometer. Unit-cell parameters were obtained from a least-squares refinement of 25 reflections in the θ range $15-25^\circ$. 4665 independent intensities were measured with the $\omega/2\theta$ scan technique to a maximum θ of 75° ($0 \leq h \leq 12$, $-13 \leq k \leq 13$, $-15 \leq l \leq 15$), 4259 of which had $I \geq 2\sigma(I)$. Three standard reflections monitored during data collection did not show any significant change in intensity. No correction for absorption was applied. The structure was solved by direct methods (*SHELXS86*; Sheldrick, 1986). H atoms were located from a subsequent difference synthesis. The positions of all atoms were refined by full-matrix least squares on *F* (*SHELX76*; Sheldrick, 1976) with anisotropic temperature factors for non-H atoms and isotropic ones for H atoms. In the final refinement the parameters of each independent molecule were varied in alternate cycles, the largest Δ/σ ratio was 0.04 and $w^{-1} = \sigma^2(F_o) + 0.00142F_o^2$. The final difference synthesis showed no peaks above $0.18 \text{ e } \text{Å}^{-3}$ while ρ_{min} was $-0.22 \text{ e } \text{Å}^{-3}$. $R = 0.052$, $wR = 0.074$. The calculations for (2) were performed on an Amstrad 1512 microcomputer.

Discussion. The molecular conformations and atomic labeling of (1) and (2) are shown in Fig. 1, while atomic coordinates for non-H atoms are given in Tables 1 and 2, and selected bond distances and angles in Table 3.* Crystals of (2) contain two crystallographically independent molecules which are structurally nearly identical. Bond lengths and angles agree within experimental error and corresponding torsional angles to within 10° .

* Lists of anisotropic thermal parameters for non-H atoms, coordinates and thermal parameters for H atoms, and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53064 (31 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

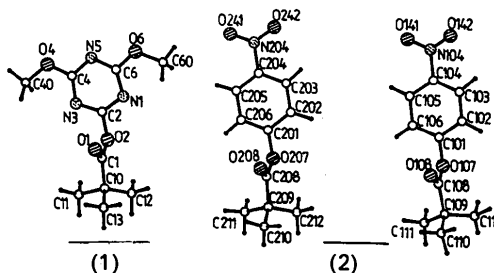


Fig. 1. Views of molecule (1) and of the two independent molecules of (2) with atom labeling. The dotted atoms are N and the hatched ones are O.

Table 3. Selected bond lengths (Å), valency angles (°) and torsion angles (°) for (1) and (2)

The atom numbering shown in the upper line corresponds to that used for compound (1) and the numbering in the lower line refers to compound (2).

	(1)	(2)	Aryl esters*	Alkyl esters*
C(2)—O(2)	1·384 (2)	1·387 (2)	1·402 (3)	1·451 (2)
C(1)—O(7)		1·393 (2)		
O(2)—C(1)	1·379 (2)	1·359 (2)	1·368 (2)	1·340 (2)
O(7)—C(8)		1·362 (3)		
C(1)=O(1)	1·192 (2)	1·181 (2)	1·194 (2)	1·203 (1)
C(8)=O(8)		1·184 (2)		
C(1)—C(10)	1·517 (2)	1·520 (2)	1·501 (4)	1·515 (2)
C(8)—C(9)		1·516 (2)		
N(1)—C(2)	1·315 (2)			
N(3)—C(2)	1·314 (2)			
N(1)—C(6)	1·343 (2)			
N(3)—C(4)	1·347 (2)			
N(5)—C(4)	1·330 (2)			
N(5)—C(6)	1·321 (2)			
C(2)—O(2)—C(1)	115·3 (1)	118·5 (2)	117·8 (4)	116·7 (2)
C(1)—O(7)—C(8)		118·4 (2)		
O(2)—C(1)=O(1)	120·9 (1)	121·4 (2)	122·2 (4)	123·7 (2)
O(7)—C(8)=O(8)		121·6 (2)		
O(2)—C(1)—C(10)	111·2 (1)	110·9 (2)	110·0 (5)	111·1 (2)
O(7)—C(8)—C(9)		110·6 (2)		
O(1)=C(1)—C(10)	127·8 (1)	127·7 (2)	126·8 (3)	125·2 (2)
O(8)=C(8)—C(9)		127·8 (2)		
N(1)—C(2)—O(2)—C(1)	94·0 (2)	96·3 (3)		
C(2)—C(1)—O(7)—C(8)		106·9 (3)		
N(3)—C(2)—O(2)—C(1)	-88·3 (2)	-88·5 (3)		
C(6)—C(1)—O(7)—C(8)		-77·2 (3)		
C(2)—O(2)—C(1)=O(1)	-6·3 (2)	2·3 (3)		
C(1)—O(7)—C(8)=O(8)		-10·0 (3)		
C(2)—O(2)—C(1)—C(10)	171·5 (1)	-177·9 (2)		
C(1)—O(7)—C(8)—C(9)		169·4 (2)		

* The mean bond lengths and valency angles for 27 aryl esters and 77 alkyl esters from the *Cambridge Structural Database* (1988) were evaluated. Only structures with $R < 5\%$ were considered.

The most significant difference between (1) and (2) concerns the O(ester)—C(carbonyl) bond length which is longer in (1) by 0·020 (3) (2a) and 0·017 (2) Å (2b), respectively. Unexpectedly, the C(aromatic)—O(ester) bond lengths in the two structures are almost the same [1·384 (2) Å in (1), 1·387 (2) and 1·393 (2) Å in (2)] though the average length of this bond in aryl esters is 1·402 (3) Å (Table 3). The electron-withdrawing *p*-nitro group may be the reason for this shortening in (2). As the average C(*sp*³)—O ester bond in alkyl esters has a length of 1·451 (2) Å, the shortening of the bond in aryl esters is obviously caused by conjugation of the aromatic π system with lone-pair electrons of the ester O atom. In the *s*-triazine ester (1) the conjugation is restricted mainly to the N(1), C(2), N(3) and O(2) fragment [the mean C(2)—N bond length is 1·315 (1) Å while the other C—N distances in the triazine ring are significantly longer (Table 3)]. The limited conjugation in *s*-triazine esters is corroborated by the structure of the hydrolysis product of (1), 4,6-dimethoxy-1,3,5-triazin-2(1*H*)-one (Głowska & Bertolasi, 1987). The conjugation may also stabilize the charge of the leaving group in the acylation reaction and facilitate departure of the group.

The spatial orientation of the 2-(2,2-dimethylpropanoyloxy) group may also affect the reactivity of (1) and (2). Surprisingly, the orientation of this group is the same in both esters (Table 3 and Fig. 1) though the absence of *ortho*-substituted H atoms in the aromatic *s*-triazine ring allows the *tert*-butyloxy group in (1) more rotational freedom.

The results therefore suggest that the enhanced reactivity of *s*-triazine esters of 2,2-dimethylpropanoic acid, as compared with the phenyl type of aromatic ester, may be due to weakening of the O(ester)—C(carbonyl) bond which has to be broken during acylation reactions. The length of this bond is 1·379 (2) Å in (1), 1·359 (2) and 1·362 (3) Å in (2) and only 1·340 (2) Å in alkyl esters (Table 3) which indeed are generally less active as acylating agents than their aromatic analogues. These findings also corroborate the different reactivities of various esters in the acylation of aniline (Fig. 2). However, it could be argued that the differences in O(ester)—C(carbonyl) bond lengths between (1) and (2) are small and that the comparison is complicated by the differences in thermal motion and the different temperatures (223 and 293 K) at which the structures were determined. The other explanation of the

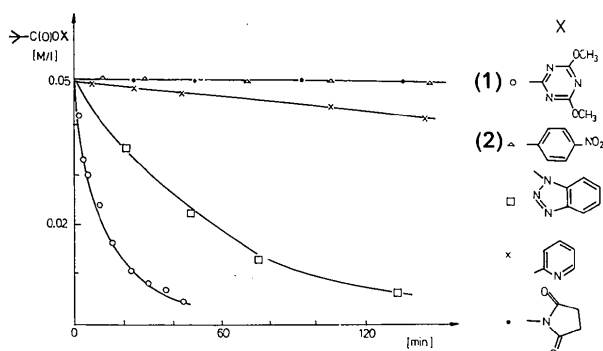
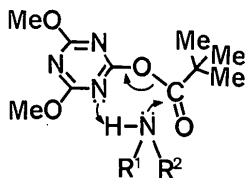


Fig. 2. The rate of aniline acylation by selected 'active' esters shown by decrease of substrate concentration with time (Kamiński, 1990).

enhanced reactivity of triazine esters may be the stabilization of the cyclic transition state (see below) in the acylation reaction by interaction of the nucleophilic agent with lone-pair electrons at a ring N (sp^2) atom (Kamiński, 1990) but there is no direct evidence for this.



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Structure of *syn*-1,2,3,4-Diepoxy-1,2,3,4-tetrahydronaphthalene

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Abstract. *syn*-3,6-Dioxatetracyclo[6.4.0^{2,4}.0^{5,7}]dodeca-1(12),8,10-triene, C₁₀H₈O₂, $M_r = 160.2$, monoclinic,

$P2_1/n$, $a = 8.075$ (2), $b = 8.041$ (1), $c = 12.057$ (2) Å, $\beta = 107.59$ (1)°, $V = 746.2$ (4) Å³, $Z = 4$, $D_x = 1.426$ g cm⁻³, $\lambda(\text{Mo } K\alpha) = 0.71073$ Å, $\mu = 0.93$ cm⁻¹, $F(000) = 336$, $T = 297$ K, $R = 0.032$ for 926 observations having $I > 2\sigma(I)$ (of 1313 unique

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