

Synthesis and ^{13}C NMR Assignment of Ammonium Benzylidenepropanedioates and Benzylidenepropanediamides

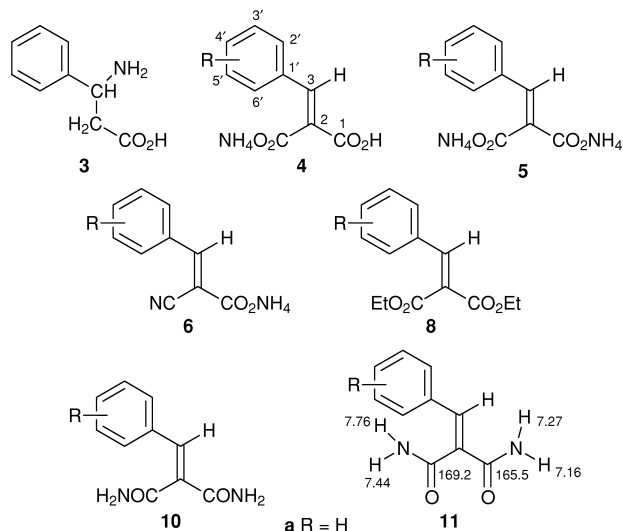
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Mono- and di-ammonium benzylidenepropanedioates are synthesised, the molecular structure of a mono-ammonium salt confirmed by X-ray diffraction, and the ^{13}C NMR spectra of the salts and the related benzylidenepropanediamides assigned.

In the course of a synthetic programme concerned with the preparation of low molecular weight compounds having potential activity as protein tyrosine kinase inhibitors,^{1,2} we have studied the reaction of aromatic aldehydes with ammonium malonate. In contrast to the reaction of aldehydes with ammonia and malonic acid (which affords the β -aminopropionic acids **3**),⁵ a mixture of mono- and di-ammonium salts (**4** and **5**) of the benzylidenepropanedioic acids is obtained, with the mono-ammonium salts predominating. (Similarly, the reaction of benzaldehyde with cyanoacetic acid and ammonia is known to afford 2-cyano-3-phenylprop-2-enoic acid,⁶ but reaction with preformed ammonium cyanoacetate affords ammonium 2-cyano-3-phenylprop-2-enoate **6**.)



In the mono-ammonium dicarboxylic acid salts, IR data indicate the presence of two separate carbonyl bands, one attributable to a free carboxy carbonyl, and the other to a carboxylate salt. The formulation **4a** is established by X-ray crystallography, which shows that salt formation is confined to one carboxy group (Fig. 1). The free carboxylic acid group is more nearly coplanar with the alkene double bond and the aryl group, than the carboxylate group.

In the ^{13}C NMR spectra of both the mono- and di-ammonium salts **4** and **5**, there is disparity between the two carbonyl signals in each compound. Similar disparities in related benzylidene compounds (2.1–2.8 Hz in the case of diethyl esters **8**) have previously been reported.⁹ In the diamide derivatives **10**, the disparity between the two carbonyl signals is still more striking (3.0–4.2 Hz). Measurements of the long range coupling constants between each carbonyl and the methylene proton establish that the coupling is

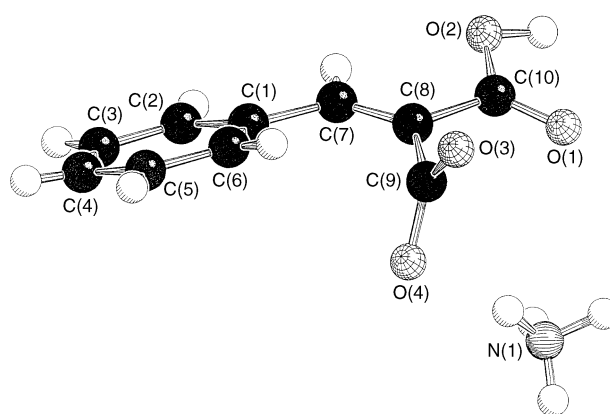


Fig. 1 Molecular structure of mono-ammonium benzylidenepropanedioate **4a**, showing the crystallographic numbering system

much stronger from the down-field carbonyl than from the up-field one, and that, accordingly, the down-field carbonyl is *trans* with respect to the methylene proton, and the up-field carbonyl is *cis*. In each of the compounds **10**, two distinct pairs of NH_2 protons can be differentiated in the ^1H NMR spectrum. Each pair can be assigned to its parent (down-field or up-field) carbonyl by HMBIC experiments, and the contiguity of each pair to the aromatic protons and methylene proton is established by NOE experiments. These experiments show that the favoured conformation is that shown in formula **11**: the shifts quoted on the formula represent average values.

Table 1 Crystallographic data for $\text{C}_{10}\text{H}_{11}\text{NO}_4$

Molecular formula	$\text{C}_{10}\text{H}_{11}\text{NO}_4$
M_r	209.20
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
$a/\text{\AA}$	16.616(2)
$b/\text{\AA}$	5.4882(7)
$c/\text{\AA}$	11.381(2)
$\beta/\text{\AA}$	95.204(10)
Volume/ \AA^3	1033.6(2)
Z	4
$D_c/\text{g cm}^{-3}$	1.344
Absorption coefficient/ mm^{-1}	0.105
$F(000)$	440
θ range/ $^\circ$	1.23–24.96
Total reflections collected	1872
Total unique reflections	1770 ($R_{\text{int}} = 0.0546$)
Refinement method	Full-matrix least-squares on F^2
Number of parameters	180
Goodness-of-fit on F^2	0.995
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.582$, $R_w = 0.1384$
R indices (all data)	$R_1 = 0.1705$, $R_w = 0.1986$
Largest diff. peak and hole/ $e \text{\AA}^{-3}$	0.259 and -0.255

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Crystal structure determination of mono-ammonium benzylidenepropanedioate 4a.—Data were collected on an Enraf-Nonius CAD-4 diffractometer (Mo radiation, graphite monochromator, ω - 2θ scans) at 20 °C. The crystal data and experimental parameters are given in Table 1. The final cell parameters were determined using the Celdim routine. It was not found necessary to apply decay or absorption corrections to the data. The data were reduced to give the number of unique reflections and those with $|F| \geq 4\sigma|F|$ were used in structure solution and refinement.

The structure was solved by automatic direct methods using SHELXS-86.¹⁷ The structure was refined by full-matrix least-squares analysis on F^2 with SHELXL.¹⁸ The non-hydrogen atoms were refined anisotropically and all the hydrogen atoms were located from subsequent difference Fourier maps and refined with individual temperature factors to a final R value of 0.0582.

Techniques used: IR, ¹H NMR, ¹³C NMR, CH COSY and NOE, HMBC and gated decoupling, X-ray crystallography, elemental analysis

Fig 2: Compound **4a**: a packing diagram showing the standard orientation of the unit cell

Table 1: ¹³C NMR spectra of benzylidenepropanediamides **10**

Table 2: ¹H NMR spectra of amide protons of the benzylidenepropanediamides **10**

Table 3: Atomic coordinates and equivalent isotopic displacement parameters for **4a**

Table 4: Bond lengths and angles for **4a**

Table 5: Anisotropic displacement parameters for **4a**

Table 6: Hydrogen coordinates and isotropic displacement parameters for **4a**

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