Crystal and Molecular Structure of Methylpropylglyoxal Bis(amidinohydrazone) Sulphate Monohydrate

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Abstract

A single-crystal X-ray diffraction study was performed on methylpropylglyoxal bis(amidinohydrazone) (MPGBG) sulphate monohydrate. The bis(amidinohydrazone) dication was found to exist exclusively in the form of the anti-anti isomer, with an all-trans configuration of the glyoxal bis(amidinohydrazone) chain, just as do the free base, the monocation and the dication of glyoxal bis(amidinohydrazone) and the dications of all mono- and dialkylglyoxal bis(amidinohydrazone)s so far studied. MPGBG sulphate monohydrate crystallizes in the triclinic space group PI with unit cell parameters \(a = 8.860(2), b = 9.195(2), c = 10.788(2) \text{Å}\). \(\alpha = 73.71(3), \beta = 77.59(3), \gamma = 65.28(3)^\circ\) and with \(Z = 2\). When the structure is compared with that of propylglyoxal bis(amidinohydrazone) (PGBG) sulphate, an analogous compound that is devoid of the methyl group of MPGBG, a distinct difference can be observed regarding the conformation of the propyl side chain. In the PGBG dication it is tangled around the glyoxal bis(amidinohydrazone) moiety. Whether this difference results from packing effects and related factors, or whether it is a result of a more fundamental difference between MPGBG and PGBG, remains to be studied. The observed difference may contribute to the biochemical differences between the two compounds.

Introduction

The bis(amidinohydrazone)s of various alkylglyoxals, including methylpropylglyoxal bis(amidinohydrazone) (MPGBG, Fig. 1), are potent inhibitors of S-adenosylmethionine decarboxylase (AdoMetDC), one of the two rate-limiting enzymes of polyamine biosynthesis [1–7]. Therefore, the compounds are important tools in the investigation of polyamine metabolism and of the largely unknown physiological functions of the natural polyamines. Some bis(amidinohydrazone)-type polyamine antimitabolites are also antileukemic agents [1, 2]. Among them, methylglyoxal bis(amidinohydrazone) (MGBG) is the most deeply studied one.

In previous studies, the structure-activity relationships of bis(amidinohydrazone)-type antineoplastic agents have been found to be unusually strict [1–7]. Structural studies, employing X-ray diffraction [5, 6, 8–15] as well as NMR spectroscopy [16, 17], have proved to be of great value in investigations concerning these relationships and

Abbreviations: AdoMetDC, S-Adenosylmethionine Decarboxylase; GBG, Glyoxal Bis(amidinohydrazone); MGBG, Methylglyoxal Bis(amidinohydrazone); MPGBG, Methylpropylglyoxal Bis(amidinohydrazone); PGBG, Propylglyoxal Bis(amidinohydrazone); PhGBG, Phenylglyoxal Bis(amidinohydrazone).

* Reprint requests to Dr. Hannu Elo.

Fig. 1. The general structural formula of the doubly protonated (dication) form of MPGBG and of the bis(amidinohydrazone)s of other glyoxals.

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the mechanism of AdoMetDC inhibition by the agents. It has been concluded that isomerism of the bis(amidinohydrazone) backbone is not involved in the biochemical differences between various C-alkylated bis(amidinohydrazones) and the unsubstituted parent compound GBG [2]. However, in a recent study [7, 14, 18], we found that this result cannot be generalized to aromatic bis(amidinohydrazones). Thus, phenylglyoxal bis(amidinohydrazone) (PhGBG) was found to exist in the form of different geometrical isomers depending on the conditions used in its crystallization [14]. PhGBG was also found to be a markedly weaker inhibitor of AdoMetDC [7] than any of its C-alkylated analogues so far studied, possibly because of the lack of structural rigidity. In the light of these recent results, further studies on the isomerism as well as other structural properties of bis(amidinohydrazones) are warranted. Therefore, we now report the structural properties of MPGBG sulphate (Fig. 1), a more highly alkylated bis(amidinohydrazone) than any congener so far investigated by X-ray or neutron diffraction.

Materials and Methods

Formation of crystals

MPGBG sulphate was synthesized from 2,3-hexanediol and amidoguanidine sulphate according to classical procedures [2, 19]. The details of the synthesis will be published elsewhere. In order to obtain single crystals, 0.21 g of the compound were dissolved at 80 °C in 50 ml of water containing 1 ml of concentrated sulphuric acid. When the solution was allowed to slowly evaporate at room temperature for one month, colourless prismatic crystals were obtained.

X-ray crystallography

Information concerning X-ray data collection and structure refinement is summarized in Table I. The crystal was mounted on a glass fibre using the oil-drop method [20]. Data were collected at 193 K on a Rigaku AFC-7S single-crystal X-ray diffractometer using graphite-monochromatized MoKα radiation (λ = 0.71073 Å). The cell parameters were determined by least-squares treatment of the adjusted angular settings of 25 reflections (7° < 2θ < 12°). The intensity measurements were carried out by the ω-2θ scan technique. The scan rate varied from 2.0° to 6.0° min⁻¹ depending on the number of counts measured in a fast preliminary scan. Three standard reflections measured every 200 reflections showed the intensity variation to be random and within 1% with respect to the mean. The intensities were corrected for Lorentz, polarization and extinction effects. Absorption correction was done by the ψ-scan technique [21]. The structure was solved by direct methods [22]. Hydrogen atoms were found from the difference map and were refined with isotropic displacement factors. All other atoms were refined anisotropically [23].

Results and Discussion

A drawing of MPGBG sulphate as observed in the crystal studied is shown in Fig. 2. The stereoo-
Fig. 2. A drawing of the MPGBG dication as present in MPGBG sulphate monohydrate. The thermal ellipsoids are drawn at the 50% probability level.

range ment of the ions in a unit cell is shown in Fig. 3. Interatomic distances and bond angles are listed in Table II*. MPGBG sulphate was found to exist exclusively in the form of the anti-anti isomer, with an all-trans configuration of the bis(amidinohydrazo) chain, just as do the free base, the monocation and the dications of GBG [10, 13] and the dications of all mono- and dialkylglyoxal bis(amidinohydrazones) [5, 6, 8, 9, 11, 12, 15] so far studied by crystallography. The bis(amidinohydrazone) backbone of the MPGBG dication is planar just like that of GBG and of all of its alkylglyoxal analogues so far studied, except the dication of ethylmethylglyoxal bis(amidinohydrazone) in crystals of its sulphate salt [5]. The crystal of MPGBG sulphate monohydrate consists of stacks of parallel planes which are held together by extensive hydrogen bonding through the sulphate ions and the water of crystallization (Fig. 3). From each sulphate oxygen originate two and from the oxygen atom of the water molecule four hydrogen bonds directed to the nitrogen-bound hydrogen atoms of MPGBG.

When the structure of MPGBG sulphate monohydrate is compared with that of propylglyoxal bis(amidinohydrazone) (PGBG) sulphate dihydrate [11], a different conformation of the propyl group is obvious. In the MPGBG dication, the propyl group is directed away from the glyoxal bis(amidinohydrazone) chain (see Figs 2 and 3), whilst in the case of PGBG dication it is tangled around the glyoxal bis(amidinohydrazone) moiety. Further crystallographic studies on the bases or on various salts of MPGBG and PGBG are warranted, as they would probably reveal whether this difference results from packing effects and related factors, or whether it is a result of a more funda-

* Additional material to the structure determination may be ordered from Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Federal Republic of Germany, referring to the deposition number CSD-59436.

Table II. Selected bond lengths (Å) and angles (°) of MPGBG sulphate monohydrate.

<table>
<thead>
<tr>
<th>Bond/Angle</th>
<th>Length/Angle</th>
</tr>
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<tbody>
<tr>
<td>N(1) - C(1) - N(2)</td>
<td>121.7(2)</td>
</tr>
<tr>
<td>N(1) - C(1) - N(3)</td>
<td>121.0(2)</td>
</tr>
<tr>
<td>N(2) - C(1) - N(3)</td>
<td>117.3(2)</td>
</tr>
<tr>
<td>N(1) - N(3) - N(4)</td>
<td>118.2(1)</td>
</tr>
<tr>
<td>C(1) - N(3) - N(4)</td>
<td>115.9(1)</td>
</tr>
<tr>
<td>N(4) - C(2) - C(3)</td>
<td>118.2(1)</td>
</tr>
<tr>
<td>C(2) - N(4) - N(6)</td>
<td>115.0(1)</td>
</tr>
<tr>
<td>N(4) - C(2) - C(5)</td>
<td>124.4(1)</td>
</tr>
<tr>
<td>C(3) - C(2) - C(5)</td>
<td>120.6(1)</td>
</tr>
<tr>
<td>N(5) - C(3) - C(6)</td>
<td>114.2(1)</td>
</tr>
<tr>
<td>N(5) - C(3) - C(4)</td>
<td>125.3(1)</td>
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<tr>
<td>C(2) - C(3) - C(4)</td>
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</tr>
<tr>
<td>C(3) - N(5) - N(6)</td>
<td>117.1(1)</td>
</tr>
<tr>
<td>C(4) - N(6) - N(5)</td>
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</tr>
<tr>
<td>N(7) - C(4) - N(8)</td>
<td>123.1(2)</td>
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<tr>
<td>N(7) - C(4) - N(6)</td>
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</tr>
<tr>
<td>N(8) - C(4) - N(6)</td>
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</tr>
<tr>
<td>C(3) - C(6) - C(7)</td>
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</tr>
<tr>
<td>C(3) - C(6) - C(8)</td>
<td>111.7(1)</td>
</tr>
<tr>
<td>C(8) - C(7) - C(6)</td>
<td>121.6(1)</td>
</tr>
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</table>
mental difference between MPGBG and PGBG. In this respect, the steric hindrance caused by the methyl group in MPGBG may possibly be of importance. If there is a distinct difference between PGBG and MPGBG as regards the tendency of the propyl group to adopt conformations “away from” or “tangled around” the glyoxal bis(amidinohydrazone) chain, these differences may have significance concerning the biochemical properties and structure-activity relationships of the compounds. Any tendencies of the propyl side chains to adopt certain conformation(s) are of interest also for the NMR spectroscopy of the compounds, since it has been found that as long as the longest substituent of the glyoxal moiety of a bis(amidinohydrazone) is not longer than ethyl, there is a strikingly good linear correlation between the mean of the $^{13}$C chemical shifts of the glyoxal carbons and the total number of the carbon atoms present in the side chains. This remarkable correlation ($r = 0.997$), however, breaks down if at least one of the substituents is a propyl or butyl group [2, 16]. Since the reasons for the correlation as well as for its breakdown are obscure at present, any information on the conformations of propyl, butyl and longer side chains in bis(amidinohydrazone) is of great interest. This is even more so because it has been found that the ability of a bis(amidinohydrazone) to inhibit AdoMetDC increases remarkably as a function of an increase in the total number of side-chain carbon atoms from 0 up to 4. If, however, at least one of the side chains is a propyl group or a longer substituent, the ability to inhibit AdoMetDC no longer increases but instead decreases, possibly because of steric hindrance [2]. Also, MPGBG that contains one methyl group in addition to the three-carbon side chain has been shown to be a more potent inhibitor of AdoMetDC than is the monoalkylated analogue PGBG [2]. The present results indicate that the differences in the inhibitory potencies of MPGBG and PGBG may result not only from differences in the electron distributions and the hydrophobicities and the size of the side chain, but also from the different conformations of the bulky side chains.