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Structure of Aminoguanidine Hemioxalate. Implications for the Synthesis of Amidinohydrazones

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Summary. The crystal and molecular structure of aminoguanidine hemioxalate, a salt in which aminoguanidine exists in the monocation form, was determined by single crystal X-ray diffraction. The salt crystallizes in the monoclinic space group P2(1)/n with unit cell dimensions of $a = 4.95$, $b = 10.46$, $c = 10.40$ Å, $\beta = 92.57°$, and $Z = 4$. The structure contains one oxalate ion for every two $CN_4H_7^+$ ions, the latter being practically planar. The structure of the monocation is largely similar to those of aminoguanidine dications except that the monocation is devoid of one of the protons attached to the terminal hydrazine nitrogen. This result is of interest considering the synthesis of amidinohydrazones, indicating that the concentration of the active nucleophile is nearly maximal even when aminoguanidine exists in the monocation form. Therefore, the synthesis of amidinohydrazones should be performed in the *pH* range in which aminoguanidine exists mainly in the monocation form, *i.e.* at a *pH* higher than 2. There is, however, no need to elevate the *pH* to values at which a considerable proportion of aminoguanidine exists as the free base.

Keywords. Guanylhydrazones; Diamine oxidase inhibitors; Nitric oxide synthase inhibitors; Tautomerism; X-ray structure.

Die Struktur von Aminoguanidinhemioxalat und ihre Bedeutung für die Synthese von Amidinohydrazonen

Zusammenfassung. Die Kristallstruktur von Aminoguanidinhemioxalat, einem Salz, in dem Aminoguanidin als Monokation existiert, wurde mit Einkristallröntgenmethoden aufgeklärt. Das Salz kristallisiert in der monoklinen Raumgruppe P2(1)/n mit den Zellparametern $a = 4.95$, $b = 10.46$, $c = 10.40$ Å, $\beta = 92.57°$ und $Z = 4$. In der Einheitszelle kommt ein Oxalation auf je zwei flache $CN_4H_7^+$-Ionen. Die Struktur des Monokations ist bekannten Strukturen des Aminoguanidindikations ähnlich, mit der Ausnahme, daß dem Monokation eines der an das äußere Stickstoffatom der Hydrazingruppe gebundenen drei Protonen fehlt. Dieses Ergebnis ist interessant bezüglich der Synthese von Amidinohydrazonen, da es bedeutet, daß die Konzentration des aktiven Nukleophils auch dann beinahe maximal ist, wenn Aminoguanidin in der Monokationform vorliegt. Synthesen von Amidinohydrazonen sollten daher unter solchen Bedingungen ausgeführt werden, unter denen Aminoguanidin hauptsächlich in der Monokationform existiert (*pH* höher als 2). Es ist

jedoch nicht nötig, bei *pH*-Werten zu arbeiten, die so hoch sind, daß ein bedeutender Teil der Verbindung als freie Base vorliegt.

Introduction

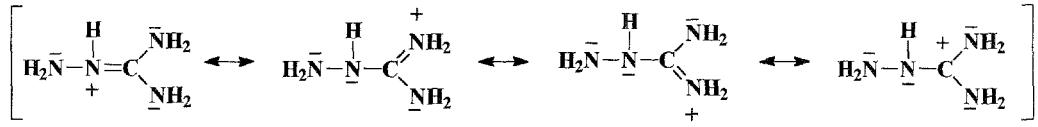
Aminoguanidine (see Fig. 1 for structural formula) is an important starting material for the synthesis of various amidinohydrazones (guanylhydrazones) and related compounds with many important pharmacological applications [1–4]. For example, many *bis*(amidinohydrazones) are potent inhibitors of adenosylmethionine decarboxylase, one of the two rate-limiting enzymes of polyamine biosynthesis [4–10]. Further, some *bis*(amidinohydrazones) are potent antineoplastic agents [4, 11, 12]. In the synthesis of amidinohydrazones, salts of aminoguanidine are allowed to react with various carbonyl compounds [1–4]. The reaction, in which the nucleophilic hydrazine nitrogen attacks the electrophilic carbonyl carbon, is acid catalyzed.

In addition to being a starting material for various syntheses, aminoguanidine itself is also a well-known enzyme inhibitor. For example, it inhibits copper containing amine oxidases and it has also been found to inhibit nitric oxide synthase [13, 14].

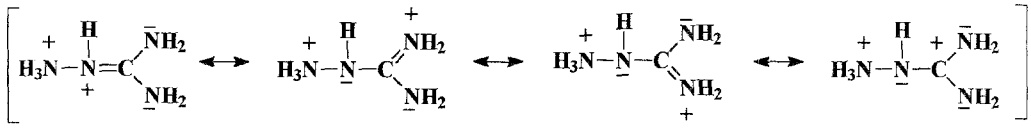
We have previously studied the chemical and structural properties of many *bis*(amidinohydrazone) type derivatives of aminoguanidine in detail [4, 15–28]. These studies created an interest in the structure of aminoguanidine itself. Thus, we have reported the crystal structures of two dicationic species of aminoguanidine, *i.e.* aminoguanidine sulfate [29] and dinitrate [30]. In these species, aminoguanidine was found to exist in the form of the tautomer in which the terminal hydrazine nitrogen is protonated (Fig. 1b). Therefore, it was concluded that it is advisable not to use the dicationic form for syntheses, even though the reactions are acid catalyzed [29]. It was also of interest to study the structure of the monocationic (monoprotonated) form of aminoguanidine. Thus, we have recently reported the crystal structure of aminoguanidine monohydrochloride; at the same time, we have performed computational studies on aminoguanidine (free base, monocation, and dication) [31]. In the present paper we describe the crystal and molecular structure of aminoguanidine hemioxalate, another species in which aminoguanidine exists in the monoprotonated form. A comparison of mono- and dicationic species is presented together with implications concerning the synthesis of amidinohydrazones.

Results and Discussion

The monocationic form of aminoguanidine can, in principle, exist in the form of several different tautomers. In the crystal of aminoguanidine hemioxalate studied, it was found to exist exclusively in the form of the tautomer shown in Fig. 1a. A structural representation of the compound is shown in Fig. 2, and a stereoview of molecular packing in Fig. 3. Atomic parameters are listed in Table 1, bond lengths and angles in Table 2, and coordinates and isotropic displacement coefficients of hydrogen atoms in Table 3.



a



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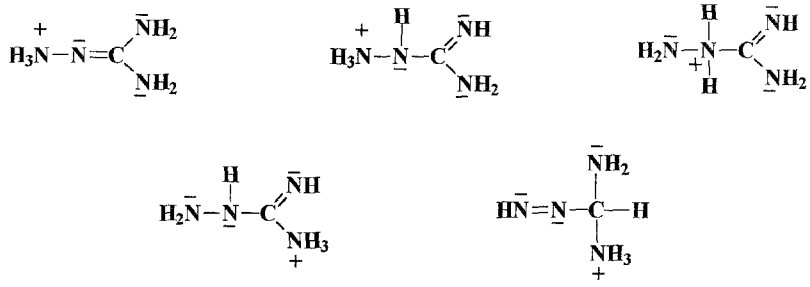

c

Fig. 1. (a) Resonance forms of the tautomer in the form of which the aminoguanidine monocation was found to exist in the solid state; (b) resonance forms of the tautomer in the form of which the aminoguanidine dication [29, 30] has been found to exist; (c) some tautomers of the aminoguanidine monocation that are possible in principle but have not been detected experimentally

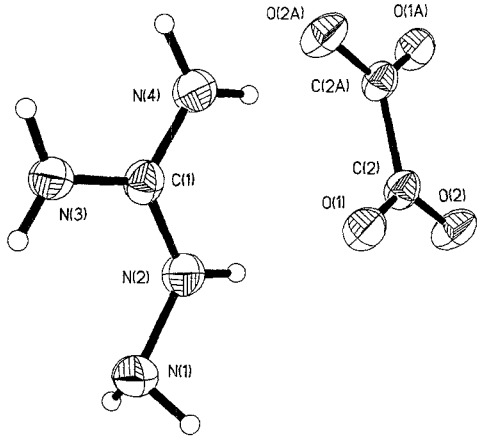

Fig. 2. Aminoguanidine hemioxalate; the ellipsoids are drawn at a 50% probability level

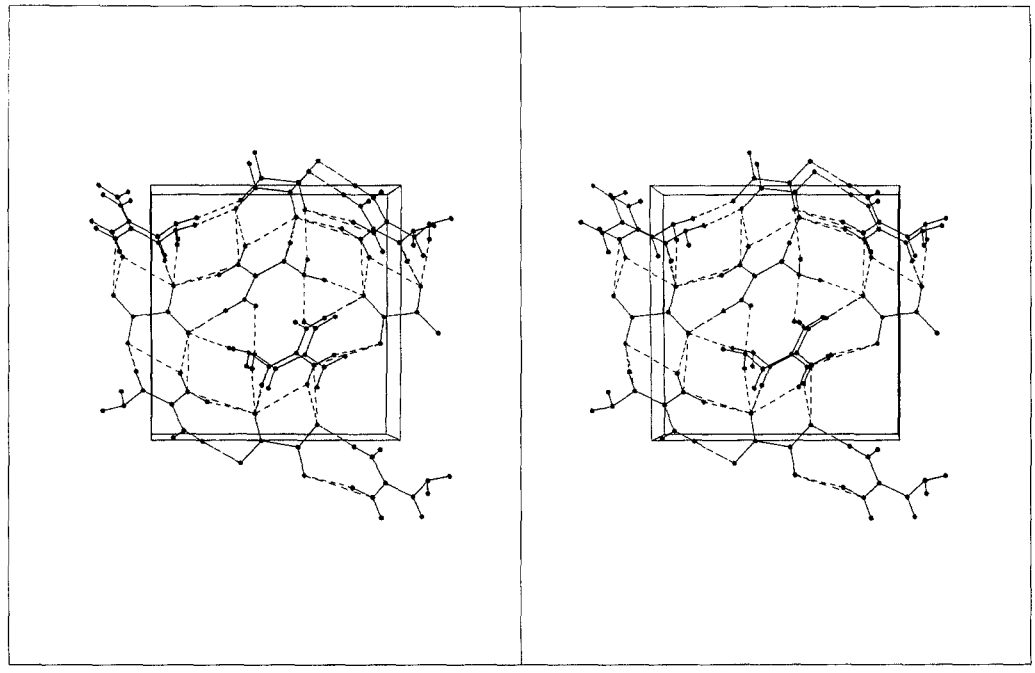

Fig. 3. Arrangement of ions in a unit cell of aminoguanidine hemioxalate viewed along *a* (stereo view); intermolecular hydrogen bonds are shown by dashed lines

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($Å^2 \times 10^3$) of aminoguanidine hemioxalate; U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

	x	*y*	*z*	*U*(eq)
N(1)	8284(3)	1013(1)	8472(2)	33(1)
N(2)	6112(3)	284(1)	7935(1)	32(1)
C(1)	5497(3)	−824(2)	8473(2)	28(1)
N(3)	6998(3)	−1295(1)	9441(2)	34(1)
N(4)	3325(3)	−1455(1)	8024(2)	35(1)
C(2)	546(3)	699(1)	5108(2)	29(1)
O(1)	1872(2)	914(1)	6138(1)	37(1)
O(2)	−18(3)	1499(1)	4253(1)	39(1)

Because the crystals of aminoguanidine monohydrochloride have recently been found to consist exclusively of the same tautomer as the hemioxalate salt crystals now studied, it seems that the aminoguanidine monocation has an intrinsic tendency to exist only in the form of that tautomer at least in the solid state and probably also in solution. The predominance of this tautomer can be explained by the strong resonance in the guanidino group, the positive charge being delocalized on three different nitrogens and probably also on the carbon atom. Other tautomers that can be envisioned for the aminoguanidine monocation (see Fig. 1c) are indeed less probable, lacking the above mentioned resonance forms.

Table 2. Selected bond lengths (Å) and angles (°) of aminoguanidine hemioxalate

N(1)-N(2)	1.412(2)
N(1)–H(1A)	0.94(3)
N(1)–H(1B)	0.85(2)
N(2)–C(1)	1.328(2)
N(2)–H(2A)	0.91(2)
C(1)–N(3)	1.320(2)
C(1)–N(4)	1.328(2)
N(3)–H(3A)	0.92(2)
N(3)–H(3B)	0.83(2)
N(4)–H(4A)	0.92(2)
N(4)–H(4B)	0.92(2)
N(2)–N(1)–H(1A)	108.5(14)
N(2)–N(1)–H(1B)	109(2)
H(1A)–N(1)–H(1B)	109(2)
C(1)–N(2)–N(1)	119.33(14)
C(1)–N(2)–H(2A)	120.6(13)
N(1)–N(2)–H(2A)	120.1(13)
N(3)–C(1)–N(4)	120.1(2)
N(3)–C(1)–N(2)	121.0(2)
N(4)–C(1)–N(2)	118.9(2)
C(1)–N(3)–H(3A)	119.3(12)
C(1)–N(3)–H(3B)	118(2)
H(3A)–N(3)–H(3B)	123(2)
C(1)–N(4)–H(4A)	116.5(13)
C(1)–N(4)–H(4B)	120.4(14)
H(4A)–N(4)–H(4B)	123(2)

Table 3. Hydrogen atom coordinates ($\times 10^4$) and isotropic displacement coefficients (Å$^2 \times 10^3$) of aminoguanidine hemioxalate

	x	y	z	U(eq)
H(1A)	7637(44)	1830(25)	8669(23)	52(6)
H(1B)	9490(44)	1085(21)	7923(22)	44(6)
H(2A)	5185(40)	560(21)	7213(21)	41(5)
H(3A)	6423(37)	−2015(20)	9858(20)	36(5)
H(3B)	8269(47)	−889(21)	9682(22)	51(6)
H(4A)	2985(39)	−2232(21)	8405(20)	41(5)
H(4B)	2366(45)	−1171(21)	7295(24)	51(6)

The structure of aminoguanidine hemioxalate is largely similar to the structures of aminoguanidine sulfate and dinitrate [29, 30] as well as to that of aminoguanidine monohydrochloride [31]. The cation is planar, the only atoms deviating markedly from the plane being the hydrogens attached to the terminal hydrazine nitrogen. In the guanidino group, all bonds between the carbon atom and the adjacent nitrogens are essentially of equal length (1.320–1.328 Å), and no bond

Table 4. Distances (Å) and angles (°) in interactions of type *XHY*

Distance H···*Y*		Angle *X*-H···*Y*	
H(3B)···N(1)	2.353 (0.022)	N(3)–H(3B)···N(1)	106.06 (1.78)
H(2A)···O(1)	1.977 (0.021)	N(2)–H(2A)···O(1)	154.30 (1.76)
H(1A)···O(2)[1]	2.285 (0.025)	N(1)–H(1A)···O(2)[1]	163.80 (1.90)
H(1B)···O(1)[2]	2.251 (0.024)	N(1)–H(1B)···O(1)[2]	163.62 (1.97)
H(3A)···O(2)[3]	1.953 (0.021)	N(3)–H(3A)···O(2)[3]	177.02 (1.69)
H(4A)···O(1)[3]	1.998 (0.022)	N(4)–H(4A)···O(1)[3]	162.20 (1.73)
H(4B)···O(2)[4]	1.973 (0.024)	N(4)–H(4B)···O(2)[4]	150.98 (1.94)

Symmetry code: [1] $x+1/2, -y+1/2, z+1/2$; [2] $x+1, y, z$; [3] $-x+1/2, y-1/2, -z+3/2$; [4] $-x, -y, -z+1$

can be considered as a localized double bond. Thus, each carbon-nitrogen bond obviously must have an approximately equal amount of double-bond character. In comparison to the previously determined structures of salts containing diprotonated aminoguanidine [29, 30], the monocation is devoid of one of the three protons attached to the terminal hydrazine nitrogen (see Fig. 1). In the aminoguanidine monocation as well as in the dication, the terminal nitrogen atom of the hydrazine moiety is clearly sp^3 hybridized, whereas the other non-hydrogen atoms must be sp^2 hybridized. The crystals of aminoguanidine hemioxalate consist of parallel stacks of planes held together by an extensive hydrogen bond network *via* the oxalate ions (Fig. 3 and Table 4). Interestingly, there is also an intramolecular hydrogen bond (2.35 Å) between the terminal hydrazine nitrogen atom N(1) and hydrogen atom H(3B) of the guanyl moiety. This explains the observed conformation around N(1) as well as the absence of an intermolecular hydrogen bond originating from H(3B).

The present results indicate that the terminal hydrazine nitrogen atom N(1) of the aminoguanidine monocation bears only two hydrogen atoms. To verify this point, a difference electron density map has been calculated from all atoms except the hydrogen atoms bound to N(1). A cross section of this map at the plane of the three maxima around N(1) is shown in Fig. 4, clearly displaying two strong

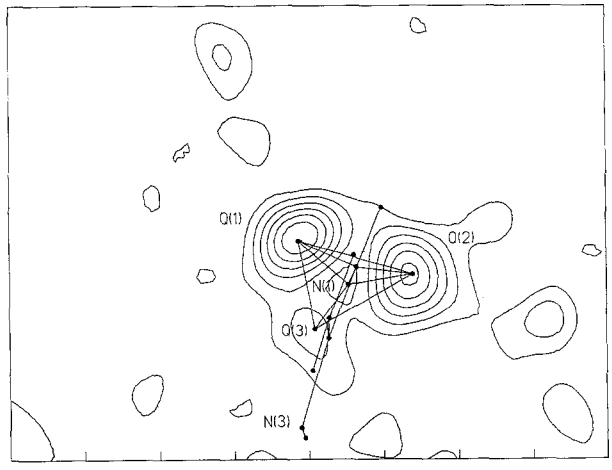

Fig. 4. Cross section of a difference electron density map at the plane of the three maxima around the terminal hydrazine nitrogen atom N(1) of the aminoguanidine monocation in the hemioxalate salt; each contour represents 0.1 $eÅ^{-3}$

maxima (the hydrogen atoms) and one far weaker maximum (the lone pair). Thus, N(1) has a free electron pair and constitutes an active nucleophile. Therefore, it is obvious that in the synthesis of amidinohydrazones the reactions between aminoguanidine and aldehydes or ketones should be performed in the *pH* range where aminoguanidine exists mainly in the form of the monocation. Even if an aminoguanidine salt containing exclusively the monocationic form of the compound is employed, the concentration of the free nucleophile will be nearly maximal. An elevation of the *pH* of the synthesis mixture to values at which a considerable proportion of aminoguanidine exists as the free base is thus totally unnecessary. The use of the monocation instead of the free base is implicated also by the fact that the protonation of the guanyl group would be expected to decrease its reactivity and thus to decrease the probability of side reactions. In the case of the dication, the concentration of the active nucleophile is, on the contrary, practically zero. We have studied the solution equilibria of aminoguanidine monohydrochloride and have found that the compound exists almost exclusively in the form of the monocation between *pH* 2 and *pH* 10. By potentiometric titrations with 0.1 *M* aqueous sodium hydroxide and 0.1 *M* aqueous hydrochloric acid at 37°C in a 0.1 *M* aqueous sodium chloride solution, the following two pK_a values have been obtained:

$$CN_4H_8^{2+} + H_2O \rightleftharpoons CN_4H_7^{+} + H_3O^{+};\ pK_{a1} = 0.7 \pm 0.2$$

$$CN_4H_7^{+} + H_2O \rightleftharpoons CN_4H_6 + H_3O^{+};\ pK_{a2} = 11.5 \pm 0.1$$

On the basis of crystallographic studies, it is obvious that the first value relates to the protonation of the hydrazine moiety and the second one to that of the guanyl moiety. Further details of the potentiometric studies will be reported elsewhere.

The intramolecular hydrogen bond between N(1) and H(3B) might be postulated to slightly decrease the nucleophilicity of N(1), but a similar slight decrease would be expected to take place also in the case of the free base, since a similar hydrogen bond will most probably exist there, too. Therefore, this aspect by no means changes the recommendations concerning the optimum *pH* in the synthesis of amidinohydrazones.

Experimental

Synthesis of aminoguanidine hemioxalate; formation of crystals

Aminoguanidine hemioxalate was prepared by dissolving 13.61 g (0.1 mol) of aminoguanidine bicarbonate (Aldrich Chemie, Steinheim, Germany) in 50 ml of water, after which 50 ml of a 1 *M* aqueous solution of oxalic acid (0.05 mol) was added. The solution was stirred for one hour at 40 °C in an open beaker. The colourless solution obtained was allowed to evaporate at room temperature until colourless single crystals were obtained.

Crystal structure determination

Information concerning X-ray data collection and structure refinement are summarized in Table 5. The crystal was mounted on a glass fibre using the oil-drop method [32]. Data were collected at 193(2) K on a Rigaku AFC-7S single crystal diffractometer using graphite-monochromatized MoK_α radiation ($\lambda = 0.71073$ Å). The cell parameters were determined by least-squares treatment of the

Table 5. Crystal data and summary of intensity data collection and structure refinement for aminoguanidine hemioxalate

Compound formula	$CN_4H_7^+ \cdot 0.5C_2O_4^{2-}$
M_r	119.12
Space group	P2(1)/n
Crystal system	monoclinic
a(Å)	4.947(1)
b (Å)	10.463(2)
c (Å)	10.400(2)
β (deg)	92.57(3)
V (Å^3)	537.8(2)
Z	4
D_{calc} ($g$cm^{-3})	1.471
F(000)	252
μ(MoK_α) (mm^{-1})	0.127
θ range (deg)	2.76 $<\theta<$26.50
Crystal size (mm)	0.30 × 0.30 × 0.25
No. of data collected	2286
No. of unique data	1090
hkl range	0 → 6, −13 → 13, −13 → 13
No. of refined parameters	102
Final R ($I>2\sigma(I)$)	$R_1 = 0.045$, w$R_2 = 0.113$ ($R_w = 1/\sigma^2(F_o^2) + (0.0611P)^2 + 0.16P$ with $P = (F_o^2 + 2F_c^2)/3$)
Goodness of fit, S	1.017
Extinction coefficient	0.059(9)
Largest remaining feature in electron density map (eÅ^{-3})	+0.23 (max), −0.28 (min)

adjusted angular settings of 25 reflections ($7° < 2\Theta < 12°$). 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 performed by the ψ-scan technique [33]. The structure was solved by direct methods [34] and refined using full matrix least-squares procedure on F^2. Hydrogen atoms were found from the difference map and were refined with isotropic temperature factors. Successive calculations and full matrix least-squares refinement with anisotropic non-hydrogen atoms and isotropic hydrogen atoms [35] led to $R = 0.045$ and $R_w = 0.113$[1].

[1] Additional material to the structure determination may be ordered from Fachinformationszentrum Karlsruhe, Gesellshaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Federal Republic of Germany, referring to the deposition number CSD-59433, the names of the authors, and the citation of the present paper.

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