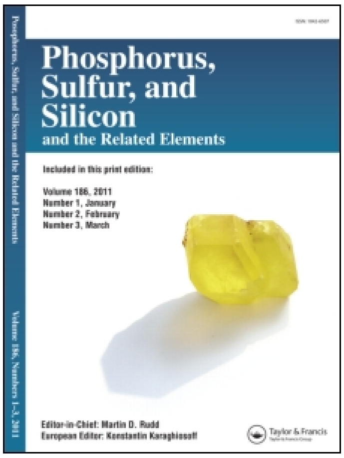

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CRYSTALLINE DIMETHYLAMINOMETHANE-DIPHOSPHONIC ACID: THE EXISTENCE OF ANHYDROUS AND MONOHYDRATE FORMS

Lawrence H. Merwin[a]; Wayne A. Dollase[ab]; Gerhard Hagele[c]; Helmut Blum[d]
[a] Bayerisches Geoinstitut, Universität Bayreuth, Bayreuth, Federal Republic of Germany [b] Department of Earth and Space Sciences, University of California, Los Angeles, CA, USA [c] Institut für Anorganische Chemie und Strukturchemie, Heinrich-Heine-Universität Düsseldorf, Düssldorf, Federal Republic of Germany [d] Henkel KGaA, Düsseldorf, Federal Republic of Germany

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CRYSTALLINE DIMETHYLAMINOMETHANE-DIPHOSPHONIC ACID: THE EXISTENCE OF ANHYDROUS AND MONOHYDRATE FORMS

LAWRENCE H. MERWIN* and WAYNE A. DOLLASE†
Bayerisches Geoinstitut, Universität Bayreuth, Postfach 10 12 51, D-8580 Bayreuth, Federal Republic of Germany

and

GERHARD HÄGELE
Institut für Anorganische Chemie und Strukturchemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, D-4000 Düsseldorf 1, Federal Republic of Germany

and

HELMUT BLUM
Henkel KGaA, Henkelstraße 67, Postfach 1100, D-4000 Düsseldorf 1, Federal Republic of Germany

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There has been some discrepancy in the literature as to whether solid dimethylaminomethanediphosphonic acid existed as the anhydrous form or the monohydrate. We report the synthesis and characterization of both forms. ^{31}P solid-state NMR data are given.

Key words: Aminophosphonates; NMR; solid; structure; dimethylaminomethanediphosphonic acid.

INTRODUCTION

As a class of compounds, the aminophosphonic acids are of interest for a wide range of reasons. From a theoretical standpoint, there are challenging aspects of structure, hydrogen bonding and the zwitterionic nature of the molecule. A number of aminophosphonates occur naturally[1] and are thought to play a role in the metabolism of certain organisms. Practically, these compounds are of interest from their possible use in the areas of medicine, agriculture and industry.

Of concern here is the compound dimethylaminomethanediphosphonic acid, which will be abbreviated as DAMDA. The correct molecular formula, as deter-

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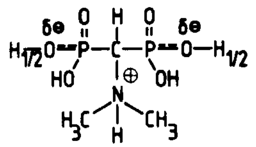
*Author to whom correspondence should be addressed.

†Permanent address: Department of Earth and Space Sciences, University of California, Los Angeles, CA 90024, USA.

mined in the diffraction study of Kulpe *et al.*,[2] is given below **1**. It will be noted that the structure in the solid is zwitterionic. This is common for the aminophosphonates, as has been demonstrated in the relevant diffraction studies of a number of related compounds.[3,4,5,6]



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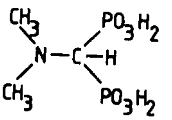
Now, there exists in the literature a discrepancy concerning the exact nature of DAMDA. Specifically, is the structure of the solid the anhydrous compound or the monohydrate? Synthetic methods for this compound have been reported in the literature twice. In 1972, Plöger and co-workers[7] reported the synthesis of DAMDA. In the work-up of the synthesis, the molecular weight, as determined by titration, is given as: expected: 219.1; found: 218. It will be noted that this is the molecular weight one would expect from the anhydrous compound; however, a footnote in Reference 7 gives the structure as that of the monohydrate, $C_3H_{13}NO_7P_2$. A second synthetic path to this compound was published by Gross and co-workers in 1976.[8] Again, the monohydrate compound is clearly the product formed. The molecular weight is given as that of the hydrated form $C_3H_{13}NO_7P_2$ (237.1). Further, the experimental values for elemental analysis are in close agreement with expected values calculated on the basis of the monohydrate structure. In contrast to these findings, however, is a single-crystal x-ray diffraction study of this material performed by Kulpe, Seidel and Szulzewsky in 1984.[2] In this paper, it is stated categorically that in contradiction to the previous literature reports, DAMDA *does not* contain crystal water and that the proper structure is that of the anhydrate, $C_3H_{11}O_6NP_2$. Which of these two positions is correct? Is the solid structure anhydrous or the monohydrate?

In fact, we intend to show that both forms exist as stable, crystalline compounds. Both forms have been prepared and characterized as the results below will indicate.

RESULTS AND DISCUSSION

For this study, dimethylaminomethanediphosphonic acid **2** was prepared by reaction of dimethylformamide, PCl_3 and H_2O according to the equation:



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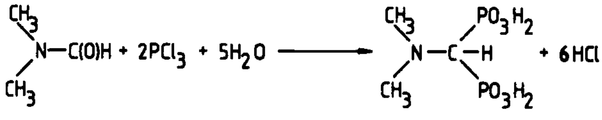
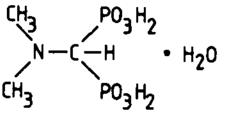


in analogy to the methods described by Plöger, Schindler, Wollmann and Worms.[7] The corresponding monohydrate **3**:



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was obtained by recrystallization of **2** from H_2O.

Both compounds were isolated as colorless crystals. The results of elemental analysis and molecular weight determinations (see experimental section below) were as expected for the anhydrous and monohydrate forms **2** and **3** respectively, proving the structures. In addition, however, we wished to further characterize these compounds in the solid-state to ensure that we were, indeed, seeing two distinct crystal forms. This characterization was carried out using the techniques of x-ray powder diffraction and solid-state NMR.

X-ray powder diffraction patterns were made of anhydrous and monohydrate forms of DAMDA using Co-Kα_1 radiation, and an entrance-beam curved-crystal Ge-monochromator which gave line widths of less than 0.1° 2θ. First, the low angle portion of the x-ray diffraction pattern of anhydrous DAMDA **2** was compared with the theoretical location of lines corresponding to the monoclinic, $P2_1/c$, unit cell reported by Kulpe *et al.*[2] for this compound. The observed pattern matched the calculated pattern exactly, indicating that the sample has, indeed, this unit cell and space group, and, furthermore, that there were no observable impurity phases present.

The powder x-ray diffraction pattern of the anhydrous and monohydrate were then compared. Examination showed that (1) the major (strongest) peaks of the two samples are entirely disparate and (2) the set of peaks corresponding to the strongest lines of the anhydrous sample are also present in the diffraction pattern of the hydrous sample but with reduced intensity. Thus, it may be concluded that the two materials are both crystalline but have quite different unit cells (and therefore may well have different crystal structures and chemical compositions), and that the monohydrate sample contains, as a minor impurity phase, a small amount of the anhydrate. (This is confirmed by solid-state NMR measurements discussed below.) Attempts to index the peaks belonging only to the hydrous crystals were not successful, but the number and separations of the peaks suggests that these crystals are likely to have low symmetry with moderate unit cell dimensions.

Phosphorus-31 cross-polarization magic angle spinning (CP/MAS) NMR spectra have also been run for the solid anhydrous and monohydrate compounds. Before detailing these results, several points concerning solid-state NMR spectroscopy need to be made. First, in high-resolution NMR spectra of solids, line multiplicity is a function of chemical equivalence in the usually understood NMR sense combined with the symmetry of the crystal environment. The ^{31}P CP/MAS spectrum of anhydrous DAMDA, for example, has two resonances. This implies two crystallographically distinct phosphorus sites in the solid-state NMR spectrum. This is in agreement with the published x-ray structure.[2] Furthermore, the width of resonance lines give some indication of sample crystallinity. Relatively narrow lines indicate crystalline samples, while noticeably broadened lines for a similar material

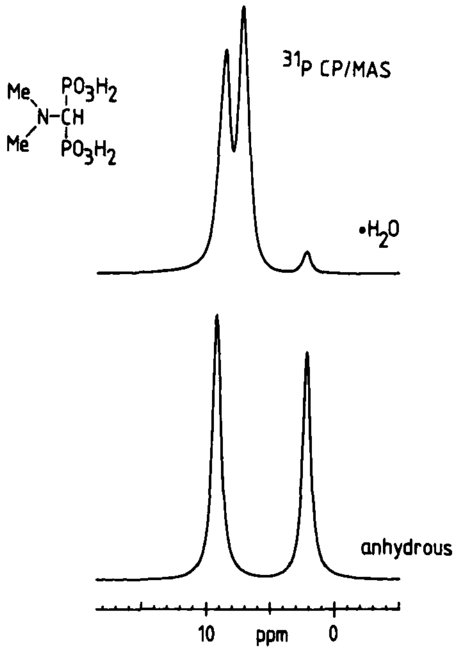

FIGURE 1 The ^{31}P CP/MAS centerband spectra of the anhydrous and monohydrate forms of DAMDA. Both spectra were obtained using the following parameters: 5 μs 90° pulse; ^{31}P contact time: 1 ms; recycle delay: 10 s; MAS rate: 3.2 kHz. Note that for both materials the intensity ratio of the lines in each spectrum is 1:1 when integrated over the complete spinning sideband manifold.[9]

may indicate a less ordered structure. Secondly, as will become apparent, the chemical shift in the solid is highly sensitive to subtle changes in local environment. Differences in structure caused by, for example, crystal water should show clear effects on the spectra. Finally, the use of CP/MAS techniques on modern instrumentation makes the solid-state NMR of organophosphorous compounds a relatively straightforward and rapid analytical technique. The spectra shown here were each obtained in six minutes.

The ^{31}P CP/MAS spectra of the anhydrous and monohydrate forms of DAMDA are shown in Figure 1. The spectrum of the anhydrous compound, which has been published previously,[9] shows two lines at $\delta_P = 9.1$ and 2.0 ppm, each having a half-height line width of 90 Hz. The intensity ratio of the two lines is 1:1 if integration is done over the complete spinning sideband manifold for the respective resonances.[9] Each of these lines correspond to one of the two crystallographically distinct phosphonic acid groups in the asymmetric unit in agreement with the published diffraction study. However, we cannot assign specifically the two resonances to the two individual stereochemical positions.

In the spectrum of the monohydrate, again two phosphorus environments in a 1:1 ratio are resolved, though with a somewhat reduced shift difference ($\delta_P = 8.4$ and 7.1 ppm, half-height linewidth for each of 120 Hz). Further, it will be noted that the linewidths for the two samples are reasonably similar. The presence of two, narrow resonances indicates two phosphorus sites in another well crystallized material consistent with the results of the powder diffraction study described above.

Now, by way of further explanation for these spectra, one may consider that the ideal DAMDA zwitterion, as for example in solution, would have a mirror plane of symmetry and consequently only one type of P-site. The NMR spectrum of the anhydrous crystals shows two well separated and equal area (if one takes into account the spinning sidebands) resonance lines. Thus, the symmetry in the solid is "broken," no doubt due to the localization of the hydrogens making the two phosphonate groups inequivalent. The smaller splitting of the hydrated compound suggests that the water of crystallization is hydrogen-bonded to the molecule in such a way as to reduce the shielding difference between the two phosphonate groups.

Further examination of the monohydrate spectrum also shows that, in addition to the main resonances, there is a small resonance at 2.0 ppm, which indicates that a small amount of the anhydrous phase (ca. 5–10%) is present in this sample (the 9.1 ppm resonance is hidden under the main band). Solid-state ^{31}P NMR can thus be used to determine both which form is present (from shift arguments) and also to determine the purity of the sample. (Solution-state NMR would not be useful in distinguishing the two solid forms because only one species is present in solution.) It should also be noted that solid-state ^{31}P NMR spectra were run again after six months and show no change in either sample, suggesting that both forms are stable under storage conditions of room temperature and atmosphere.

We would like to emphasize here the utility of the ^{31}P solid-state NMR results. It has been shown: 1) That there is a significant chemical shift difference between the lines of the anhydrous and monohydrate forms of DAMDA, and that solid-state NMR spectra may be used to identify which form is present quickly and easily. And, furthermore, that solid-state NMR spectra provide a clear indication of the presence in the sample of the opposite phase. 2) That such spectra may be used to confirm aspects concerning sample crystallinity and structure.

EXPERIMENTAL

Preparation of Dimethylaminomethanediphosphonic Acid **2**. A mixture consisting of 219 g (3 mole) of dimethylformamide and 27 ml (1.5 mole) of H_2O is dropped into 412.5 g (3 moles) of PCl_3 under stirring and nitrogen atmosphere. The rate of dropping and eventually the cooling are adjusted to maintain a temperature of about 60 to 70°C. After the reaction has subsided, a viscous, barely stirrable product results which is hydrolyzed cautiously by adding dropwise 180 ml (10 mole) of H_2O. After cooling the reaction mixture, crystals of anhydrous DAMDA are formed. These crystals were filtered, washed with acetone and dried *in vacuo*. The procedure yielded 230–250 g (70–75%) of colorless crystals with a melting point of 234°C.

Analysis: Titration of **2** vs. 0.1117 N tetramethylammonium hydroxide. Molecular mass found: 221.25 (calculated: 219.12).
Comment on the analysis by alkalimetric titration: For DAMDA the following pK_s values have been reported in the literature:

	Ref. 10	Ref. 11	Ref. 12
pK_{S1}	2.16	2.05	2.5
pK_{S2}	5.01	4.90	5.2
pK_{S3}	8.82	8.74	9.2
pK_{S4}	11.15	11.04	—

DAMDA clearly behaves as an effectively tribasic acid. On titration versus strong alkaline solution (NaOH or tetramethylammonium hydroxide), it exhibits two inflection points which correspond to the second and third acidic hydrogens respectively. The second inflection point was used to determine the analytical concentration. Our findings are consistent with the observations made in References 10 to 12.

Preparation of DAMDA Monohydrate **3**. Crystallization of **2** from water gives the monohydrate **3**. The precipitation of **3** may be completed by addition of acetone or ethanol to the aqueous phase. The resulting colorless crystals had a m.p. of 232°C and a solubility in water at 20°C of 8.6%.

Analysis: Titration of **2** vs. 0.1117 N tetramethylammonium hydroxide. Molecular mass found: 236.98 (calculated: 237.13).

C: 15.37% found (15.19% calculated), H: 5.61 (5.53), N: 5.68 (5.91), P: 26.20 (26.14).

Loss in weight by drying **3** over P_4O_{10} at 110°C *in vacuo*: 7.55% found (7.60% calculated).

NMR Analysis

The solid-state ^{31}P NMR spectra were run on a Bruker MSL-300 spectrometer operating at a field of 7 Tesla (corresponding to a ^{31}P frequency of 121.498 MHz). In both cases, cross-polarization and magic-angle spinning were used. The relevant parameters are noted in the figure caption. Phosphorus chemical shifts are indirectly referenced to 85% aqueous phosphoric acid (H_3PO_4). The secondary reference used was brushite, $CaHPO_4 \cdot 2H_2O$, the shift of which was determined to be 1.2 ± 0.1 ppm by replacement with the standard. The high-frequency-positive convention has been used.

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