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Synthesis and crystal structure of 1-(aminomethyl)vinylphosphonic acid

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ABSTRACT

A highly efficient and versatile approach to the synthesis of 1-(aminomethyl)vinylphosphonic acid, a constituent of the antibiotic A53868A, is reported. In the crystal, molecules of the acid are linked by strong, linear, symmetric hydrogen bonds involving hydrogen atoms of the phosphonic group.

1. Introduction

Antibiotic A53868A **1** is produced by fermentation of *Streptomyces luridus* NRRL 15001.[1] This tripeptide is composed of 1-(aminomethyl)vinylphosphonic acid **5**, leucine, and glycine (Fig. 1). The structure of **1** was elucidated on the basis of spectroscopic data, but the absolute configuration of the stereogenic center present in **1** is not known.[2]

Over the past decades, tremendous effort has been devoted to the development of synthetic methods for naturally occurring compounds containing a C–P bond.[3–5] However, the synthesis of both peptide **1** and its parent aminophosphonic acid **5** remains unexplored. The discovery of new synthetic sequences leading to **5** is thus important. Very recently, Loreto and co-workers reported the synthesis of diethyl 1-(ethoxycarbonylaminomethyl)vinylphosphonate.[6]

Our studies led us to discover the potential of dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate **2** in a self-catalytic Michael reaction. We have demonstrated that the conjugate addition of selected carbon and nitrogen pronucleophiles to the acrylate **2**, proceeding without the presence of any external catalyst, provides a concise and efficient entry to synthetically valuable 2-(diethoxyphosphoryl)alkanoic acids and *N*-protected-2-diethoxyphosphoryl-3-aminopropionic acids, respectively.[7–9] We have also developed a general and highly efficient method for the preparation of 1-substituted vinylphosphonates based on a Knoevenagel reaction of 2-(diethoxyphosphoryl)alkanoic acids with formaldehyde.[10] The strategic potential offered by these reactions led us to target 1-(aminomethyl)vinylphosphonic acid **5**. Herein, we report the first synthesis of 1-(aminomethyl)vinylphosphonic acid **5** that makes use of dicyclohexylammonium 2-(diethoxyphosphoryl)-acrylate **2** as the starting material.

2. Results and discussion

Scheme 1 outlines the transformation of the acrylate **2** into the acid **5**. It was anticipated that 3-phthalimido-2-(diethoxyphosphoryl)propionic acid **3** would be the most suitable intermediate on the way to aminophosphonic acid **5**. Compound **3** was obtained from acrylate **2** and phthalimide following the previously reported two-step procedure.[9] Treatment of the acid **3** with paraformaldehyde (3 equiv) in the presence of catalytic piperidine (0.3 equiv) in boiling ethanol for 20 h provided the expected vinylphosphonate **4** in 90% yield. Subsequent cleavage of the diethyl ester combined with N-deprotection in **4** was accomplished by conventional acidic hydrolysis in boiling hydrochloric acid. Using this procedure we were able to obtain the acid **5** in 80% yield.

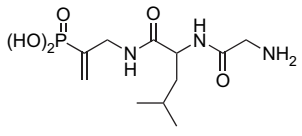

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Figure 1. Antibiotic A53868A.

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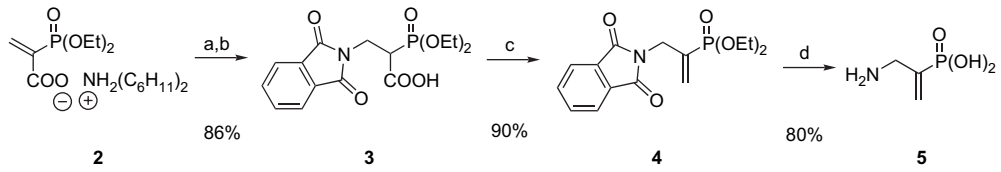

Scheme 1. *Reagents and conditions*: (a) phthalimide (1 equiv), CH_2Cl_2, rt, 48 h; (b) Dowex 50 W, acetone/water; (c) $(HCHO)_n$ (3 equiv), piperidine (0.3 equiv), EtOH, Δ, 20 h; (d) HCl (5 N), Δ, 12 h.

The structure of the acid **5** was assigned on the basis of spectroscopic data and unambiguously confirmed by X-ray crystallography.

Compound **5**, like its phosphonic acid analogues investigated by crystal structure analysis (i.e., 2-aminoethylphosphonic acid[11,12] **6**, 2-amino-1,1-difluroethylphosphonic acid[13] **7**, and 2-amino-1-fluoroethylphosphonic acid[14] **8**) adopts an antiperiplanar conformation around the C1–C3 bond. In the crystal the molecule of **5** exists as a zwitterion (Fig. 2). The N atom of the terminal amine group is protonated and adopts a virtually tetrahedral geometry with all three hydrogen atoms involved in the intermolecular hydrogen bonding (Fig. 3). The negative charge is located on the phosphonic group. The phosphorus atom is located within the center of a distorted tetrahedron with valency angles ranging in value from 104.39(5) to 113.61(5)°. On an average the O–P–O type angles [111.94(9)°] are larger than O–P–C [106.87(9)°]. This is a general feature, often encountered in phosphorus compounds, indicating a significance of repulsive Coulombic type interactions between the oxygen atoms bearing the negative charge.[15] The α-vinyl C1–C2 and N–C3 bonds are in the synperiplanar configuration in respect to the C1–C3 bond. The bond lengths are consistent with the commonly accepted data as tabulated by Allen et al.[16] and are very similar to values observed in **6**–**8**. In **5**, the α-vinyl bond is coplanar with the P–C1–C3–N moiety (rms deviation for the mean plane is 0.02 Å). However, the length of P–C1 [1.8059(11) Å], C1–C3 [1.5015(14) Å], and N–C3 [1.4822(14) Å] bonds (standard values are 1.800, 1.503, and 1.488 Å, respectively) accompanied by a classical vinyl C1–C2 bond [1.3183(17) Å, standard value 1.322 Å] indicates very limited scale of the mesomeric interactions.

This effect was further investigated with the natural bond orbital methodology.[17] Wavefunctions were calculated at the b3lyp/6-31G++(d,p) level of theory[18] for the X-ray determined coordinates of **5**–**8**. In all four compounds the main electron density delocalizations involve back-donation from the n_π lone pairs of the phosphonic oxygen atoms to the σ^* orbital of the adjacent P–C1 bond. Those interactions act against the depletion of electron density in the phosphorus originated by the neighboring electronegative oxygen atoms. The molecular conformation is stabilized by the mutual *anti* σ–σ^* stereoelectronic interactions of the P–C1 and N–C3 bonds (Fig. 4, Table 1).

In the crystal, all prone hydrogen atoms are involved in the network of hydrogen bonds (Table 2). In particular, the H4 and H5 atoms participate in the strong symmetrical, linear H-bonds linking pairs of molecules related by the symmetry centers.

3. Conclusions

In summary, an efficient synthesis of 1-(aminomethyl)vinylphosphonic acid **5** has been achieved for the first time.

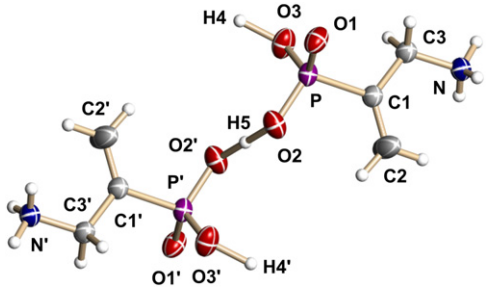

Figure 2. Centrosymmetric dimer of **5** linked by the strong symmetric hydrogen bond. Atoms H4 and H5 placed at the symmetry centers *011* and *01/21*, respectively, were refined with the site occupation factors constrained to 0.5. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are represented by spheres of an arbitrary radius. Selected geometric parameters: P–O1 1.5053(8), P–O2 1.5380(9), P–O3 1.5322(8), P1–C1 1.8059(11), N–C3 1.4822(14), C1–C3 1.5015(14), C1–C2 1.3183(17) Å; P–C1–C3–N 175.82(9), C2–C1–C3–N −4.71(9)°.

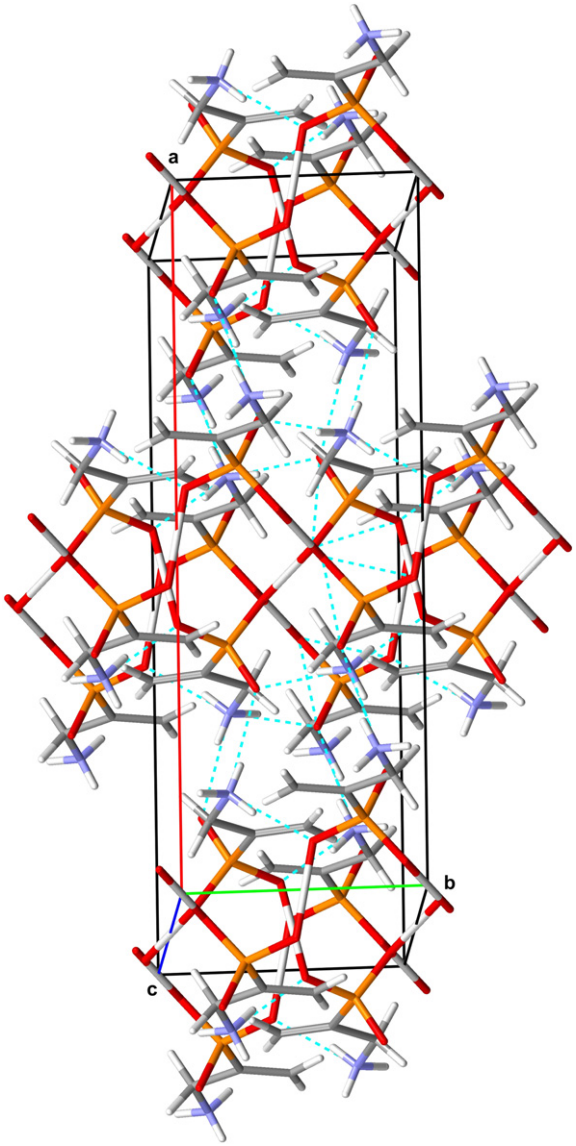

Figure 3. Crystal packing of **5**. Hydrogen bonds are indicated with dashed lines except for the symmetric hydrogen bonds involving H4 and H5 atoms of the phosphonic group. Those are displayed as covalent bonds.

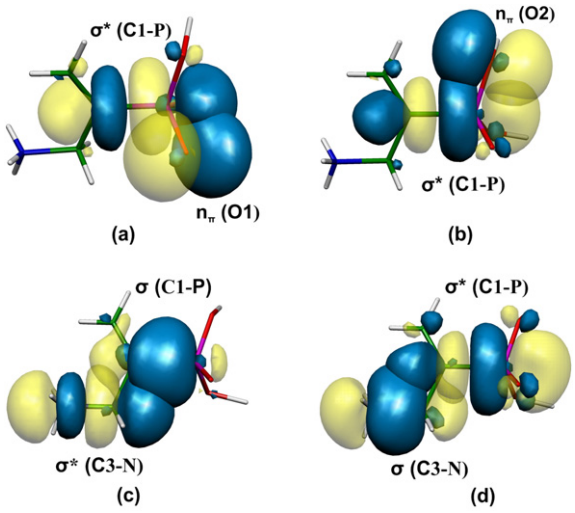

Figure 4. Natural bond orbitals involved in the stabilizing through space interactions as in **5**: (a) n_π (O1)–σ^* (P–C1); (b) n_π (O2)–σ^* (P–C1); (c) σ (C1–P)–σ^* (C3–N); (d) σ (C3–N)–σ^* (C1–P).

Table 1
Energy of the non-bonding stereoelectronic interactions (kcal mol^{-1}) calculated with the natural bond orbital theory at the b3lyp/6-31G++(d,p) level for the X-ray determined coordinates

Interaction	5	6	7	8
n_π (O1)–σ^* (C1–P)	4.9	29.2	28.5	31.3
n_π (O2)–σ^* (C1–P)	22.4	20.3	24.2	28.3
σ (C1–P)–σ^* (C3–N)	9.0	8.7	9.1	7.8
σ (C3–N)–σ^* (C1–P)	1.0	1.1	1.0	0.9

A standard orbital deletion procedure was applied.[17c]

Table 2
Hydrogen bond geometry (Å, °)

D–H···A	D–H	H···A	D···A	D–H···A
O3–H4···O3^{i}	1.232(1)	1.232(1)	2.464(1)	180
O2–H5···O2^{ii}	1.241(1)	1.241(1)	2.482(1)	180
N–H1···O1^{iii}	0.91(2)	1.86(2)	2.754(1)	169(2)
N–H2···O1^{iv}	0.78(2)	1.99(3)	2.751(2)	169(2)
N–H3···O2^{v}	0.84(2)	2.01(2)	2.839(1)	167(2)

Symmetry codes: (i) $-x$, $-y+2$, $-z+2$; (ii) $-x$, $-y+1$, $-z+2$; (iii) x, $-y+2$, $z-1/2$; (iv) $-x+1/2$, $-y+3/2$, $-z+2$; (v) x, $-y+1$, $z-1/2$.

The protocol benefits from easily available starting materials, short synthetic scheme, experimental simplicity, and high yields. The acid **5** due to different functionalities should become a useful supramolecular synthon,[19] which can act as either a donor or acceptor of hydrogen bonds with interesting topological properties. It is readily available for biological evaluation.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker DPX 250 instrument at 250.13 MHz for ^{1}H, 62.9 MHz for ^{13}C, and 101.3 MHz for ^{31}P NMR, respectively, using tetramethylsilane as internal and 85% H_3PO_4 as external standard. The multiplicity of carbons was determined by DEPT experiments. IR spectra were measured on a Specord M80 (Zeiss) instrument. Elemental analyses were performed on a Perkin–Elmer PE 2400 analyzer. Melting points were determined in open capillaries and are uncorrected. 3-Phthalimido-2-(diethoxyphosphoryl)propionic acid **3** was prepared according to the literature procedure.[9]

4.2. Procedure for the preparation of diethyl 1-(phthalimidomethyl)vinylphosphonate (4)

A mixture of acid **3** (3.55 g, 10 mmol), paraformaldehyde (0.9 g, 30 mmol), and piperidine (0.255 g, 3 mmol) in ethanol (30 mL) was heated at reflux for 20 h. The reaction progress was occasionally monitored with ^{31}P NMR spectroscopy. After the acid **3** was completely reacted the solvent was evaporated and the residue dissolved in chloroform (50 mL). The chloroform solution was washed with 5% HCl (2×5 mL) and water (2×5 mL), and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a crude product, which was purified by column chromatography (eluent: $CHCl_3$/acetone 98:2).

4.2.1. *Diethyl 1-(phthalimidomethyl)vinylphosphonate (**4**)*

Yield 2.91 g, 90%; colorless oil; R_f ($CHCl_3$/acetone 98:2) 0.34; IR (film): 1776, 1716, 1612, 1424, 1392, 1256, 1116, 1024 cm^{-1}; ^{31}P NMR (101 MHz, $CDCl_3$): δ=16.5; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.31 (dt, 6H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.4 Hz, 2×CH_3CH_2OP), 4.04–4.18 (m, 4H, 2×CH_3CH_2OP), 4.48 (dt, 2H, $^3J_{HP}$=8.5 Hz, $^4J_{HH}$=1.6 Hz, CH_2), 5.85 (ddt, 1H, $^3J_{HP}$=45.6 Hz, $^4J_{HH}$=1.6 Hz, $^2J_{HH}$=0.8 Hz, C=CH_2), 6.22 (ddt, 1H, $^3J_{HP}$=22.0 Hz, $^4J_{HH}$=1.6 Hz, $^2J_{HH}$=0.8 Hz, C=CH_2), 7.73–7.78 (m, 2H, 2×CH_{Ar}), 7.86–7.90 (m, 2H, 2×CH_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=15.8 (d, $^3J_{CP}$=6.3 Hz, 2×CH_3CH_2OP), 38.5 (d, $^2J_{CP}$=16.4 Hz, CH_2), 61.9 (d, $^2J_{CP}$=5.5 Hz, 2×CH_3CH_2OP), 123.0 (2×CH_{Ar}), 130.6 (d, $^2J_{CP}$=8.2 Hz, C=CH_2), 131.6 (2×C_{Ar}), 133.3 (d, $^1J_{CP}$=176.3 Hz, C=CH_2), 133.9 (2×CH_{Ar}), 167.1 (CO). Anal. Calcd for $C_{15}H_{18}NO_5P$: C, 55.73; H, 5.61; N, 4.33. Found: C, 55.64; H, 5.55; N, 4.23.

4.3. Procedure for the preparation of 1-(aminomethyl)-vinylphosphonic acid (5)

A mixture of phosphonate **4** (2.26 g, 7 mmol) and 5 N HCl (12 mL) was heated at reflux for 12 h. After cooling the solid was removed by filtration and the filtrate was evaporated to give an oily residue. The residue was dissolved in minimum amount of methanol and treated with an excess of propylene oxide to give the crystalline product. Recrystallization from methanol afforded **5** as white solid.

4.3.1. *1-(Aminomethyl)vinylphosphonic acid (**5**)*

Yield 768 mg, 80%; white solid, mp 244–246 °C; IR (CCl_4): 2152, 1560, 1228, 760 cm^{-1}; ^{31}P NMR (101 MHz, D_2O): δ=10.1; ^{1}H NMR (250 MHz, D_2O): δ=3.72 (d, 2H, $^3J_{HP}$=10.4 Hz, CH_2), 5.73 (d, 1H, $^3J_{HP}$=40.9 Hz, C=CH_2), 5.92 (d, 1H, $^3J_{HP}$=20.3 Hz, C=CH_2); ^{13}C NMR (62.9 MHz, D_2O): δ=39.4 (d, $^2J_{CP}$=15.6 Hz, CH_2), 125.5 (d, $^2J_{CP}$=6.4 Hz, C=CH_2), 135.5 (d, $^1J_{CP}$=169.4 Hz, C=CH_2). Anal. Calcd for $C_3H_8NO_3P$: C, 26.29; H, 5.88; N, 10.22. Found: C, 26.36; H, 5.97; N, 10.33.

4.4. Crystal and X-ray data for 1-(aminomethyl)vinylphosphonic acid (5)

Formula: $C_3H_8NO_3P$, M_w=137.07, colorless crystal 0.30×0.20×0.30 mm, a=19.1417(6), b=6.1195(2), c=12.3461(4) Å, β=121.150(1)°, V=1237.67(2) (7) Å^3, ρ_{calcd}=1.471 g cm^{-3}, λ=0.71073 Å, μ=3.66 cm^{-1}, semi-empirical absorption correction based on multiple scanned equivalent reflections (0.771<T<0.937), Z=8, crystal system: monoclinic, space group: $C2/c$, T=293 K, ω scans, 13,195 reflections collected ($\pm h$, $\pm k$, $\pm l$), $2\theta_{max}$=55.0°, 1410 unique reflections (R_{int}=0.014) and 1374 observed reflections [$I\geq 2\sigma(I)$], 103 refined parameters, refinement on F^2, R_{obs}=0.0270, R_{all}=0.0274, wR (F^2)=0.0911, max (min) residual electron density $\Delta\rho_{max}$=0.34 e Å^{-3} ($\Delta\rho_{min}$=−0.31 e Å^{-3}), X-ray data collected with Bruker SMART APEX2 CCD area detector diffractometer. Computer programs used: data collection *APEX2*,[20] data reduction

SAINT-PLUS,[21] absorption correction *SADABS*,[22] structure solution, refinement, and molecular graphics *SHELXTL*.[23] Crystallographic data (excluding structure factors) for the structure reported herein, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 669329. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Any request should be accompanied by a full literature citation.

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References and notes

1. Johnson, R. D.; Gordee, R. S.; Kastner, R. E. Larsen, S. H.; Ose, E. E. Brit. UK Patent Appl. 2,127,413, 1984; *Chem. Abstr.* **1984**, *101*, 88837r.
2. Hunt, A. H.; Elzey, T. K. *J. Antibiot.* **1988**, 802.
3. Seto, H.; Kuzuyama, T. *Nat. Prod. Rep.* **1999**, *16*, 589.
4. Fields, S. C. *Tetrahedron* **1999**, *55*, 12237.
5. Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899.
6. Loreto, M. A.; Pompili, C.; Tardella, P. A. *Tetrahedron* **2001**, *57*, 4423.
7. Krawczyk, H. *Synlett* **1998**, 1114.
8. Krawczyk, H.; Śliwiński, M. *Tetrahedron* **2003**, *59*, 9199.
9. Krawczyk, H. *Synth. Commun.* **2000**, *30*, 1787.
10. Krawczyk, H.; Koszuk, J.; Bodalski, R. *Pol. J. Chem.* **2000**, *74*, 1123.
11. Okaya, Y. *Acta Crystallogr.* **1966**, *20*, 712.
12. Trávniček, Z.; Kašpárek, F.; Marek, J.; Hendrych, J. *Acta Univ. Palacki Olomuc., Fac. Rerum Nat.* **1996**, *35*, 43.
13. Chambers, R. D.; O'Hagan, D.; Lamont, R. B.; Jain, S. C. *J. Chem. Soc., Chem. Commun.* **1990**, 1053.
14. Nieschalk, J.; Batsanov, A. S.; O'Hagan, D.; Howard, J. A. K. *Tetrahedron* **1996**, *52*, 165.
15. Gillespie, R. J.; Popelier, P. L. A. *Chemical Bonding and Molecular Geometry: From Lewis to Electron Densities*; Oxford University Press: New York, NY, 2001; p 126.
16. Allen, F. H.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *Typical Interatomic Distances: Organic Compounds*; Price, E., Ed.; International Tables for Crystallography; Kluwer: Dordrecht, 2004; Vol. C, pp 790–811.
17. (a) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899; (b) Weinhold, F.; Landis, C. R. *Valency and Bonding*; Cambridge University Press: Cambridge, 2005; Chapter 1.5; (c) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO, Version 3.1*.
18. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Wallingford, CT, 2004.
19. (a) Chisholm, J.; Pidcock, E.; van de Streek, J.; Infantes, L.; Motherwell, S.; Allen, F. H. *CrystEngComm* **2006**, *8*, 11; (b) Desiraju, G. R. *J. Mol. Struct.* **2003**, *656*, 5; (c) Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311.
20. Bruker. *APEX2, Version 2.1-4*; Bruker AXS: Madison, WI, 2006.
21. Bruker. *SAINT-PLUS, Version 7.23A*; Bruker AXS: Madison, WI, 2006.
22. Bruker. *SADABS—Bruker Nonius Area Detector Scaling and Absorption Correction, Version 2.10*; Bruker AXS: Madison, WI, 2003.
23. Sheldrick, G. M. *SHELXTL, Version 6.12*; Bruker AXS: Madison, WI, 2001.