Journal of Fluorine Chemistry 131 (2010) 278–281

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Octafluoro-4,4′-bipyridine and its derivatives: Synthesis, molecular and crystal structure

Alexey V. Gutov *, Eduard B. Rusanov, Alexey B. Ryabitskii, Alexander N. Chernega

Institute of Organic Chemistry NAS Ukraine, Murmanska st. 5, 02660 Kyiv -94, Ukraine

ARTICLE INFO

Article history:
Received 9 September 2009
Received in revised form 23 November 2009
Accepted 26 November 2009
Available online 5 December 2009

Keywords:
Perfluoro-4,4′-bipyridine
Fluorine-containing bipyridines
X-ray structure determination

ABSTRACT

The structure and chemical properties of perfluoro-4,4′-bipyridine have been studied. It was found that octafluoro-4,4′-bipyridine is a quite electron deficient system stable to the action of alkylating agents and sensitive to nucleophilic substitution of fluorine atoms. Depending on the reaction conditions and reagents used products could be obtained in which two and six fluorine atoms are substituted by nucleophiles. For all isolated compounds X-ray structure determination has been performed and the main peculiarities of the molecular and crystal structure of fluorine-containing bipyridines have been determined.

1. Introduction

Bipyridine derivatives as convenient bidentate ligands [1–5] are quite useful tectons in crystal engineering of new functional materials. Moreover, among the bipyridine derivatives there are many compounds of practical interest. For example, the viologens (4,4′-bipyridine tertiary salts) are unique photochromic materials [3]. Nevertheless, there are no known fluorine-containing viologens, whereas it is well-known that the properties of the fluorine-substituted compounds usually are noticeably different from their nonfluorinated analogues. It is common in pharmacology to substitute hydrogen with fluorine in drugs with the aim to reinforce and prolong their action. Moreover some compounds containing polyfluoropyridine moiety possess high biological activity [6].

Chemistry of pentafluoropyridine, 4-bromo-2,3,5,6-tetrafluoropyridine and other analogues is well-established [7,8]. However, the structure and the chemical properties of octafluorobipyridine have not been studied yet, although the products of its reactions are perspective for the design of small molecule scavengers [9], novel electron acceptors [10], etc. Therefore, we have investigated the structural peculiarities and chemical properties of octafluorobipyridine.

2. Results and discussion

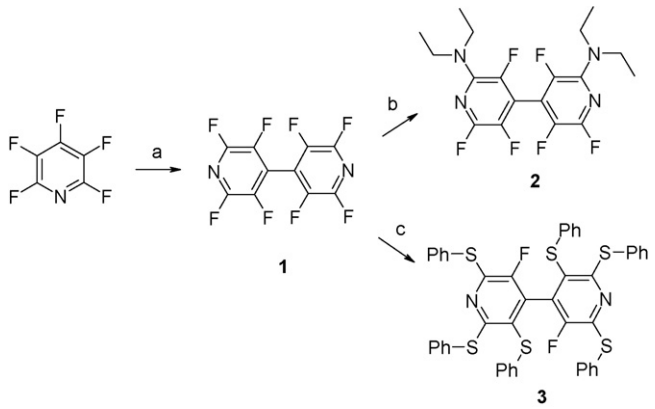
There are several methods of perfluorobipyridine (**1**) synthesis but they all need expensive reagents and equipment, in addition to a pretty low yield of the product [11]. The most convenient method of perfluorobipyridine synthesis is the reaction of perfluoropyridine with hexaethyl triamidophosphite [12] (Scheme 1). To obtain **1** we have used this reaction with some important improvements in the product isolation.

The DFT-calculations in B3LYP 6-31+G** basis set have shown that the electronic density (NBO charge) on the nitrogen in **1** (−0.47 a.u.) is quite similar to that for the unsubstituted bipyridine (−0.45 a.u.). Therefore, one would expect that **1** would react with common alkylating agents to form the fluorinated viologens. Nevertheless, we have found that **1** remained unreacted under the usual alkylation conditions (including heating) with dimethylsulphate, alkylhalogenides, triethyloxonium tetrafluoroborate and even with ethyl-*p*-toluenesulphonate and methyl triflate at 100–200 °C. Moreover **1** did not give an N-oxide with H_2O_2 in acetic or trifluoroacetic acid and did not form salts with mineral acids (HCl, H_2SO_4). Also we were unable to obtain complexes of **1** with $AgNO_3$, AgBr, $NiCl_2{\cdot}6H_2O$, $Ni(NO_3)_2{\cdot}6H_2O$, $CoCl_2{\cdot}6H_2O$, CoS_2O_6, $Cu(ClO_4)_2{\cdot}6H_2O$, CuCl, $CuCl_2$, $Zn(NO_3)_2$ and $Zn(ClO_4)_2{\cdot}6H_2O$ using different solvents and pH-values. Apparently the F-atoms have substantial effect on the electronic structure of **1** that makes N-atoms of **1** inert, though the results of DFT-calculations do not show that.

At the same time it was shown that **1** is a very electron deficient system sensitive to the nucleophilic attack (similar to pentafluoropyridine [13]) and it reacts with excess of diethylamine in boiling EtOH during 10 h and gives **2** as a main product. The similar substitution of the two fluorine atoms in the pyridine moiety was recently reported for the related 4-(perfluoroisopropyl)-2,3,5,6-tetrafluoropyridine in the reaction with diethylamine [14].

* Corresponding author. Tel.: +380 044 499 46 46; fax: +380 044 573 26 43.
E-mail address: AVGutov@mail.ru (A.V. Gutov).

0022-1139/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2009.11.022



Scheme 1. Synthesis of **1** and its reactions with the nucleophiles. (a) $P(NEt_2)_3$, Et_2O; (b) Et_2NH, EtOH; and (c) PhSH, Na_2CO_3, EtOH.

Compound **1** reacts with thiophenol in boiling EtOH in the presence of sodium carbonate for 8 h resulting in substitution of six fluorine atoms and formation of **3**.

X-ray investigation of **1** revealed that in the solid state there are two crystallographically independent molecules **A** and **B** (Fig. 1) with virtually identical bond lengths and angles (Table 1). The inter-ring dihedral angles in the two independent molecules of **1** are noticeably different (53.0° in **1A** and 64.7° in **1B**) and are in a good agreement with the results of *ab initio* quantum chemical calculations of this molecule in the free state (Table 1) demonstrating the flexibility of the fluorinated bipyridine core. In this connection it is worth to note that in the crystal of **1** there is no π-stacking interaction between the neighboring pyridine moieties.

In both molecules **1A** and **1B** the intra-ring C–C and especially C–N distances (Table 1) are somewhat (0.01–0.03 Å) shorter than in the nonfluorinated bipyridine [15]. Distribution of endocyclic angles in **1** (CNC 116.0–117.1(3)°, avg. 116.6°, NCC 123.9–124.5(4)°, avg. 124.2° and the internal angle at the ring-connecting carbon 115.6–116.7(3)°, avg. 116.3°) is similar to the unsubstituted bipyridine, alkyl substituted bipyridines and pyridines [16–19].

In the crystal structure of **2** (Fig. 2) the bipyridine core has a conformation similar to **1** (Table 1). The molecule is on the crystallographic twofold axis of rotation, thus only a half of the molecule is independent. The amino N(3) atom has trigonal-planar bond configuration (sum of bond angles is 360°) and a shortened bond length C(1)–N(3) 1.358(3) Å, that indicates the common for the aminopyridines conjugation. In contrast the neighboring distance C(1)–N(1) of 1.343(3) Å is elongated in comparison with the perfluorobipyridine and unsubstituted bipyridine, whereas the intra-ring angle at C(1) is reduced to 117.0(2)°. That leads to the opening up of the adjacent C(1)C(2)C(3) angle up to 122.8(2)°. All the other angles are usual for bipyridines. The similar angles

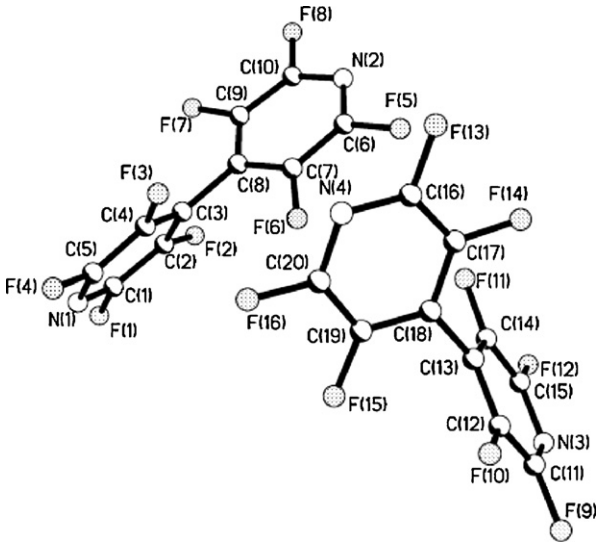


Fig. 1. Two independent molecules in the crystal structure of **1**.

distribution was previously observed in the halogenated 2-aminopyridines [20,21].

Two different-shape crystals of **3** were isolated and investigated by X-ray diffraction and it was found that in this compound molecules can adopt at least two conformations in the solid state – *opened* (**A**) and *closed* (**B**) (Fig. 3). In conformation **A**, the β-SPh substituents (i.e. at C(4), C(7) or C(9)) are situated on a significantly larger distance than in the conformation **B** (centroid–centroid distances between the corresponding phenyl substituents for **3A** and **3B** are 8.54 and 6.58 Å, respectively). Such a difference is due to the rotation of nearly 180° of SPh group around the C(4)–S(2) bond and some rotation of phenyl groups along S–Ph bond. Angles between phenyl at S(2) and S(5) planes are 60.05° for **3A** and 82.11° **3B**. However, it is interesting that the dihedral angles between pyridine rings in both structures are similar (Table 1). The conformations of α-SPh substituents (i.e. at C(1), C(5), C(6) and C(10)) are also close for **3A** and **3B** (the centroid–centroid distances of phenyl groups are similar: 4.00, 4.09 Å for **3A** and 3.92, 3.96 Å for **3B**).

The endocyclic C–C bond in **3A** is some longer than that in **3B** (Table 1). Angles distribution in the central bipyridine core of **3A** and **3B** is slightly changed compared to the symmetrical 4,4′-bipyridines, the internal angle at the carbon bearing fluorine is opened to 122.4° (averaged for both the structures). For example in the nonsubstituted 4,4′-bipyridine [15] corresponding angle is 119.2° and 119.3° in **1** averaged.

The C–F distances for all the studied compounds are similar, however they slightly increased from **1** to **3** (Table 1) with the

Table 1
Geometrical parameters of the molecules **1–3** from X-ray diffraction and [B3LYP 6-31+G**] – calculations.

Molecule	Geometry parameters				
	Inter-ring dihedral angle(°)	Ring-connecting C–C bond (Å)	C(2)-F, Å or C(12)-F (Å)	C–F (Å) avg.	N–C_{endo} avg.
1A	53.0	1.487(5)	1.340(4)	1.33	1.30
1B	64.7	1.495(5)	1.344(4)	1.34	1.31
2	59.1	1.492(4)	1.351(3)	1.35	1.33
3A	80.4	1.494(6)	1.362(5)	1.36	1.33
3B	81.9	1.475(7)	1.359(5)	1.36	1.34
1(calculated)	61.0	1.483	1.341	1.34	1.31
Unsubstituted bipyridine in crystal [13]	18.5	1.494(3)	–	–	1.33
	34.9	1.494(3)	–	–	1.33
Calculated	37.2	1.485	–	–	1.34

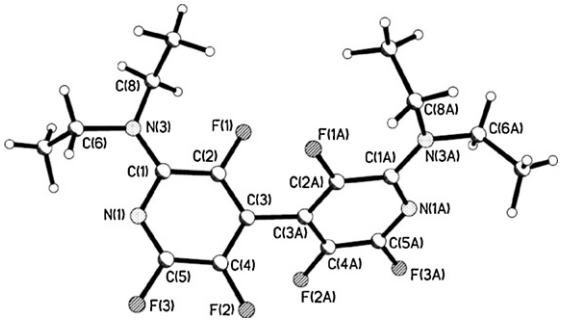


Fig. 2. The perspective view and numbering scheme of **2**. Symmetry code: $-x$, $+y$, $0.5-z$.

decreasing number of fluorine atoms and with the increasing number of donor substituents in the molecule.

It is worth to note that the energy barrier of rotation along inter-ring C–C bond is 66.73 kJ/mole for **1** and there is no π-stacking in its crystals, whereas in the unsubstituted 4,4′-bipyridine barrier of rotation along inter-ring C–C bond is only 8.61 kJ/mole, and in the solid state molecules tend to be planar and form π-stacked structure. For all the studied fluorinated bipyridines the central bipyridine core is substantially twisted on 50–80° (Table 1) and it is the scope of its lability in such systems.

3. Conclusion

It was found that octafluoro-4,4′-bipyridine is a very electron deficient system stable to the action of alkylating agents, mineral acids and susceptible to nucleophilic substitution of fluorine atoms. The isolated products are molecules in which nucleophiles substituted two and six fluorine atoms in the bipyridine core, depending on the reaction conditions and reagents. The molecular and crystal structure peculiarities of the fluorine-containing 4,4′-bipyridines have been determined.

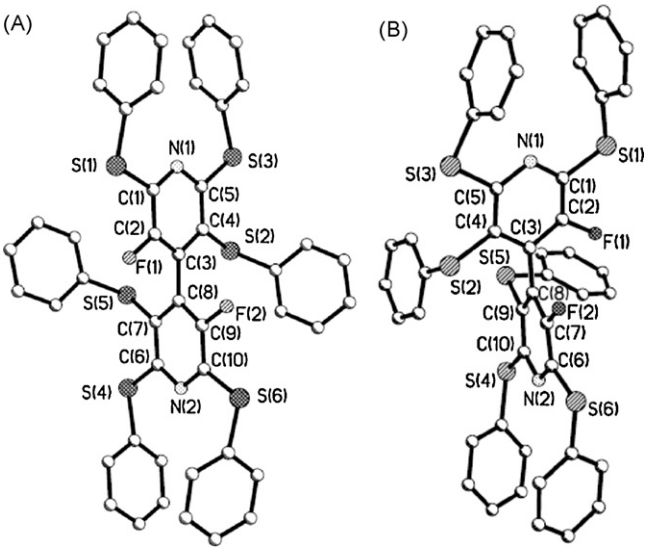


Fig. 3. A and **B** conformations of **3** in the crystal state.

4. Experimental

4.1. General

Starting materials were obtained commercially. Solvents were dried according to literature procedures. Mass spectra were recorded on the Agilent 1100 LC/MS. NMR spectra were recorded on the Bruker spectrometer, 282.2 MHz. Melting points were recorded at the atmospheric pressure.

Table 2
Data collection, structure solution and refinement parameters.

Compound	**1**	**2**	**3A**	**3B**
Empirical formula	$C_{10}F_8N_2$	$C_{18}H_{20}F_6N_4$	$C_{46}H_{30}F_2N_2S_6$	$C_{46}H_{30}F_2N_2S_6$
Formula weight	300.11	406.38	841.08	841.08
Crystal system	triclinic	monoclinic	monoclinic	monoclinic
Space group	*P*-1	*C* 2/*c*	*P* $2_1/n$	*P* $2_1/n$
Unit cell dimensions (Å and°)				
a	10.082(6)	25.269(2)	18.2214(14)	14.038(4)
b	10.533(9)	8.7702(11)	11.6368(9)	17.659(4)
c	11.777(5)	9.0067(10)	19.4795(17)	16.886(5)
α	66.49(5)	90.0	90.0	90.0
β	83.75(4)	109.606(6)	97.440(2)	105.957(16)
γ	65.67(6)	90.0	90.0	90.0
Volume (Å^3)	1042.7(14)	1880.3(4)	4095.6(6)	4024.9(18)
Z	4	4	4	4
d_{calc} (g/cm^3)	1.91	1.44	1.36	1.39
μ(Mo-K$_\alpha$) (mm^{-1})	0.217	0.129	0.379	0.386
F(000)	584	840	1736	1736
θ Range for data collection (°)	1.9–25.0	1.7–28.4	2.0–25.1	1.9–26.5
Limiting indices	$0\le h\le 11$ $-11\le k\le 12$ $-13\le l\le 13$	$-33\le h\le 30$ $-6\le k\le 11$ $-10\le l\le 12$	$-20\le h\le 21$ $-13\le k\le 13$ $-23\le l\le 14$	$-15\le h\le 17$ $-21\le k\le 20$ $-15\le l\le 21$
Reflections: collected/unique	3893/3664	6186/2309	22110/7110	16673/8152
R(int)	0.017	0.021	0.062	0.081
GOF	1.087	1.090	0.966	0.922
Final *R* indices:				
R(F)	0.049	–	–	–
*R*1(F)	–	0.056	0.081	0.066
*R*w(F)	0.054	–	–	–
w*R*2(F^2)	–	0.179	0.151	0.113
Largest diff. peak/hole (e/Å^3)	0.23/−0.27	0.19/−0.16	0.45/−0.23	0.22/−0.27
CCDC number	740216	740217	740218	740219

The calculations of the equilibrium molecular geometry of **1** in the ground state were performed by using the Gaussian 98 software [22]. The optimisation procedure has included consecutively the calculation in the AM1 method (as an initial approximation), then Hartree–Fock (HF) with different basis sets (3–21G**, 6–31+G**) and finally the DFT Becke3LYP method with 6–31+G** basis set. After finishing of the geometry optimisation procedure, force constants and the resulting vibrational frequencies were calculated. The charges at atoms were obtained using the Natural Bond Orbital analysis (NBO).

4.2. Crystal structure determination

The single crystals were grown from ethanol (**1**, **2**) or dimethylformamide (**3**). All crystallographic measurements were performed at room temperature on a CAD-4-Enraf-Nonius (for (**1**)) and a Bruker Apex II CCD diffractometer using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). Structures were solved using SHELXS-97 [23] and refined using full-matrix list squares based on F^2 in SHELXL-97 [24] apart from **1** structure which was solved and refined using CRYSTALS program package [25]. Hydrogen atoms were placed at calculated positions. The main crystallographic parameters are summarized in Table 1. Full crystallographic details for the compounds studied have been deposited at the Cambridge Crystallographic Data Centre (CCDC numbers – Table 2).

4.3. Synthesis of compounds

4.3.1. Perfluoro-4,4′-bipyridine (1)

1.478 g (0.00874 mol) of pentafluoropyridine was dissolved in 10 ml of anhydrous ether and cooled to −10 °C. 1.08 g (0.00437 mol) of hexaethyltriamidophosphite in 5 ml of ether was added during 1 h. The mixture was stirred at −10 °C for 10 h and additional 10 h at the room temperature. Then diluted hydrochloric acid was added to the mixture. The ether layer was separated, washed with water and dried over sodium sulphate. The solvent was removed in vacuum and the product was distilled (70 °C at 0.4 Torr). Yield 1.1 g (84%) of white solid, m.p. 83 °C. ^{19}F NMR (282.2 MHz, CCl_3F): δ −89.4 (m, 4F, F-3, F-5, F-3′, F-5′), −138.1 (m, 4F, F-2, F-6, F-2′, F-6′).

4.3.2. 2,2′-Di-N,N′-diethylamino-3,3′,5,5′,6,6′-hexafluoro-4,4′-bipyridine (2)

0.1 g of **1** was refluxed with 0.1 g (excess) of diethylamine for 10 h in 1 ml of EtOH. The progress of the reaction was monitored by the LC–MS. Then the mixture was diluted with water, filtered and air-dried. The recrystallization from cyclohexane afforded 0.068 g (50%) of **2** as a white solid. m.p. 67 °C. ^{19}F NMR (282.2 MHz, CCl_3F): δ −93.1 (m, 2F, F-5), −135.9 (d, 2F, J = 32.3 Hz, F-6), −158.1 (d, 2F, J = 24.3 Hz, F-3).

4.3.3. 3,3′-Difluoro-2,2′,5,5′,6,6′-hexaphenylthio-4,4′-bipyridine (3)

0.05 g of **1** was refluxed with stirring for 8 h in 1 ml of EtOH with 0.15 g (excess) of thiophenol and 0.15 g (excess) of sodium carbonate. The progress of the reaction was monitored by LC–MS. The mixture was diluted with water, filtered and the precipitate was recrystallized from dimethylformamide. The yield of **3** as yellow crystals was 0.06 g (43%) m.p. 63 °C. ^{19}F NMR (282.2 MHz, CCl_3F): δ −125.2 (s, 2F, F-3).

Acknowledgements

The authors are grateful to Yu.L. Yagupolskii, L.M. Yagupolskii and Yu.G. Shermolovich for fruitful discussions.

References

[1] P.S. Wheatley, A.J. Laugh, G. Ferguson, C. Glidewell, Acta Crystallogr. C 55 (1999) 1489–1492.
[2] G.R. Lewis, A.G. Orpen, J. Chem. Soc. Chem. Commun. (1998) 1873–1874.
[3] P.M.S. Monk, The Viologens: Physicochemical Properties, Synthesis, and Applications of the Salts of 4,4′-Bipyridine, John Wiley & Sons, New York, 1998.
[4] O.M. Yaghi, H. Li, C. Davis, D. Richardson, T.L. Groy, Acc. Chem. Res. 31 (1998) 474–484.
[5] T.R. Musgrave, C.E. Mattson, Inorg. Chem. 7 (1968) 1433–1436.
[6] P.L. Coe, A.J. Rees, J. Whittaker, J. Fluorine Chem. 107 (2001) 13–22.
[7] R.D. Chambers, P.R. Hoskin, G. Sandford, D.S. Yufit, J.A.K. Howard, J. Chem. Soc. Perkin 1 1 (2001) 2788–2792.
[8] J.A. Christofer, L. Brofy, S.M. Lynn, D.D. Miller, L.A. Sloan, G. Sandford, J. Fluorine Chem. 129 (2008) 447–454.
[9] C.J. Gilmore, D.D. MacNicol, A. Murphy, M.A. Russell, Tetrahedron Lett. 25 (1984) 4303–4306.
[10] J.R. Tucker, M. Gingras, H. Brand, J.-M. Lehn, J. Chem. Soc. Perkin 1 2 (1997) 1303–1307.
[11] R.D. Chambers, W.K.R. Musgrave, C.R. Sargent, Tetrahedron 37 (1980) 591–595.
[12] L.N. Markovskii, G.G. Furin, Yu.G. Shermolovich, O.N. Tychkin, G.G. Yakobson, Russ. J. Gen. Chem. 49 (1979) 464–468.
[13] A. Baron, G. Sandford, R. Slater, D.S. Yufit, J.A.K. Howard, A. Vong, J. Org. Chem. 70 (2005) 9377–9381.
[14] R.D. Chambers, M.A. Hassan, P.R. Hoskin, A. Kenwright, P. Richmond, G. Sandford, J. Fluorine Chem. 111 (2001) 135–146.
[15] N.M. Boag, K.M. Koward, A.C. Jones, M.E. Pemble, J.R. Thomson, Acta Crystallogr. C 55 (1999) 672–674.
[16] A. Gourdon, Acta Crystallogr. C 49 (1993) 1011–1013.
[17] P. Sehnal, P. Holy, M. Tichy, J. Zavada, I. Cisarova, Collect. Czech. Chem. Commun. 67 (2002) 1236–1246.
[18] I.G. Phillips, P.J. Steel, Aust. J. Chem. 48 (1995) 1617–1624.
[19] G.R. Clark, G.J. Palenik, J. Am. Chem. Soc. 94 (1972) 4005–4009.
[20] H. Zheng, Y. Liu, D. Xu, Z. Xu, Acta Crystallogr. E 62 (2006) o3101–o3102.
[21] L.I. Goryunov, V.D. Shteingarts, J. Grobe, B. Krebs, M.U. Triller, Z. Anorg. Allg. Chem. 628 (2002) 1770–1779.
[22] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Cui.F Q., A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 98, Gaussian Inc., Pittsburgh, PA, 2001.
[23] G.M. Sheldrick, Acta Crystallogr. A 46 (1990) 467–473.
[24] G.M. Sheldrick, SHELXL-97, Computer Program for Crystal Structure Refinement, University of Göttingem, 1997.
[25] D.J. Watkin, C.K. Prout, J.R. Carruthers, P.W. Betteridge, CRYSTALS, Issue 10, Chemical Crystallography Laboratory, University of Oxford, Oxford, 1996.