The structure of 2,4,6-tris[di(*tert*-butoxycarbonyl)methylidene]-hexahydro-1,3,5-triazine

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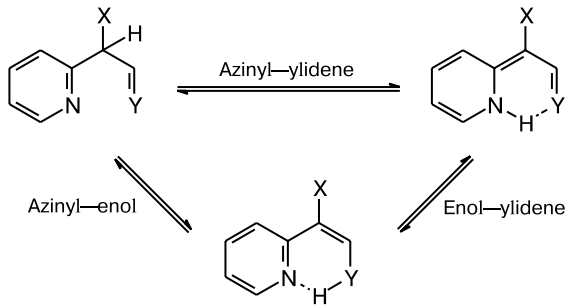
The structure of 2,4,6-tris[di(*tert*-butoxycarbonyl)methylidene]hexahydro-1,3,5-triazine was studied by quantum chemistry, NMR and IR spectroscopy, and X-ray diffraction. This compound exists exclusively in the hexahydro-1,3,5-triazine form both in solution and in the solid phase, although due to the loss of the aromatization energy, this structure should be less stable than a 1,3,5-triazine structure. The formation of strong intramolecular hydrogen bonds confirmed by NMR and IR spectroscopy and X-ray diffraction data may be a main reason for stabilization of the hexahydro-1,3,5-triazine isomer.

Key words: prototropic tautomerism, 2,4,6-tris[di(*tert*-butoxycarbonyl)methylidene]hexahydro-1,3,5-triazine, structure, ^{1}H and ^{15}N NMR spectra, X-ray diffraction, semiempirical quantum chemical calculations.

A specific feature of substituted methylazines is prototropic tautomerism, which determines the structure of these compounds and affects the reactivity. The azinyl—ylidene tautomerism of a number of methyl-substituted six-membered N-heterocycles has been discussed in detail previously.[1,2] It was shown that an increase in the CH-acidity of α- or γ-methyl substituents caused by the introduction of acceptor groups results in predominance of the polar ylidene tautomer. All other factors being the same, an increase in the solvent polarity also leads to a higher content of the ylidene tautomer. In the presence of keto or aldehyde groups in the side chain (β-oxoalkylazines), keto—enol tautomerism occurs along with the azinyl—ylidene tautomerism (Scheme 1).[1,3] The energy range corresponding to a comparable tautomer contents is 0—5 kcal mol^{-1}; according to spectroscopy, only one tautomer exists in many cases, which means that tautomerism is practically missing.[1]

Scheme 1



Y = O, NR, S

In the 1,3,5-triazine series, compounds containing one di(alkoxycarbonyl)methyl group are believed to be aromatic.[4,5] According to available data,[6—8] bis[di(alkoxycarbonyl)methyl]-1,3,5-triazines exist in the ylidene form; however, their structure was estimated only on the basis of ^{1}H NMR spectra without taking into account the possibility of existence of the enol form[9] and detailed investigation. Hydroxy-1,3,5-triazines with one or two di(alkoxycarbonyl)methyl groups exist only in the hexahydrotriazine form.[10] The data on the structure of 2,4-dimethoxy-6-(cyanoethoxycarbonylmethyl)-1,3,5-triazine presented in various sources are contradictory.[1] 2,4,6-Tris[di(alkoxycarbonyl)methyl]-1,3,5-triazines are known to exist in solution as hexahydrotriazine (ylidene) tautomers, *i.e.*, 2,4,6-tris[di(alkoxycarbonyl)methylidene]hexahydro-1,3,5-triazines.[5,10,11] No data on the existence of aromatic tautomers of these compounds or the equilibrium

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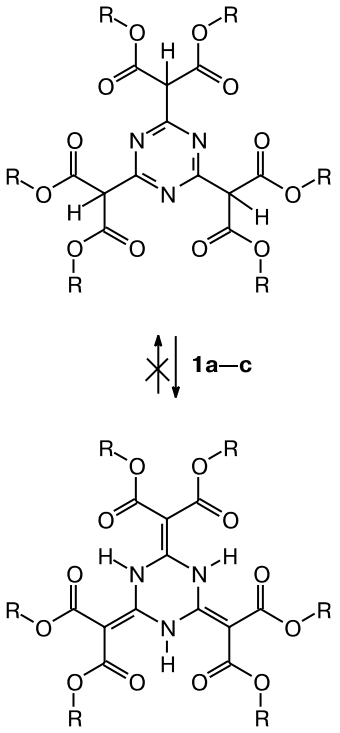
between the aromatic and ylidene forms have been reported. The corresponding methyl, ethyl, and *tert*-butyl derivatives **1a—c** are described; however, no data on their structures in the solid phase are available. The presence of only hexahydrotriazine isomers in solution (Scheme 2) can be attributed to specific interactions with the solvents and also to intra- or intermolecular hydrogen bonds.

Scheme 2



R = Me (**a**), Et (**b**), Bu^t (**c**)

One can also suggest that the electron-withdrawing alkoxycarbonyl substituents play a crucial role in the stabilization of the hexahydrotriazine form of these compounds. An approximate calculation of the energies for the aromatic and hexahydrotriazine tautomers of the unsubstituted 2,4,6-trimethyl-1,3,5-triazine (using average bond energy values) shows that even without allowance made for the aromatization energy of 1,3,5-triazine, which is equal to ~40 kcal mol^{-1} (43 kcal mol^{-1} (see Ref. 12), 44.9 kcal mol^{-1} (see Ref. 13)), the hexahydrotriazine (ylidene) structure is thermodynamically less stable by ~45—62 kcal mol^{-1}. In the series of benzene derivatives (phenylmalonic esters), no isomerism of this type is observed. Thus, the replacement of hydrogen atoms in 2,4,6-trimethyl-1,3,5-triazine by three di(alkoxycarbonyl)methyl groups gives rise to a nonaromatic hexahydrotriazine form, which is itself a rather nontrivial fact. Interestingly, the NMR spectra of symmetrically substituted tris(nitromethyl)triazines[14] and tris[(alkoxycarbonyl)methyl]triazines[15] contain absolutely no signals for the hexahydrotriazine form. One can say that the 2,4,6-trimethyl-1,3,5-triazine skeleton responds in a special way to the number and nature of substituents in the methyl groups.

Compounds **1a—c** are highly reactive and can be used to prepare various 2,4,6-trimethyltriazine derivatives,[16] as they react with electrophilic reagents (halogens, acetyl nitrate) only at the carbon atom of the *exo*-methylene group under mild conditions and in high yield.

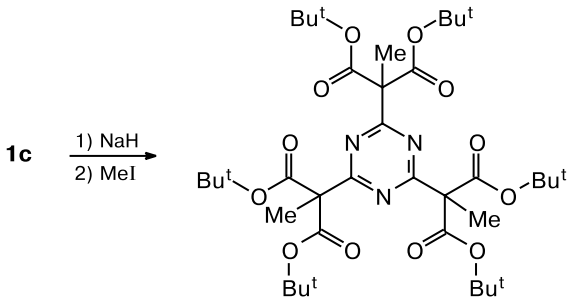
NMR spectroscopy is widely used to determine the tautomer structures in the series of azaheterocycles. It was found[1] that polar solvents stabilize the ylidene form, while the less polar aromatic form predominates in nonpolar solvents. We studied the effect of the solvent polarity on the pattern of the NMR spectra of compound **1c** in deuterochloroform, deuteroacetone, and in a deuterochloroform—DMSO mixture. Compound **1c** has a rather simple ^{1}H NMR spectrum consisting of two narrow signals at δ 1.05 and 12.95 with a 18 : 1 intensity ratio in any of the solvents used. The ^{15}N NMR spectrum (deuterochloroform, one signal at δ –271.5, $^1J_{N,H}$ = 95.9 Hz) attests in favor of the hexahydrotriazine form. Comparison of the IR spectra of the crystalline phase (a KBr pellet) and a CCl_4 solution of compound **1c** showed no shift of the N—H stretching band, which implies then same nature of the hydrogen bond in the solid state and in solution. On substantial dilution (from $1 \cdot 10^{-3}$ to $1 \cdot 10^{-5}$ mol L^{-1}), no band for free NH groups appears, which is indicative of a chelating character of the hydrogen bond in this molecule. The characteristic signals of the triazine form (1534 cm^{-1}) are totally missing from the IR spectra. The spectral pattern attests to pronounced conjugation in the molecule, in particular, a substantial frequency shift and abnormally low intensity of the carbonyl stretching band (1583 cm^{-1}) and a pronounced increase in the intensity of the C=C stretching band (1601 cm^{-1}). The presence of NH groups was detected by the weak band overlapping with the C—H vibrations (2960 cm^{-1}) only upon comparison of the IR spectra of hexahydrotriazine **1c** with the spectrum of related compound **2** prepared by methylation of the initial hexahydrotriazine (Scheme 3) and not subject to azinyl—ylidene tautomerism.

Quantum chemical calculations are commonly used to determine thermodynamic or other characteristics of substances if these are difficult to obtain experimentally. In order to theoretically evaluate the relative stability of aromatic and ylidene isomers **1c**, we carried out semiempirical calculations of the enthalpy of formation (ΔH_f°), dipole moments (μ), energies of the frontier molecu-

Table 1. Enthalpies of formation (ΔH_f°), dipole moments (μ), HOMO (E_{HOMO}) and LUMO (E_{LUMO}) energies, the energy gap between them (Δ), and total electronic energies (E_{tot}) of compound **1c** in the triazine (TF) and hexahydrotriazine (HTF) forms according to quantum chemical calculations by various methods

Parameter	AM1		MINDO/3		MNDO		PM3	
	TF	HTF	TF	HTF	TF	HTF	TF	HTF
ΔH_f° /kcal mol^{-1}	−492.55	−502.45	−609.35	−639.11	−457.49	−436.79	−524.14	−522.37
μ/D	4.42	0.00	4.82	1.58	5.80	0.90	0.04	0.14
E_{HOMO}/	−10.873/	−9.342/	−8.150/	−8.667/	−11.242/	−9.493/	−10.679/	−8.990/
E_{LUMO}/eV	−0.858	−1.066	0.110	−0.643	−1.035	−0.881	−0.851	−1.081
Δ/eV	10.015	8.276	8.260	8.024	10.207	8.612	9.828	7.909
E_{tot}/eV	−9861.99549	−9862.42493	−9728.75338	−9729.91355	−9899.89325	−9729.91355	−9258.38715	−9158.31069

Scheme 3



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lar orbitals (HOMO and LUMO), the energy gap between them (Δ), and the total electronic energies (E_{tot}) for compound **1c** in the triazine and hexahydrotriazine forms using the MOPAC software[17] (Table 1) and the density functional theory (DFT) with the B3LYP hybrid potential[18] and the standard valence-split 6-31G* basis set.

The resulting ΔH_f° values attest to a higher thermodynamic stability of the hexahydrotriazine tautomer according to AM1 (by 9.9 kcal mol^{-1}) and MINDO/3 (by 29.76 kcal mol^{-1}) calculations or the triazine tautomer according to MNDO (by 20.7 kcal mol^{-1}) and PM3 (by 1.77 kcal mol^{-1}) data. The smaller energy gap (Δ) between the frontier MO found for hexahydrotriazine isomer (data from all semiempirical methods) suggests that this isomer is more reactive in orbitally controlled reactions than the triazine form of compound **1c**. Generally, the dipole moments were higher for the triazine form than for the hexahydrotriazine form when calculated by any of the methods used except for PM3. This result is inconsistent with the known view on the higher polarity of the ylidene forms.[1]

The results of DFT calculations with the 6-31G**/3-21G basis set distinguish the hexahydrotriazine tautomer as the most stable one (the total energy of this form is 23.82 kcal mol^{-1} lower than that for the aromatic structure).

The calculations of the formation enthalpies of the tautomers in the liquid phase based on the additive schemes[19] indicate a higher thermodynamic stability of the triazine form **1c** (ΔH_f° = −647.1 kcal mol^{-1} *vs.* ΔH_f° = −592.5 kcal mol^{-1} for the hexahydrotriazine structure). Thus, the calculation results do not provide unambiguous conclusion of which of the two forms is thermodynamically preferred.

The structure of compound **1c** in the solid phase was determined by X-ray diffraction. The central part of molecule **1c** is nearly planar (Fig. 1). Analysis of the molecular packing in the crystal (Fig. 2) indicates the absence of intermolecular hydrogen bonds; however, intramolecular hydrogen bonds in which each of three hydrogen atoms is in contact with two carbonyl oxygen atoms can be clearly seen. According to their length, these hydrogen bonds (1.9—2.1 Å) can be assigned to medium-strength ones

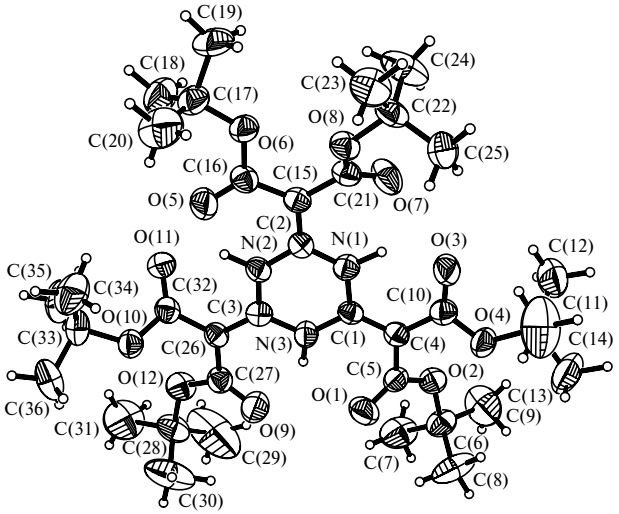

Fig. 1. Structure of hexahydrotriazine **1c** according to X-ray diffraction.

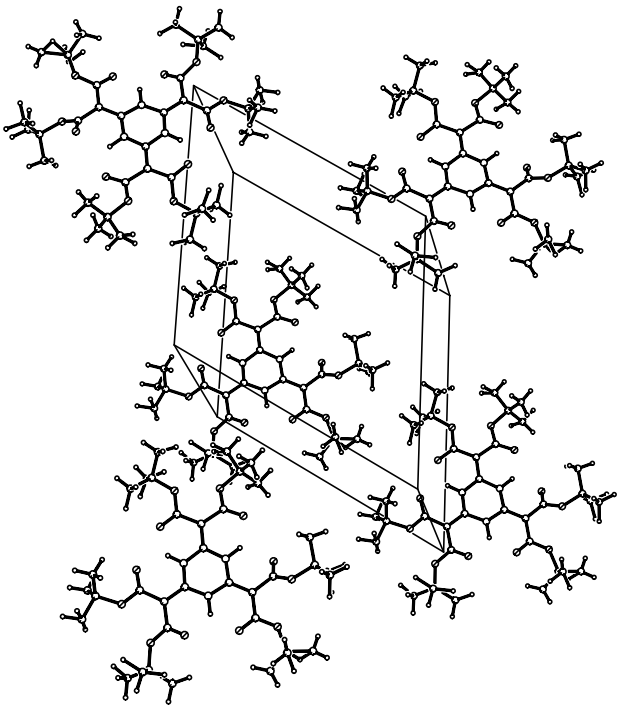

Fig. 2. Fragment of the packing of molecules **1c** in the crystal.

(length 1.5—2.2 Å, energy 5—20 kJ mol^{-1}, the angle between the bonds is close to 180°). Estimation of their energy from the relation[20]

$$\Delta G = 1.88n \pm 0.7f,$$

where n is the number of hydrogen bonds, f is the number of attractive (repulsive) interactions, gives ΔG of 11.3 to 9.2 kcal mol^{-1}. Note that this energy is close to the energy difference between the hexahydrotriazine and triazine isomers of **1c** found by AM1 calculations.

The presence of six intramolecular bridging O...H(N)...O hydrogen bonds and the absence of intermolecular hydrogen bonds (according to X-ray diffraction and IR spectroscopy) is a rather rare situation. Note that intramolecular O—H hydrogen bonds weaken the ring N—H bonds (as also indicated by IR and NMR spectroscopy). Thus the chemical shift and the spin-spin coupling constant (δ −271.5, $^1J_{N,H}$ = 95.9 Hz) are close to the corresponding values for amides rather than amines. The form and frequency of the NH group vibrations in the IR spectra also attest to their unusual nature (chelation retained upon high dilution).

For comparison, data on the bond lengths and angles in the molecules of known hexahydrotriazine and triazine compounds are presented in Table 2.

The bonds and angles in the cyanuric acid dimer[23] (N—H...O 1.80 Å, N...O 2.78 Å, angles N—H...O 179°) are almost identical to those in compound **1c**. Cyanuric acid is known (X-ray diffraction) to exist in the keto form (hexahydrotriazine) as a dimer bound by strong hydrogen bonds.[24] Nevertheless, the spectrum exhibits bands at 1535—1560 cm^{-1} and 784—810 cm^{-1} typical of the aromatic 1,3,5-triazine ring together with the bands characteristic of C=O (1695—1720 cm^{-1}) and NH groups (2828—2907 cm^{-1}). In compound **1c**, no intermolecular hydrogen bonds are present.

The data obtained suggest that the presence of intramolecular hydrogen bonds (N—H...O=C) is a principal reason for the stability of the hexahydrotriazine isomer of compound **1c** both in solution and in the solid phase (this can be called a "proton lock"). Note that judging by IR and NMR spectroscopy and X-ray diffraction data, the di(alkoxycarbonyl)methylidene group affects the 1,3,5-triazine ring similarly to an oxygen atom, thus converting the triazine ring into a hexahydrotriazine one. Transformations of this type caused by recognition and response of the molecule to a change in the environment (in this case, the response of 1,3,5-triazine to the change in the structure of exocyclic substituents) could find diverse applications in the control of properties (change in the reactivity, structure, solubility, *etc.*) of 1,3,5-triazine derivatives.

Experimental

Compounds **1c** and **2** were synthesized by reported procedures.[11,25] IR spectra were recorded on a Specord M82 spectro-

Table 2. Geometric parameters of some 1,3,5-triazines and 1,3,5-hexahydrotriazines according to published data[13,21,22]

Structure	Bond length/Å		Angle/deg	
	C—N	C=N	C—N—C	N—C—N
1,3,5-Triazine	1.319	1.319	113.2	126.8
2,4,6-Trichloro-1,3,5-triazine	1.325	1.325	112.7	127.4
2,4,6-Tris(dimethylamino)-1,3,5-triazine	1.345	1.345	112.7	127.3
2,4,6-Trimethylhexahydro-1,3,5-triazine	1.47	—	113.2	126.8
Cyanuric acid	1.37	—	124.6	115.4
2,4,6-Trimethoxy-1,3,5-triazine	1.311—1.344	—	113.3	126.8
1c	1.354—1.369	—	124.1—125.0	115.1—115.3

Table 3. Crystal data and X-ray experiment details for compound **1c**

Parameter	**1c**
Formula	$C_{36}H_{57}N_3O_{12}$
Molecular weight	723.87
Space group	$P\bar{1}$
a/Å	9.708(3)
b/Å	15.725(3)
c/Å	16.070(4)
α/deg	60.82(2)
β/deg	83.63(2)
γ/deg	76.49(3)
V/Å^3	2083.04(15)
Z	2
d_{calc}/g cm^{-3}	1.154(6)
μ/cm^{-1}	0.086
Scanning range over θ/deg	23.05
The number of measured reflections (R_{int})	5854
The number of reflections with $I > 2\sigma(I)$	3556
The number of refined parameters	689
R_1 ($I > 2\sigma(I)$)	0.070
wR_2	0.24

photometer, and ^{1}H and ^{15}N NMR spectra were measured on Bruker AM-300 and Bruker DRX-500 instruments using Me_4Si as the internal standard (^{1}H) or $MeNO_2$ as the external standard (^{15}N).

The single crystals of compound **1c** were obtained by crystallization from ethanol on slow cooling. X-Ray diffraction experiment was carried out on a KM-4 diffractometer (KUMA-Diffraction, graphite monochromator, λ(Mo-Kα) = 0.71073 Å, 293 K, ω/2θ-scan mode). The crystal data and main refinement parameters for compound **1c** are summarized in Table 3. No absorption corrections were applied. The positions and thermal parameters of nonhydrogen atoms were refined in the isotropic and then in the anisotropic approximation by the full-matrix least-squares methods. The positions of hydrogen atoms were determined in a difference Fourier syntheses and then refined using the DFIX program. The C—C bonds in the *tert*-butyl groups were also refined using the DFIX program due to the great thermal vibrations of the terminal methyl groups. The calculations were carried out using the SHELX-97 program package.[26,27]

2,4,6-Tris[di(*tert*-butoxycarbonyl)methylidene]hexahydro-1,3,5-triazine (1c). ^{1}H NMR ($CDCl_3$), δ: 12.95 (s, 3 H, NH); 1.05 (s, 54 H, CMe_3). ^{15}N NMR ($CDCl_3$), δ: −271.5 (d, NH, $^1J_{N,H}$ = 95.9 Hz). IR (KBr), ν/cm^{-1}: 3009, 2984, 2936 (CH_3); 2967 (NH); 1686, 1669, 1246, 1158 (O—C=O); 1602 (C=C); 1540.

2,4,6-Tris[1,1-di(*tert*-butoxycarbonyl)ethyl]-1,3,5-triazine (2). IR (KBr), ν/cm^{-1}: 3005, 2982, 2973 (CH_3); 1746, 1732, 1280, 1121, (O—C=O); 1540, 1366, 777 (triazine).

Quantum chemical calculations were carried out using the MOPAC[17] and GAUSSIAN 98[28] program packages at the Computation Center of the N. D. Zelinsky Institute of Organic Chemistry.

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References

1. V. V. Lapachev, O. P. Petrenko, and V. P. Mamaev, *Usp. Khim.*, 1990, **99**, 457 [*Russ. Chem. Rev.*, 1990, **99** (Engl. Transl.)].
2. O. A. Zagulyaeva and I. V. Oleinik, *Khim. Geterotsikl. Soedin.*, 1995, 816 [*Chem. Heterocycl. Compd.*, 1995, **31** (Engl. Transl.)].
3. J. Bessiere-Cretiene and H. Serne, *Bull. Soc. Chim. Fr.*, 1973, 2039.
4. K. F. Turchin, E. M. Peresleni, Yu. N. Sheinker, G. A. Bogdanova, I. V. Persianova, N. V. Alekseeva, G. M. Vakhatova, V. V. Lapachev, V. P. Mamaev, and L. N. Yakhontov, *Khim. Geterotsikl. Soedin.*, 1987, 241 [*Chem. Heterocycl. Compd.*, 1987, **23** (Engl. Transl.)].
5. G. M. Vakhatova and L. N. Yakhontov, *Khim. Geterotsikl. Soedin.*, 1980, 554 [*Chem. Heterocycl. Compd.*, 1980, **16** (Engl. Transl.)].
6. G. M. Vakhatova and L. N. Yakhontov, *Khim. Geterotsikl. Soedin.*, 1981, 264 [*Chem. Heterocycl. Compd.*, 1981, **17** (Engl. Transl.)].
7. G. M. Vakhatova, O. S. Anisimova, and L. N. Yakhontov, *Khim. Geterotsikl. Soedin.*, 1979, 1557 [*Chem. Heterocycl. Compd.*, 1979, **15** (Engl. Transl.)].
8. G. M. Vakhatova, O. S. Anisimova, and L. N. Yakhontov, *Khim. Geterotsikl. Soedin.*, 1981, 684 [*Chem. Heterocycl. Compd.*, 1981, **17** (Engl. Transl.)].
9. A. V. Shastin, O. A. Rakitin, T. I. Godovikova, Yu. A. Strelenko, F. I. Dubovitskii, and L. I. Khmel´nitskii, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1988, 1447 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1988, **37**, 1282 (Engl. Transl.)].
10. G. F. Reynolds, R. Berner, and W. Boutwell, *J. Heterocycl. Chem.*, 1972, 1009.
11. A. V. Shastin, T. I. Godovikova, S. P. Golova, V. S. Kuz´min, L. I. Khmel´nitskii, and B. L. Korsunskii, *Mendeleev Commun.*, 1995, 17.
12. A. A. Korkin and R. J. Bartlett, *J. Am. Chem. Soc.*, 1996, **118**, 12244.
13. *Comprehensive Heterocyclic Chemistry II. A Review of the Literature 1982—1995*, Eds A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon Press, Oxford, 1996, Vol. **6**, 576.
14. A. V. Shastin, T. I. Godovikova, L. I. Khmel´nitskii, and B. L. Korsunskii, *Khim. Geterotsikl. Soedin.*, 1997, 1254 [*Chem. Heterocycl. Compd.*, 1997, **33** (Engl. Transl.)].
15. A. V. Shastin, T. I. Godovikova, and B. L. Korsunskii, *Khim. Geterotsikl. Soedin.*, 1999, 76 [*Chem. Heterocycl. Compd.*, 1999, **35** (Engl. Transl.)].
16. A. V. Shastin, T. I. Godovikova, and B. L. Korsunskii, *Usp. Khim.*, 2003, **72**, 279 [*Russ. Chem. Rev.*, 2003, **72** (Engl. Transl.)].
17. T. Clark, *A Handbook of Computational Chemistry*, *A Practical Guide to Chemical Structure and Energy*, Wiley, New York, 1985.
18. W. Koch and M. C. Holthausen, *A Chemists´s Guide to Density Functional Theory*, Wiley—VCH, Weinheim, 2001, 300 pp.

19. Yu. A. Lebedev, E. A. Miroshnichenko, and Yu. K. Knobel´, *Termokhimiya nitrosoedinenii* [*Thermochemistry of Nitro Compounds*], Nauka, Moscow, 1970, 168 pp. (in Russian).
20. J. Sartorius and H.-J. Schnider, *Chem. Eur. J.*, 1996, 1446.
21. *Comprehensive Heterocyclic Chemistry*, Eds A. R. Katritzky and C. W. Rees, Pergamon press, Oxford, 1984, Vol. **3**, Pt. 2B, 457.
22. G. B. Seifer, *Koord. Khim.*, 2002, **28**, 323 [*Russ. J. Coord. Chem.*, 2002, **28** (Engl. Transl.)].
23. A. Ranganathan, V. R. Pedireddi, G. Sanjayan, K. N. Ganesh, and C. N. R. Rao, *J. Mol. Struct.*, 2000, **522**, 87.
24. J. Geith and T. M. Klapötke, *J. Mol. Struct. (Theochem.)*, 2001, **538**, 29.
25. A. V. Shastin, T. I. Godovikova, and B. L. Korsunskii, *Khim. Geterotsikl. Soedin.*, 1998, 1404 [*Chem. Heterocycl. Compd.*, 1998, **34** (Engl. Transl.)].
26. G. M. Sheldrick, *SHELXS97. Program for the Solution of Crystal Structures*, University of Göttingen, Germany, 1997.
27. G. M. Sheldrick, *SHELXL97. Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, 1997.
28. *Programmnyi kompleks Gaussian-98* [*Gaussian-98 Program Package*], Tsentr komp´yuternogo obespecheniya khimicheskikh issledovanii RAN.

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