CSIRO PUBLISHING

Full Paper

www.publish.csiro.au/journals/ajc

Aust. J. Chem. **2006**, *59*, 211–217

Configurational Assignment and Conformational Study of Methylglyoxal Bisdimethylhydrazones Derived from the 2-Ethoxypropenal Precursor

Leonid B. Krivdin,[A,B] *Lyudmila I. Larina*,[A] *Kirill A. Chernyshev*,[A] *and Natalia A. Keiko*[A]

[A] A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russia.

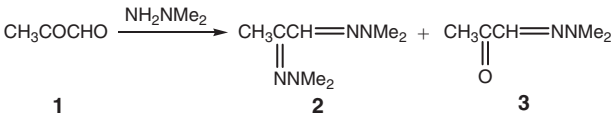
[B] Corresponding author. Email: krivdin@irioch.irk.ru

A configurational assignment of the isomeric methylglyoxal bisdimethylhydrazones derived from the 2-ethoxypropenal precursor has been performed based on experimental measurements and high-level ab initio calculations of ^1J(C,C) and ^1J(C,H) couplings. The results reveal the marked stereochemical dependence upon the orientation of the lone pairs of both nitrogen atoms in different isomers. Methylglyoxal bisdimethylhydrazone is shown to exist in a mixture of the *EE* and *ZE* isomers (ca. 75:25), both of which adopt predominant *s-trans* conformations with minor (up to 8°) out-of-plane deviations.

Manuscript received: 16 November 2005.
Final version: 21 February 2006.

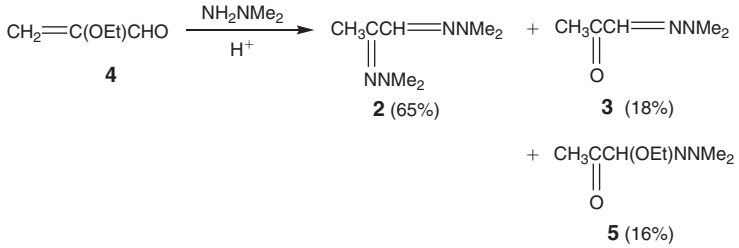
Introduction

Methylglyoxal bishydrazones, in particular, substituted bisguanylhydrazone and bisthiosemicarbazone, show a clearly expressed biological activity, which has led to molecules of this type being used as drugs.[1] In a preliminary investigation that involves the reaction of 2-ethoxyacrolein with an equimolar amount of *N*,*N*-dimethylhydrazine, a new methylglyoxal bishydrazone with potential biological action is obtained in 8% yield. The reaction of the aqueous methylglyoxal **1** with a four-fold excess of *N*,*N*-dimethylhydrazine leads to the formation of methylglyoxal bis-*N*,*N*-dimethylhydrazone **2** (Scheme 1) with methylglyoxal monodimethylhydrazone **3** as a by-product. The formation of the latter can be accounted for by the reversible hydrolysis of the bishydrazone **2** at the ketoimine group. In order to exclude water, the methylglyoxal is prepared in an anhydrous solvent (acetonitrile) from 2-ethoxypropenal by a technique described elsewhere[2] (Scheme 2). The water produced as a result of the condensation is adsorbed using $MgSO_4$ and K_2CO_3. However, even with a stoichiometric two-fold excess of *N*,*N*-dimethylhydrazine, the yield of the bisdimethylhydrazone **2** is 65%, whereas the monohydrazone **3** is formed in 18%. Another reaction product is 1-dimethylhydrazino-1-ethoxy-2-oxopropane **5** (yield 16%) which seemingly appears as a result of the ethanolysis of methylglyoxal monodimethylhydrazone **3**.



Scheme 1.

A quite unexpected property of **2** is that, judging from the ^{1}H NMR and gas/liquid chromatography mass spectrometry (GLC-MS) spectra, it is always obtained as a mixture of two isomers (in an ratio of ca. 1:3) of unknown configuration at the two C=N bonds. In view of the prospective chemical



Scheme 2.

 10.1071/CH05309 0004-9425/06/030211

interest of **2** for use as a potential precursor in a stereoselective heterocyclic synthesis, it is highly desirable to establish the configuration of both isomers once and for all.

The goal of the present communication is to establish the isomeric composition of methylglyoxal bisdimethylhydrazone **2** (Scheme 2) including the configurational assignment of the observed isomers as well as to carry out a conformational study of all possible isomers of **2** using high-level ab initio calculations.

Results and Discussion

The signal assignment in the ^{13}C NMR spectrum of **2** (obtained from 2-ethoxypropenal as shown in Scheme 2) is mostly straightforward, and is in accord with the existence of two isomeric forms of **2** in a ratio of ca. 1:3. Additional proof is gained from the $^{1}J(C,C)$ coupling constants measured from the ^{13}C satellites in the proton-decoupled ^{13}C NMR spectra, as exemplified in Fig. 1. Spectroscopic assignment of the ^{13}C resonances of the two different $=NNMe_2$ groups (attached to either C^2 or C^3) in both isomers are performed by means of the combined application of 2D NOESY, HSQC, and HMBC ^{15}N–^{1}H techniques. Configurational assignment of the two isomers of **2** is performed unambiguously based on the $^{1}J(C,C)$ and $^{1}J(C,H)$ constants measured from the INADEQUATE and the proton-coupled ^{13}C NMR spectra, respectively (see below).

It has been well established in our early[3] and more recent[4] publications that $^{1}J(C,C)$ couplings in azomethines demonstrate a profound stereochemical dependence on the orientation of the nitrogen lone pair. Indeed, the difference between J_{cis} and J_{trans} (Fig. 2) amounts to 20% of their total values and provides an unambiguous guide to the configurational assignment at the C=N bond in several azomethines, RR′C=N–X (X = OH, $OCH{=}CH_2$, Alk, Ar, SO_2Ar).[3,4] The same is true for the $^{1}J(C,H)$ couplings involving the α-imino carbon, however, this remarkable feature of $^{1}J(C,H)$ is much less known and is much less exploited in the stereochemical analysis. Apart from the main goal of the present study lying in the configurational assignment of the isomers of **2**, another interesting aspect that is dealt with is the potential applicability of the $^{1}J(C,H)$ involving the α-imino carbon used for the same purposes, namely for the configurational analysis of azomethines.

What is most remarkable in the present object of this study, methylglyoxal bisdimethylhydrazone **2**, is the presence of

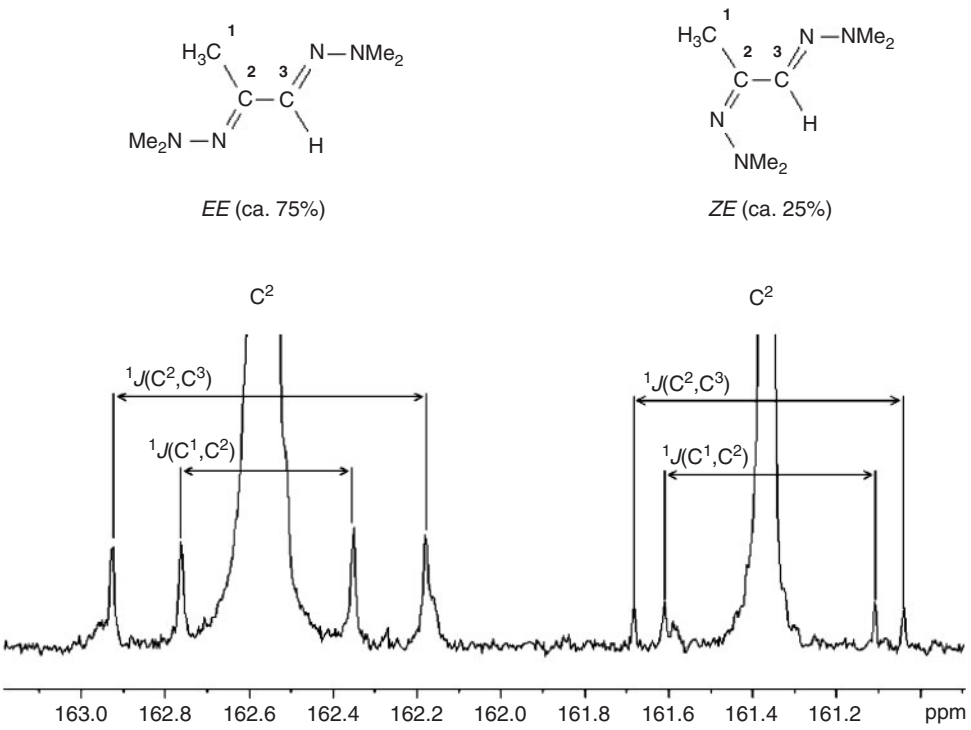


Fig. 1. ^{13}C satellites in the low-field region of the ^{13}C NMR spectra of **2** in $CDCl_3$ (101.61 MHz).

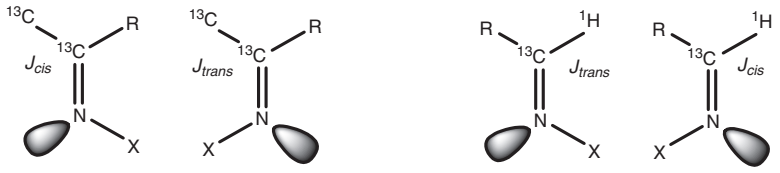


Fig. 2. Orientation of the N lone pair for J_{cis} and J_{trans}.

two azomethine functions, both of which impart a nitrogen lone pair effect (LPE) upon the values of ^1J(C,C) and ^1J(C,H) of the neighbouring C—C and C—H bonds.

According to our earlier theoretical results,[5] the nitrogen lone pair of the azomethine moiety contributes positively to J_{cis} (+LPE) and negatively to J_{trans} (−LPE) of the adjacent C—C or C—H bond.

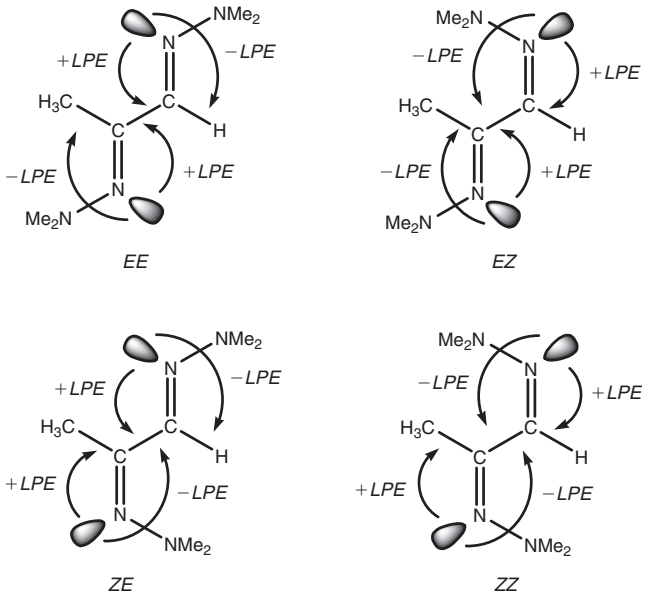


Fig. 3. LPE contributions to ^1J(C,C) and ^1J(C,H) in the four possible isomers of **2**.

Thus the marked difference between J_{cis} and J_{trans} is contributed to by three different factors, namely the effects of (a) the nitrogen lone pair, (b) the carbon–carbon bonds containing coupled carbons, and (c) the carbon inner core orbitals.[5] The first one relates to the direct nitrogen lone pair participation in the transmission of ^{13}C–^{13}C spin–spin coupling to give a positive contribution to J_{cis} and a negative contribution to J_{trans} (primary lone pair effect). On the other hand, the second and the third contributions originate mainly in the charge transfer from the nitrogen lone pair to the antibonding orbital of the adjacent carbon–carbon bond in *trans* orientation to the nitrogen lone pair as explained in detail by Juaristi et al.[6] This charge transfer interaction, which is very similar to the anomeric effect, results in the substantial lengthening of the *transoid* carbon–carbon bond and, hence, in the negative contribution to J_{trans} (secondary lone pair effect).

Manifestation of these LPE contributions to ^1J(C,C) and ^1J(C,H) in the four possible isomers of **2**, namely *EE*, *EZ*, *ZE*, and *ZZ*, is shown in Fig. 3. Statistical treatment of the calculated ^1J(C,C) and ^1J(C,H) values in each conformation of each isomer of **2** (Table 1) leads to the following average values of +LPE and −LPE: 5.3 ± 1.2 and -5.3 ± 1.2 Hz for $J(C^1,C^2)$, 6.4 ± 1.5 and -6.9 ± 2.4 Hz for $J(C^2,C^3)$, and 6.9 ± 3.5 and -6.9 ± 2.4 Hz for $J(C^3,H)$, respectively. These values are more than enough to perform the required configurational assignment of the two isolated isomers of **2**. What

Table 1. Spin–spin coupling constants ^1J(C,C) and ^1J(C,H) of the isomers of methylglyoxal bisdimethylhydrazone 2 calculated at the SOPPA(CCSD) level in comparison with experimental results[A]

Isomer	Coupled nuclei	Conformation	J_{DSO}	J_{PSO}	J_{SD}	J_{FC}	J	Experiment
EE	C^1,C^2	*s-cis*	0.3	−1.2	0.7	41.9	41.7	41.5
		s-trans	0.3	−1.3	0.7	42.1	41.8	
	C^2,C^3	*s-cis*	0.3	−1.7	0.9	75.3	74.8	75.3
		s-trans	0.3	−2.1	0.9	75.4	74.5	
	C^3,H	*s-cis*	1.2	0.1	0.1	152.7	154.1	162.7
		s-trans	1.2	−0.2	0.1	161.0	162.1	
EZ	C^1,C^2	*s-cis*	0.3	−1.1	0.7	40.9	40.8	
		s-trans	0.3	−1.3	0.7	39.6	39.3	
	C^2,C^3	*s-cis*	0.3	−1.8	0.9	62.9	62.3	
		s-trans	0.3	−1.3	0.9	57.4	57.3	
	C^3,H	*s-cis*	1.1	0.2	0.1	168.4	169.8	
		s-trans	1.1	−0.4	0.1	177.8	178.6	
ZE	C^1,C^2	*s-cis*	0.3	−0.9	0.7	51.0	51.1	50.3
		s-trans	0.3	−1.1	0.7	50.3	50.2	
	C^2,C^3	*s-cis*	0.3	−1.9	0.9	64.6	63.9	64.8
		s-trans	0.3	−2.0	0.9	65.1	64.3	
	C^3,H	*s-cis*	1.2	0.1	0.1	152.6	154.0	166.8
		s-trans	1.3	−0.2	0.1	165.2	166.4	
ZZ	C^1,C^2	*s-cis*	0.3	−0.8	0.7	52.8	53.0	
		s-trans	0.3	−0.9	0.7	51.7	51.8	
	C^2,C^3	*s-cis*	0.3	−1.8	0.9	52.3	51.7	
		s-trans	0.3	−1.2	0.9	44.5	44.5	
	C^3,H	*s-cis*	1.1	0.0	0.1	170.2	171.4	
		s-trans	1.1	−0.5	0.1	170.7	171.4	

[A] All couplings and their contributions are in Hz. In the calculations of ^1J(C,C) and ^1J(C,H) the coupled carbons and coupled hydrogens were specified with the cc-pVDZ-Cs and aug-cc-pVTZ-J basis sets, respectively, while the rest of the elements were assigned with cc-pVDZ with no polarization p-functions on hydrogens. The equilibrium MP2/6-311G* geometries were used throughout. All calculations were performed without symmetry constraints assuming the C_1 symmetry point group.

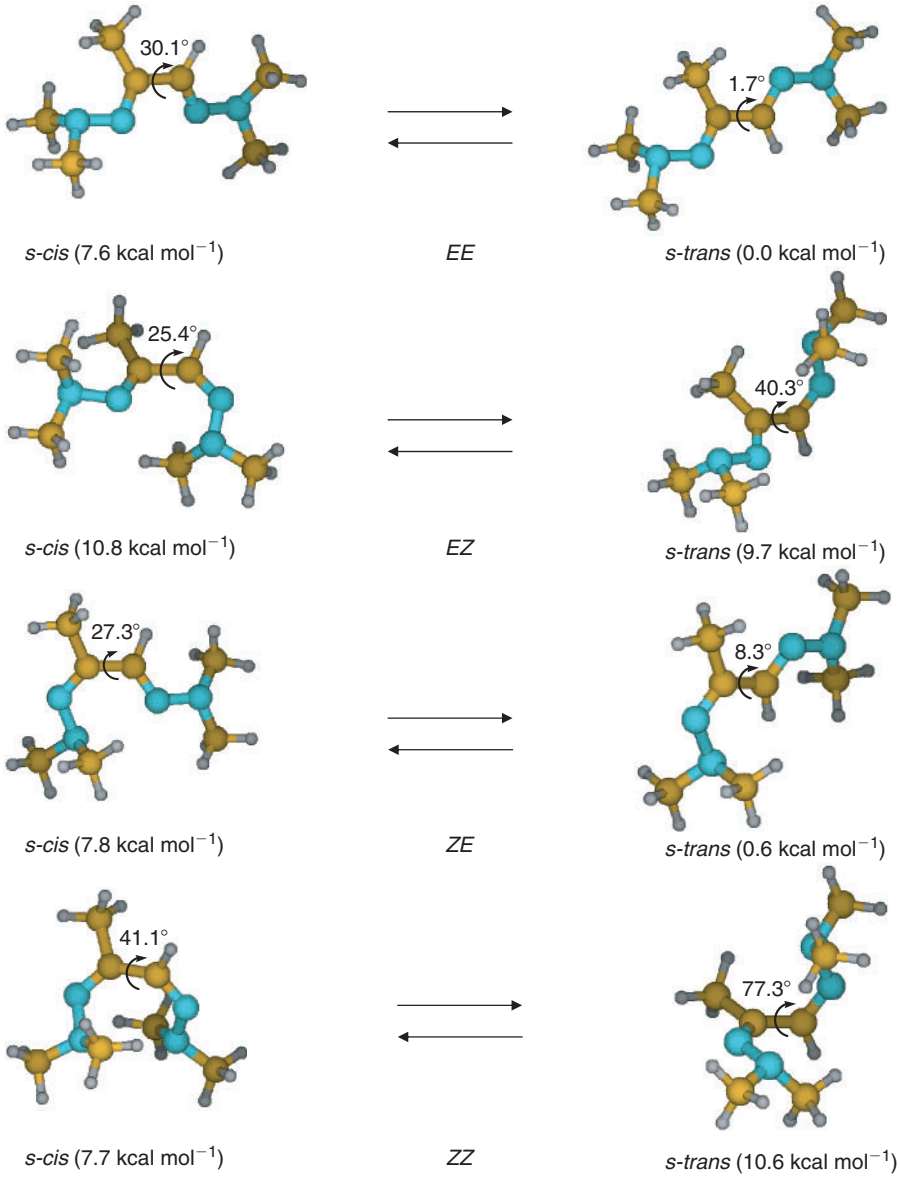


Fig. 4. MP2/6-311G* optimized equilibrium structures of *EE*, *EZ*, *ZE* and *ZZ* isomers of methylglyoxal bisdimethylhydrazone **2**. Element/color: hydrogen/gray, carbon/yellow, and nitrogen/cyan.

is still needed to solve this problem is to carry out the calculations of ^1J(C,C) and ^1J(C,H) in the four possible isomers of **2** and to compare the results with the experimental data keeping in mind the expected LPE contributions in each isomer depicted in Fig. 3.

Calculations of ^1J(C,C) and ^1J(C,H) for the four possible isomers of **2** are performed at the most sophisticated SOPPA (second-order polarization propagator approach)[7] level in combination with the CCSD (coupled cluster singles and doubles)[8] computational scheme, the so-called SOPPA(CCSD), which is approved for the calculation of spin–spin coupling constants by Sauer and coworkers.[9] The correlation-consistent basis set cc-pVDZ[10] augmented with two core *s*-functions of Woon and Dunning[11] on coupled carbons, cc-pVDZ-Cs, and a basis set of Sauer and coworkers[12] with four tight *s*-functions on coupled hydrogens, aug-cc-pVTZ-J, are applied to calculate Fermi contact, J_{FC}, spin–dipolar, J_{SD}, diamagnetic spin–orbital, J_{DSO}, and paramagnetic spin–orbital, J_{PSO}, contributions of ^1J(C,C) and ^1J(C,H), as described elsewhere.[13] It is worth noting that augmentation of the standard Dunning's correlation-consistent basis sets with either core or tight *s*-functions to account for the correlation effects of inner electrons and to improve the description of the cusp of the wave function at the position of the nucleus (which is crucial for the Fermi contact contribution) plays a key role in the accuracy of the SOPPA-based calculations of ^1J(C,C) and ^1J(C,H), as shown in several of the publications cited above.

Equilibrium structures of the four possible isomers of **2** used for the calculations of ^1J(C,C) and ^1J(C,H) are located at the MP2/6-311G* level and are shown in Fig. 4. Each of the four possible isomers of **2** is established to possess two conformers, *s-cis* and *s-trans*. Here and further on, these notations are used keeping in mind that in fact actual

Table 2. Calculated versus experimental spin–spin coupling constants ^1J(C,C) and ^1J(C,H) used for the configurational assignment of the isomeric mixture of methylglyoxal bisdimethylhydrazone 2[A]

Isomer	Predominant conformation	Relative energy [kcal mol^{-1}]	$^1J(C^1,C^2)$		$^1J(C^2,C^3)$		$^1J(C^3,H)$	
			Calc.	Exp.	Calc.	Exp.	Calc.	Exp.
EE[B]	*s-trans*	0.0	41.8	41.5	74.5	75.3	162.1	162.7
EZ	*s-trans*	9.7	39.3		57.3		178.6	
ZE[C]	*s-trans*	0.6	50.2	50.3	64.3	64.8	166.4	166.8
ZZ	*s-cis*	7.7	53.0		51.7		171.4	

[A] See footnote to Table 1. All couplings and their contributions are in Hz.
[B] Major component (ca. 75%).
[C] Minor component (ca. 25%).

conformations possess considerable out-of-plane deviations (see below) while planar *s-cis* and *s-trans* forms are just the starting points to yield the non-planar systems after geometry optimization.

As determined from the calculated relative energies (Fig. 4), the predominant conformation of the *EE*, *EZ*, and *ZE* isomers is *s-trans*, which is more favourable for π,π-conjugation, while that of the *ZZ* isomer is *s-cis*. This conformational effect should account for the very strong steric interactions in the *s-trans* conformer of the latter which gives rise to the enormous out-of-plane deviation (almost 90°!) and results in the ca. 3 kcal mol^{-1} preference of the diverse *s-cis* conformer. It is worth noting that considerable out-of-plane deviations of ca. 25–40° are also observed in most of the structures depicted in Fig. 4, except for the *s-trans* conformer of the *EE* isomer (ca. 2°) and *s-trans* conformer of the *ZE* isomer (ca. 8°), which possess remarkably lower total energies as compared to the rest in the series. Thus, it seems very likely that the two unknown isomers of **2** are *EE* (major) and *ZE* (minor), provided the reaction shown in Scheme 2 is basically under thermodynamic control.

As was pointed out by one of the referees, some conclusions drawn on the basis of the quite involved calculations (see above) are in full agreement with purely qualitative considerations. For instance, the *ZZ* isomer is obviously the least stable and assumes a non-planar conformation because of the huge steric repulsion of the methyl and dimethylamino groups together with the repulsion of the latter with the proton of the N=CH moiety. For similar reasons, the slightly higher stability of the *EZ* isomer can be assumed. Following the same reasoning one can say that *EE* and *ZE* are more stable with the former prevailing.

However, the unambiguous evidence of their formation could be gained only from the ^1J(C,C) and ^1J(C,H) data discussed below. Results of the present SOPPA(CCSD) calculations of ^1J(C,C) and ^1J(C,H) in all possible forms of **2** are compiled in Tables 1 and 2, and the numbering of atoms is given in Fig. 5.

First, it should be noted that the calculated total values of both ^1J(C,C) and ^1J(C,H) of the predominant conformations of *EE* and *ZE* isomers are in exceptionally good agreement (<1 Hz) with those measured for the major and minor isomers of **2** (Table 1), respectively, in line with the thermodynamic arguments above. All four coupling contributions have been

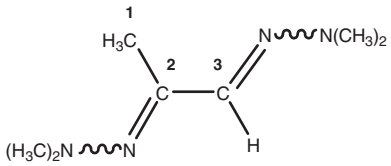


Fig. 5. Numbering of atoms in **2**.

taken into account in the calculation of ^1J(C,C) and ^1J(C,H). However, it follows from the data in Table 1 that total values of ^1J(C,C) and ^1J(C,H) and, accordingly, the orientational nitrogen lone pair effect that results in a dramatic difference between J_{cis} and J_{trans} of both types of couplings, are almost solely governed by the dominant Fermi contact mechanism while the non-contact contributions are essentially negligible, in line with our previous results for the related oximes.[4a]

Comparison of the calculated total values of ^1J(C,C) and ^1J(C,H) in all four possible isomers of **2** (Table 2) demonstrates the marked stereochemical dependence of both types of couplings upon the orientation of the lone pairs of both nitrogen atoms in the different isomers in accord with our expectations (Fig. 3). Indeed, $^1J(C^1,C^2)$ in *EE* and *EZ* are ca. 39–42 Hz (−LPE) while they are ca. 50–53 Hz in *ZE* and *ZZ* (+LPE). On the other hand, $^1J(C^2,C^3)$ in *ZZ* are ca. 52 Hz (−2LPE), ca. 75 Hz in *EE* (+2LPE), and ca. 57–64 Hz in *EZ* and *ZE* (−LPE of one azomethine nitrogen and +LPE of the other). In much the same manner, $^1J(C^3,H)$ in *EE* and *ZE* are ca. 162–166 Hz (−LPE) while they are ca. 171–178 Hz in *EZ* and *ZZ* (+LPE). The established manifestation of the LPE in the values of $^1J(C^1,C^2)$, $^1J(C^2,C^3)$, and $^1J(C^3,H)$ of the four different isomers of **2** leaves no doubt that the major isomer is *EE* and the minor isomer is *ZE*, with both adopting predominant *s-trans* conformations with minor out-of-plane deviations.

In conclusion, the most encouraging result of the present study is that experimental differences between J_{cis} and J_{trans} for both ^1J(C,C) and ^1J(C,H) induced by the nitrogen lone pair effects of two azomethine functions in methylglyoxal bishydrazones are large and essentially additive, and are very well reproduced in the SOPPA calculations, which provides a straightforward guide to the configurational assignment of the C=N bond in related systems based on the experimental measurements and theoretical calculations of their ^1J(C,C) and/or ^1J(C,H) couplings.

Experimental

Synthesis

Methylglyoxal bis-*N*,*N*-dimethylhydrazone **2** was prepared by adding 0.36 g (0.02 M) of water, 0.002 g of hydroxyquinone, and 0.12 g of a catalyst to 2 g (0.02 M) of 2-ethoxypropenal dissolved in 65 mL of acetonitrile (pH 2). The catalyst was prepared by dissolving 0.5 mL of concentrated HCl in 1 mL of acetonitrile. The mixture was heated at 60°C for 50 min and then cooled. Freshly calcined 4 Å molecular sieves (1.5 mL) and 4.58 g (0.078 M) of dimethylhydrazine were added and the mixture was stirred for 2 h and allowed to stand overnight. After distillation under argon flow, compound **2** was obtained in 65% yield, bp 55°C (1 mmHg). δ_C (100.61 MHz, $CDCl_3$) isomer *EE* (major, ca. 75%): 12.24 (C^1), 41.88 ($NNMe_2$ at C^3), 46.71 ($NNMe_2$ at C^2), 132.21 (C^3), 162.56 (C^2); isomer *ZE* (minor, ca. 25%): 18.77 (C^1), 41.71 ($NNMe_2$ at C^3), 47.26 ($NNMe_2$ at C^2), 132.65 (C^3), 161.36 (C^2). The assignment of C^1, C^2, and C^3 are shown in Fig. 1.

NMR Measurements

^{13}C NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer in a 10 mm broadband probe at 300 K in $CDCl_3$ with HMDS as an internal standard. Carbon–carbon coupling constants were measured at 25°C in $CDCl_3$ from the ^{13}C satellites in the proton-decoupled ^{13}C NMR spectra and also using the INADEQUATE[14] pulse sequence adjusted for *J* 45 and 70 Hz. Settings for the INADEQUATE experiments were as follows: 90° pulse length: 12–14 μs, spectroscopic width: 10–15 kHz, acquisition time: 4–6 s, relaxation delay: 6–10 s, characteristic delay τ 1/4J: 5.6 and 3.6 ms, digital resolution: 0.05–0.1 Hz per point, accumulation time: 12 h. Carbon–hydrogen coupling constants were measured from the proton-coupled ^{13}C NMR spectra using the same spectroscopic widths, acquisition times, relaxation delays, and digital resolutions as in the INADEQUATE experiments.

Computational Methods

Geometrical optimizations were performed with the *GAMESS* code,[15] at the MP2 level,[16] with the 6-311G** basis set of Pople and co-workers.[17] Calculations of spin–spin coupling constants were carried out using the *DALTON* package[18] at the SOPPA(CCSD) level[9] with the correlation-consistent basis set cc-pVDZ[10] augmented with the core *s*-functions cc-pVDZ-Cs of Woon and Dunning[11] on coupled carbons and aug-cc-pVTZ-J of Sauer et al.[12] on coupled hydrogens, as described elsewhere.[13] In all calculations no symmetry constraints were applied assuming the C_1 symmetry point group throughout.

Acknowledgments

Financial support of the Russian Foundation for Basic Research (grant no. 05-03-32231) is gratefully acknowledged.

References

[1] (a) S. Ekelund, P. Nygren, R. Larsson, *Biochem. Pharm.* **2001**, *61*, 1183. doi:10.1016/S0006-2952(01)00570-6
(b) N. A. Keiko, T. N. Mamashvili, *Khim. Farm. Zh. (Russ.)* **2005**, *39*, 28.
(c) M. Salvi, A. Toninello, *Biochem. Pharm.* **2002**, *63*, 247. doi:10.1016/S0006-2952(01)00827-9

[2] T. N. Mamashvili, N. A. Keiko, G. I. Sarapulova, M. G. Voronkov, *Izv. AN SSSR, Ser. Khim. (Russ.)* **1998**, 2547.

[3] (a) L. B. Krivdin, G. A. Kalabin, R. N. Nesterenko, B. A. Trofimov, *Tetrahedron Lett.* **1984**, *25*, 4817. doi:10.1016/S0040-4039(01)81528-8
(b) G. A. Kalabin, L. B. Krivdin, V. V. Shcherbakov, B. A. Trofimov, *J. Mol. Struct.* **1986**, *143*, 569. doi:10.1016/0022-2860(86)85327-3
(c) L. B. Krivdin, V. V. Shcherbakov, G. A. Kalabin, *Russ. J. Org. Chem. Engl. Transl.* **1986**, *22*, 300.

[4] (a) L. B. Krivdin, N. A. Scherbina, N. V. Istomina, *Magn. Reson. Chem.* **2005**, *43*, 435. doi:10.1002/MRC.1572
(b) L. B. Krivdin, L. I. Larina, K. A. Chernyshev, I. B. Rozentsveig, *Magn. Reson. Chem.* **2005**, *43*, 937. doi:10.1002/MRC.1645
(c) L. B. Krivdin, N. A. Nedolya, *Tetrahedron Lett.* **2005**, *46*, 7367. doi:10.1016/J.TETLET.2005.08.118

[5] (a) V. Barone, J. E. Peralta, R. H. Contreras, A. V. Sosnin, L. B. Krivdin, *Magn. Reson. Chem.* **2001**, *39*, 600. doi:10.1002/MRC.901
(b) L. B. Krivdin, S. V. Zinchenko, V. V. Shcherbakov, G. A. Kalabin, R. H. Contreras, M. F. Tufro, M. C. Ruiz de Azua, C. G. Giribet, *J. Magn. Reson.* **1989**, *84*, 1.
(c) R. H. Contreras, C. G. Giribet, M. C. Ruiz de Azua, C. N. Cavasotto, L. B. Krivdin, *J. Mol. Struct. Theochem*. **1990**, *210*, 175. doi:10.1016/0166-1280(90)80039-Q
(d) L. B. Krivdin, S. V. Zinchenko, G. A. Kalabin, M. F. Tufro, R. H. Contreras, A. Yu. Denisov, O. A. Gavrilyuk, V. I. Mamatyuk, *J. Chem. Soc., Faraday Trans.* **1992**, *88*, 2459. doi:10.1039/FT9928802459

[6] (a) E. Juaristi, G. Cuevas, A. Vela, *J. Am. Chem. Soc.* **1994**, *116*, 5796. doi:10.1021/JA00092A034
(b) G. Cuevas, E. Juaristi, A. Vela, *J. Phys. Chem. A* **1999**, *103*, 932. doi:10.1021/JP983664S
(c) G. Cuevas, E. Juaristi, *J. Am. Chem. Soc.* **2002**, *124*, 13088. doi:10.1021/JA020317U

[7] (a) E. S. Nielsen, P. Jørgensen, J. Oddershede, *J. Chem. Phys.* **1980**, *73*, 6238. doi:10.1063/1.440119
(b) M. J. Packer, E. K. Dalskov, T. Enevoldsen, H. J. A. Jensen, J. Oddershede, *J. Chem. Phys.* **1996**, *105*, 5886. doi:10.1063/1.472430
(c) T. Enevoldsen, J. Oddershede, S. P. A. Sauer, *Theo. Chem. Acc.* **1998**, *100*, 275.
(d) K. L. Bak, H. Koch, J. Oddershede, O. Christiansen, S. P. A. Sauer, *J. Chem. Phys.* **2000**, *112*, 4173. doi:10.1063/1.480963

[8] (a) J. Čížek, *J. Chem. Phys.* **1966**, *45*, 4256. doi:10.1063/1.1727484
(b) J. Čížek, J. Paldus, *Int. J. Quantum Chem.* **1971**, *5*, 359. doi:10.1002/QUA.560050402
(c) G. D. Purvis, R. J. Bartlett, *J. Chem. Phys.* **1982**, *76*, 1910. doi:10.1063/1.443164
(d) H. Koch, O. Christiansen, R. Kobayashi, P. Jørgensen, T. Helgaker, *Chem. Phys. Lett.* **1994**, *228*, 233. doi:10.1016/0009-2614(94)00898-1
(e) H. Koch, A. Sánchez de Merás, T. Helgaker, O. Christiansen, *J. Chem. Phys.* **1996**, *104*, 4157. doi:10.1063/1.471227

[9] (a) S. P. A. Sauer, *J. Phys. B* **1997**, *30*, 3773. doi:10.1088/0953-4075/30/17/007
(b) T. Enevoldsen, J. Oddershede, S. P. A. Sauer, *Theor. Chem. Acc.* **1998**, *100*, 275.

[10] (a) T. H. Dunning, Jr, *J. Chem. Phys.* **1989**, *90*, 1007. doi:10.1063/1.456153
(b) R. A. Kendall, T. H. Dunning, Jr, R. J. Harrison, *J. Chem. Phys.* **1992**, *96*, 6796. doi:10.1063/1.462569
(c) D. E. Woon, T. H. Dunning, Jr, *J. Chem. Phys.* **1993**, *98*, 1358. doi:10.1063/1.464303

[11] D. E. Woon, T. H. Dunning, Jr, *J. Chem. Phys.* **1995**, *103*, 4572. doi:10.1063/1.470645

[12] P. F. Provasi, G. A. Aucar, S. P. A. Sauer, *J. Chem. Phys.* **2001**, *115*, 1324. doi:10.1063/1.1379331

[13] (a) L. B. Krivdin, S. P. A. Sauer, J. E. Peralta, R. H. Contreras, *Magn. Reson. Chem.* **2002**, *40*, 187. doi:10.1002/MRC.989
(b) L. B. Krivdin, *Magn. Reson. Chem.* **2003**, *41*, 91. doi:10.1002/MRC.1135
(c) L. B. Krivdin, *Magn. Reson. Chem.* **2003**, *41*, 157. doi:10.1002/ MRC.1152
(d) L. B. Krivdin, *Magn. Reson. Chem.* **2003**, *41*, 417. doi:10.1002/ MRC.1198
(e) L. B. Krivdin, *Magn. Reson. Chem.* **2003**, *41*, 885. doi:10.1002/ MRC.1267

(f) L. B. Krivdin, *Magn. Reson. Chem.* **2004**, *42*, 1. doi:10.1002/MRC.1312
(g) L. B. Krivdin, *Magn. Reson. Chem.* **2004**, *42*, 500. doi:10.1002/ MRC.1367
(h) S. P. A. Sauer, L. B. Krivdin, *Magn. Reson. Chem.* **2004**, *42*, 671. doi:10.1002/MRC.1400
(i) L. B. Krivdin, *Magn. Reson. Chem.* **2004**, *42*, S168. doi:10.1002/MRC.1415
(j) L. B. Krivdin, *Magn. Reson. Chem.* **2004**, *42*, 919. doi:10.1002/MRC.1483
(k) L. B. Krivdin, *Magn. Reson. Chem.* **2005**, *43*, 101. doi:10.1002/ MRC.1515

[14] A. Bax, R. Freeman, S. P. Kempsell, *J. Am. Chem. Soc.* **1980**, *102*, 4849. doi:10.1021/JA00534A056

[15] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis, J. A. Montgomery, *J. Comp. Chem.* **1993**, *14*, 1347. doi:10.1002/JCC.540141112

[16] C. Møller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618. doi:10.1103/PHYSREV.46.618

[17] R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, *J. Chem. Phys.* **1980**, *72*, 650. doi:10.1063/1.438955

[18] H. Agren, C. Angeli, K. L. Bak, V. Bakken, O. Christiansen, R. Cimiraglia, S. Coriani, P. Dahle, E. K. Dalskov, T. Enevoldsen, B. Fernandez, C. Haettig, K. Hald, A. Halkier, H. Heiberg, T. Helgaker, H. Hettema, H. J. A. Jensen, D. Jonsson, P. Joergensen, S. Kirpekar, W. Klopper, R. Kobayashi, H. Koch, A. Ligabue, O. B. Lutnaes, K. V. Mikkelsen, P. Norman, J. Olsen, M. J. Packer, T. B. Pedersen, Z. Rinkevicius, E. Rudberg, T. A. Ruden, K. Ruud, P. Salek, A. Sanchez de Meras, T. Saue, S. P. A. Sauer, B. Schimmelpfennig, K. O. Sylvester-Hvid, P. R. Taylor, O. Vahtras, D. J. Wilson, *Dalton, A Molecular Electronic Structure Program, Release 2.0* **2005**. www.kjemi.uio.no/software/dalton/dalton.html