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The true configuration of the benzilosazone isomers

María V. Mirífico,[a,b,*] José A. Caram[a] and Enrique J. Vasini[a]

[a]*Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas (INIFTA), Facultad de Ciencias Exactas, Departamento de Química, Universidad Nacional de La Plata. C.C. 16, Suc. 4, (1900) La Plata, Argentina*
[b]*Fac. de Ingeniería, Universidad Nacional de La Plata, Argentina*

Abstract—The ^{1}H NMR-based argument previously used to assign configurations to the three stereoisomers of benzilosazone is briefly reviewed. The configuration of the stable isomer is shown to be Z,Z by single crystal X-ray diffraction analysis, instead of E,E as previously reported. This assignment, together with physical measurements and spectroscopic (NMR and UV) data, allows the establishment of the configuration of all isomers. Computational methods are employed to clarify the relation between the configuration of the isomers and their ^{1}H NMR, thus explaining the origin of the previous erroneous assignment.
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The three possible diastereoisomers of benzilosazone, which differ in the spatial arrangement around the two C=N double bonds, are shown in Scheme 1.

These isomers were obtained by Spassov,[1] who labeled the stable isomer, melting at 234 °C, as β-osazone. He named the two other isomers in accordance with their physical properties as γ_g (from *gelb* = yellow, mp 175 °C), and γ_r (from r = rhombic, mp 196 °C). Both γ-osazones revert to the β-osazone on melting and resolidification.
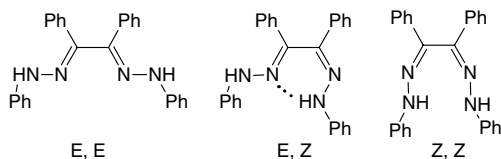
Woodward and Wintner[2] verified the work of Spassov and clarified earlier papers by showing that some reported configurational isomers of benzilosazone were instead chain isomers or mixtures of isomorphous compounds. In this context, they measured the X-ray diffraction of β-osazone crystal powder. Of course, powder X-ray diffraction does not provide information on molecular structure. Commenting on the assignment of

Scheme 1.

* Corresponding author. Tel.: +54 221 425 7430; fax: +54 221 425 4642; e-mail: mirifi@inifta.unlp.edu.ar

a configuration to the isomers, they cautiously stated 'in the absence of evidence to the contrary, it seemed not unreasonable to assume an E,E configuration for the β-osazone.' The γ_g isomer was assigned the asymmetric E,Z configuration on the basis of a doublet in the N–H band of its IR spectrum.

Spassov and Christova claimed to have established the configurations of the isomers,[3] based on their ^{1}H NMR results in DMSO-d_6. They observed that the two osazones, γ_r and β, presented only one N–H proton resonance ($\gamma_r = \delta$: 9.15, 2H; β = δ: 9.45, 2H). The γ_g-osazone showed two N–H proton resonances, at δ 11.20 and 9.45 ppm, both equal in intensity (1H). The low field signal at δ 11.20 ppm was assigned to the 'chelated' proton of the E,Z isomer (Scheme 1), which necessarily belongs to the Z-configured half of the molecule. The remaining signal, at δ 9.45, should correspond to the N–H proton of the E-configured half. Thus, they argued that the β isomer, presenting one 2H signal at δ 9.45 ppm, should be the E,E isomer. This left for the protons in the Z,Z configuration the 9.15 ppm chemical shift, corresponding to the γ_r isomer.

The authors stated that their results confirmed the X-ray structural assignment of Woodward and Wintner. However, as mentioned above, such assignment had not been made.

The present work revises these assignments on the basis of the first measurement of the single crystal X-ray diffraction of a benzilosazone isomer. A comparison of

the physical and spectroscopic properties of the symmetric isomers with those reported in the literature is also presented. It is concluded that the β-osazone (mp 234 °C) is the *Z,Z* isomer and the γ$_r$-osazone has the *E,E* configuration.

In the course of our studies on the nucleophilic addition reactions to 1,2,5-thiadiazole 1,1-dioxide derivatives, we found that phenylhydrazine not only added to both C=N double bonds of 3,4-diphenyl-1,2,5-thiazole 1,1-dioxide (**1a**), but also displaced sulfamide (reaction 1).[4] Thus, the reaction was a largely superfluous synthesis of benzilosazone:
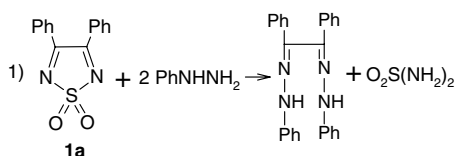
Compound **1a** (140 mg, 0.52 mmol), and 125 mg (1.16 mmol) PhNHNH$_2$ were dissolved in 1 mL dry MeCN. A yellow colored solid precipitated immediately after solution preparation. The mother liquors were concentrated at room temperature (1/10) and combined with the filtered solid. The mixture was dried under vacuum at room temperature and recrystallized from hot ethanol. Pure (TLC) product (150 mg, 0.39 mmol; 74%) (solid **S1**, mp: 234–236 °C) was obtained.

The procedure was repeated, but only the mother liquors were worked-up and the recrystallization from hot solvent was omitted. The solid obtained by concentration at room temperature of the mother liquors was washed with a small volume of MeCN and dried under vacuum at room temperature. The solid (**S2**) was a pure substance as judged by TLC analysis.

^{1}H and ^{13}C NMR spectra, IR and mp were determined for both solids.[4] The single crystal X-ray diffraction of the recrystallized solid (**S1**) was also measured and found to correspond to (1*Z*,2*Z*)-1,2-diphenylethane-1,2-dione bis(phenylhydrazone), that is, *Z,Z*-benzilosazone. An ORTEP[6] representation, showing all non-hydrogen atoms, of the X-ray results as deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 290219, is given in Figure 1. The **S1** solid melted at 235 °C, as it was reported in the literature for the stable isomer.
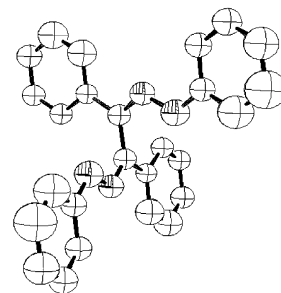

Figure 1. ORTEP representation of (1*Z*,2*Z*)-1,2-diphenylethane-1,2-dione bis(phenylhydrazone). H-atoms are not shown.

The **S2** solid, which was not recrystallized from hot ethanol or heat dried, melted at 185.0 °C, but on further heating solidified again and re-melted at 229.0–231.0 °C. As it is mentioned above, this behavior corresponds to the thermal isomerization of the γ forms into the stable β isomer.

Both solids presented single NH ^{1}H NMR resonances in DMSO-d_6 (**S1**: 9.57; **S2**: 9.45 ppm, Table 1) with a 2H intensity, as judged by comparison with the intensity for the phenyl protons. Thus, **S2** is also a symmetric isomer and must have a *E,E* configuration. Unfortunately, attempts to obtain single crystals for an X-ray diffraction from solutions of the **S2** solid produced only the *Z,Z* isomer.

Physical and spectroscopic properties measured for the two isomers are listed in Table 1 and are compared with the properties reported in the literature. Earlier configuration assignments and those resulting from the evidence presented in this work are included.

Furthermore, the ^{13}C NMR spectrum of our *Z,Z* isomer is identical, except for a small constant downfield shift to that of the β-osazone reported by Spassov and Christova.[5] The assignment of the ^{13}C resonances, shown in Figure 2, is that given in Ref. 5 (Table 2).

It was surprising to find that the apparently unambiguous argument of Spassov and Christova did not agree with our experimental measurements. A few preliminary theoretical calculations, carried out as described below, helped to clarify the issue.

The starting geometry for the *Z,Z* isomer was that of the X-ray diffraction results. The same geometry, except for

Table 1. Selected properties and assigned configuration of benzilosazone isomers

Name and configuration in Ref. 3		^{1}H NMR[a]		Mp (°C)		λ_{max} (nm)[b]		Configuration
		Ref. 3	This work	Ref. 3	This work	Ref. 3	This work	
β	*E,E*	9.45	9.57	234	235	240; 298; 341	241; 299; 341	*Z,Z*
γ$_g$	*E,Z*	11.20; 9.45	—	175	—	—	—	*E,Z*
γ$_r$	*Z,Z*	9.15	8.77	196	185	298; 368	298; 368	*E,E*

[a] δ, TMS, in DMSO-d_6, for N–H protons.
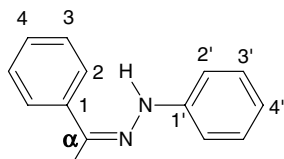[b] UV Spectrum in anhydrous EtOH solution.

Figure 2.

Figure 3.

a 180° rotation around both C=N bonds, was used for the *E,E* isomer. Only one C=N bond was rotated for the *E,Z* isomer, and the –N=C–C=N– dihedral angle was changed to 0° to obtain the cissoid conformation necessary for the intramolecular H-bond formation. These geometric operations are schematically shown in Figure 3.

An unrefined estimation of the ^{1}H NMR spectra of the isomers was obtained for these structures with the Gaussian 98 software,[6] a HF/6-31G(d,p) basis set and the GIAO method, without further ab initio minimization of the energy. As expected, the calculated NH proton chemical shifts (ca. 6 ppm) were much smaller than the experimental values, stressing the importance of the H-bonds to the DMSO solvent.

To include the DMSO molecules while keeping the calculation time at reasonable levels, the following procedure was used: six DMSO molecules were placed around each isomer and a PM3 semiempirical energy minimization was run. In the next step, only the DMSO molecules H-bonded to the osazones were kept and the energy was minimized again (PM3). For these minimized structures, ^{1}H NMR chemical shifts were calculated with Gaussian as indicated above. In the case of the *E,Z* isomer, for reasons mentioned below, the procedure was repeated after the initial –N=C–C=N– dihedral angle of 0° (Fig. 3) was changed to 60°. The calculated (PM3) total energy and the ^{1}H NMR (δ, ppm vs TMS) are listed in Table 3.
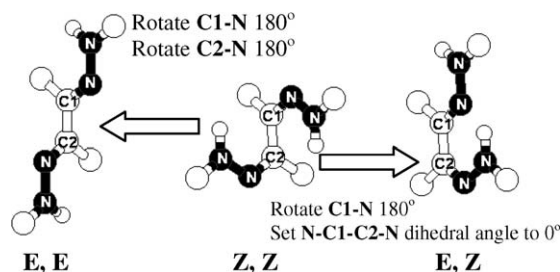
It can be observed that the total energy of the isomers differed by less than 5 kcal/mol. This is a reasonable result, given the easy interconversion reported. The order of decreasing total energy was *E, Z > E,E > Z,Z*.

The allegedly N–H···N 'strong intramolecular H-bond' (Fig. 1) for the *E,Z* isomer, which was crucial for the previous structural assignment argument, was found to have a 129.5° N–H···N angle and a H···N distance of 2.28 Å. Although these are within the accepted geometric criteria for H-bond formation,[7] they are far from the optimum geometry. An intramolecular H-bond excludes the possibility of a strong N–H···O bond with the DMSO solvent. For this reason, a calculation in which the dihedral –N=C–C=N– angle for the *E,Z* isomer was arbitrarily set at 60° was carried out, as mentioned above. With this conformation, the N–H proton on the *Z* 'side' of the molecule could form an efficient H-bond with the solvent and its calculated chemical shift increased (Table 3), approaching the reported experimental value.

Finally, it is worth mentioning that, in a similar reaction, **1a** reacted with 2-aminoethanol to give 2-({(1Z,2Z)-2-[(2-hydroxyethyl)imino]-1,2-diphenylethylidene}amino)ethanol, a benzil bis(ethanolimine) with a *Z,Z* configuration (CCDC: 290220).[4]

In conclusion, the accepted configurations of the benzilosazone isomers should be changed to those listed in the rightmost column of Table 1.

Table 2. ^{13}C NMR (δ ppm, TMS in DMSO-d_6 solution) resonances of benzilosazone in CDCl$_3$ as measured in Ref. 5 for the β-osazone and in this work for the *Z,Z* isomer

C atom (Fig. 2)	1′	α	1	3	3′	4	2	4′	2′
δ ppm (Ref. 5)	143.7	135.9	134.5	129.2	128.9	128.7	125.6	121.0	113.4
δ ppm (this work)	144.1	136.3	134.8	129.5	129.2	129.0	125.9	121.4	113.7

Table 3. Minimized (PM3) total energy and N–H ^{1}H NMR chemical shifts estimation for the isomers

Isomer	Total energy[a] (kcal/mol)	Calculated N–H δ (ppm vs TMS)[b]	Experimental N–H δ (ppm vs TMS, DMSO-d_6)
Z,Z	−7509.6	9.83; 9.87	9.57
E,E	−7506.2	9.16; 8.52	8.77
E,Z (cis)[c]	—	8.56(*E*); 8.83(*Z*)	9.45(*E*), 11.20(*Z*)
E,Z (60°)[d]	−7505.0	8.56(*E*); 10.5(*Z*)	9.45(*E*), 11.20(*Z*)

See text for details of the estimation method.
[a] Including two H-bonded DMSO molecules.
[b] δ values are different for equivalent atoms because the geometry was not optimized by ab initio methods.
[c] Geometry optimized for the intramolecular H-bond formation.
[d] Same geometry as 'c', except for the –N=C–C=N– dihedral angle, which was set at 60°.

Supplementary data

ORTEP (*.ins), postscript (*.eps) and *Z*-matrix (*.xyz) files for the *Z,Z* benzilosazone isomer and a MSWord document containing the *Z*-matrices of all PM3 minimized configurations listed in Table 3 are available as supplementary files, which can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.109.

Acknowledgments

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