Double addition of azoles to glyoxal: characterization of the bis-adducts and theoretical study of their structure

Marta Pérez-Torralba,[a*] Rosa M. Claramunt,[a*] Ibon Alkorta,[b] and José Elguero[b]

[a] *Departamento de Química Orgánica y Bio-Orgánica, Universidad Nacional de Educación a Distancia (UNED), Facultad de Ciencias, Senda del Rey 9, 28040 Madrid, Spain*
[b] *Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006, Madrid, Spain*
E-mails: rclaramunt@ccia.uned.es, mperez@bec.uned.es

Dedicated to Professor Madeleine Joullie on the occasion of her 80th anniversary

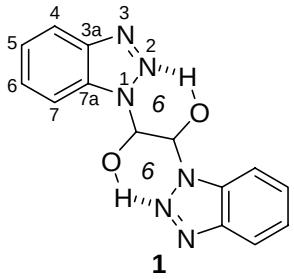
Abstract

We have studied the structure (isomerism and conformation) of the products resulting from the double addition of four N*H*-azoles, benzotriazole, pyrazole, imidazole and benzimidazole, on glyoxal and on DODO ([1,4]-dioxane-2,3-diol). The reactions result in the formation of *meso* and *d,l* diastereoisomers, although in all cases a significant amount of unreacted azole remains. The four component mixtures were analyzed by ^{1}H and ^{13}C NMR. DFT calculations (B3LYP/6-31G*) were carried out to determine the relative stabilities of the different structures.

Keywords: Bisazolylethanediols, glyoxal, DODO, benzotriazole, pyrazole, imidazole, benzimidazole

Introduction

The reversible addition of N-unsubstituted azoles to carbonyl compounds has been known for a long time. Since the most stable isomer is always isolated (thermodynamic control),[1,2] the product has generally the same structure as the most stable tautomer,[3] for instance, in the case of benzotriazole, the N1-substituted isomer and the 1*H*-tautomer are more stable than the 2-C(OH)RR' and 2*H* ones, respectively. Adduct stabilities are strongly dependent on the basicity of the azole and on the reactivity of the carbonyl compound. With acetone, the adducts are stable only at low temperature[1-3] while with formaldehyde or hexafluoroacetone the adducts can be isolated.[4-7]



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In 1987, Katritzky *et al*. reported that the reaction of benzotriazole with glyoxal affords, in 100% yield, a bis-adduct, m.p. 167-169 ºC, to which they assigned the structure **1** (represented above as in the original publication) based on a ^{1}H NMR spectrum in DMSO-d_6.[8] Besides, the IR spectrum showed an intense band at 3110 cm^{-1} characteristic of a strongly hydrogen bonded OH. It was postulated that the HB involves the pyridine-like benzotriazole N2 atom, forming a pseudo six-membered ring. In a subsequent paper, Katritzky and Fan[9] reported the same compound obtained also in quantitative yield but with a m.p. of 196-199 ºC, adding that two diastereoisomers were formed, the *meso* and the *d,l*. The melting point of a mixture of compounds is not very relevant.

Using an Eu(III) chiral shift reagent, they determined that the singlet at 6.95 ppm (methine CH) belongs to the *d,l*-form (since it split into two broad peaks) while the singlet at 7.00 ppm belongs to the *meso*-form (no splitting was observed). The ratio of *meso*- to *d,l*-adducts was 75:25 according to the integrals of the two aliphatic CH signals of 1,2-di(benzotriazol-1-yl)ethane-1,2-diol (**1**).[9] Katritzky's work on **1** was commented upon in an important review on benzotriazoles.[10] Note that the situation represented in Figure 1 is similar to those of tartaric acids.

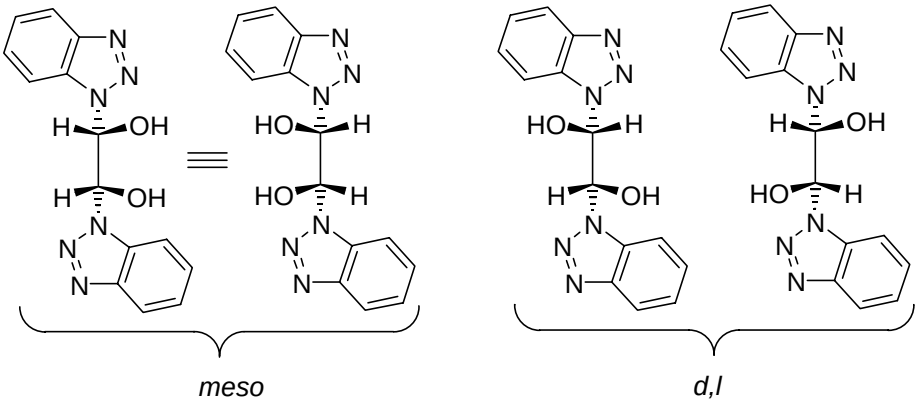

Figure 1. The three possible isomers of **1.**

The stability of compound **1** could be related to the formation of two pseudo five- (not previously considered) or two pseudo six-membered hydrogen bonded rings[9] (Figure 2). In the case of the *meso* structure, it is not possible to form two pseudo six-membered rings. As we will

discuss in the theoretical section, other conformations with one pseudo-six, one pseudo-five or no pseudo-rings are possible.

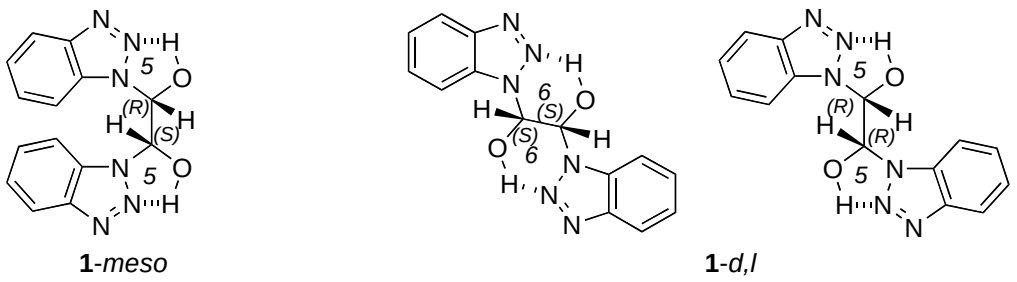

Figure 2. Stereoisomers of 1,2-di(benzotriazol-1-yl)ethane-1,2-diol (**1**).

We have prepared and characterized **1** as well as three previously unknown analogues of **1**, namely 1,2-di(pyrazol-1-yl)ethane-1,2-diol (**2**), 1,2-di(imidazol-1-yl)ethane-1,2-diol (**3**) and 1,2-di(benzimidazol-1-yl)ethane-1,2-diol (**4**) using instead of benzotriazole (**5**), pyrazole (**6**), imidazole (**7**) and benzimidazole (**8**), respectively (Figure 3).

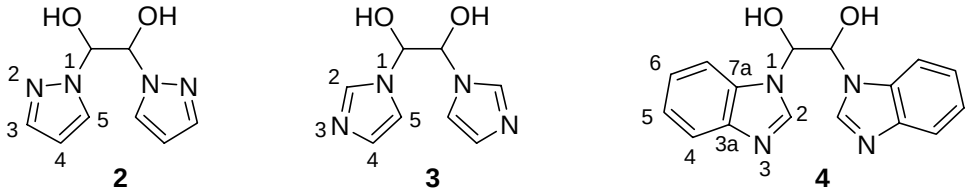

Figure 3. The three new adducts (without stereochemistry).

Results and Discussion

Synthesis

Compounds **1**, **2**, **3** and **4** have been synthesized according to the procedures described by Katritzky *et al*.[8,9] where the glyoxal reacted with two equivalents of the corresponding azole in a mixture of acetic and sulfuric acids[8] or in aqueous acetic acid[9] to give a mixture of the diol and the starting azole. Only for compounds **1** and **2**, a precipitate appeared immediately when the glyoxal was added to the reaction; this may be due to the formation of intramolecular hydrogen bonds (IMHB) between N2 and the OH groups, these kind of IMHBs cannot be formed in the cases of **3** and **4**.

In the reaction crude, the ratio of diol to starting azole is approximately 60/40 in the standard reaction for preparing 1,2-di(benzotriazol-1-yl)ethane-1,2-diol (**1**); similar results are obtained under slightly different reaction conditions (Table 1). For compounds **2**, **3** and **4** the reaction conditions are the same in the three cases (Table 1). The ratio diol/azole is 70/30 for 1,2-

di(pyrazol-1-yl)ethane-1,2-diol (**2**), while for 1,2-di(imidazol-1-yl)ethane-1,2-diol (**3**) and 1,2-di(benzimidazol-1-yl)ethane-1,2-diol (**4**), the diol appears in small amounts. Due to the facile reversibility of the double addition, these three-component mixtures cannot be purified.

We have been unable to reproduce the quantitative yield in **1** described by Katritzky.[8,9] In our hands, a significant proportion of unreacted benzotriazole (**5**) always remains. With pyrazole (**6**) the results were more satisfactory. The much more basic imidazole (**7**) and benzimidazole (**8**) yield mixtures poor in adduct (the basicities of the four azoles, as measured by their pK_as, are ~1.6 **5**, 2.48 **6**, 6.99 **7** and 5.56 **8**).[11]

Table 1. Experimental conditions and results obtained

No.	Azole (eq.)	Glyoxal (eq.)	Conditions	Adduct/azole proportions
1	**5** (2)	(1)	AcOH/H_2O	60 (**1**)/40 (**5**)
2	**5** (2)	(1)	AcOH/H_2SO_4	60 (**1**)/40 (**5**)
3	**5** (2)	(1.5)	AcOH/H_2O	50 (**1**)/50 (**5**)
4	**5** (1)	(1)	AcOH/H_2SO_4	60 (**1**)/40 (**5**)
5	**5** (1)	(2)	AcOH/H_2SO_4	50 (**1**)/50 (**5**)
6	**6** (2)	(1)	AcOH/H_2SO_4	70 (**2**)/30 (**6**)
7	**7** (2)	(1)	AcOH/H_2SO_4	15 (**3**)/85 (**7**)
8	**8** (2)	(1)	AcOH/H_2SO_4	10 (**4**)/90 (**8**)

It has been reported that [1,4]-dioxane-2,3-diol (DODO) is an convenient alternative to glyoxal.[12] The results obtained with DODO are reported in Table 2.

Table 2. Experimental conditions and results obtained with DODO (we have used the same numbering as in Table 1 to facilitate the comparisons with AcOH/H_2SO_4 experiments)

No.	Azole (eq.)	DODO (eq.)	Conditions	Adduct/azole proportions
2	**5** (2)	(1)	DMF/70 ºC	55 (**1**)/45 (**5**)
6	**6** (2)	(1)	DMF/70 ºC	65 (**2**)/35 (**6**)
7	**7** (2)	(1)	DMF/70 ºC	50 (**3**)/50 (**7**)
8	**8** (2)	(1)	DMF/70 ºC	45 (**4**)/55 (**8**)

Two results of Table 2 are worth mentioning: i) in all cases about 50% of the starting azole remains; ii) the proportion of the adduct in the first two cases is only slightly worse (about 5% less adduct) but much better in the two last examples (imidazole and benzimidazole) where there is about 35% more adduct.

NMR spectroscopy

A list of ^{1}H and the ^{13}C NMR chemical shifts in solution for 1,2-di(benzotriazol-1-yl)ethane-1,2-diol (**1**) has been reported in the literature;[8,9] in this work, we have assigned all the protons and carbons of both stereoisomers (Tables 3 and 4) using the differences in intensities of both diastereoisomers and 2D ^{1}H-^{13}C correlations. In the case of the benzotriazole derivative, the ratio of the most abundant to the less abundant in DMSO-d_6 according to the integrals of the two aliphatic CH signals (Figure 4) is 78/22, in agreement with Katritzky's results.[9] According to this author they correspond to *meso* and *d,l* forms, respectively.

All adducts have an Az-CHOH-CHOH-Az structure to which corresponds an AA'BB' system in the ^{1}H NMR. In the case of compound **2** (see Table 3) the system has been analyzed and the coupling constants determined for both isomers. Note the almost identical nature between our values and those of Katritzky for the methine CH signals (6.97/7.00 and 6.94/6.95 ppm) and for the proportions (78/22 and 75/25).

Table 3. ^{1}H NMR chemical shifts (δ/ppm) and coupling constants (*J*/Hz) in DMSO-d_6 of **1**, **2**, **3** and **4**

Comp.	H2	H3	H4	H5	H6	H7	CH	OH
1 *major*[a]	-----	-----	8.10 (m)	7.45 (m) ^{3}J=^{3}J=7.6	7.61 (t)	8.10 (m)	6.97 (s)	n.o.[c]
1 *minor*[b]	-----	-----	7.96 (m)	7.31 (t) ^{3}J=^{3}J=7.6	7.45 (m)	7.96 (m)	6.94 (s)	n.o.[c]
2 *major*	-----	7.49 (d) ^{3}J=1.6	6.27 (t)	7.79 (d) ^{3}J= 2.3	-----	-----	5.90 (m)	6.98 (m) $^{3}J_{HCCH}$= 6.90 $^{3}J_{HOCH}$= 6.43 $^{4}J_{HOCH}$= –0.35 $^{5}J_{HOOH}$= 0.00[d]
2 *minor*	-----	7.37 (d) ^{3}J=1.6	6.15 (t)	7.69 (d) ^{3}J= 2.3	-----	-----	5.86 (m)	7.26 (m) $^{3}J_{HCCH}$= 5.25 $^{3}J_{HOCH}$= 6.70 $^{4}J_{HOCH}$= –0.07 $^{5}J_{HOOH}$= 0.00[d]
3 *major*	7.71 (s)	-----	6.91 (br s)	7.23 (br s)	-----	-----	5.67 (br s)	n.o.[c]
3 *minor*	7.50 (s)	-----	6.80 (br s)	7.07 (br s)	-----	-----	5.72 (br s)	n.o.[c]
4 *major*	8.49 (s)	-----	7.69 (d) ^{3}J=7.9	7.23 (m)	7.28 (m)	7.86 (d) ^{3}J=7.7	6.29 (br s)	n.o.[c]
4 *minor*	8.16 (s)	-----	7.50 (m) ^{3}J=7.8	7.11 (m)	7.11 (m)	7.50 (m) ^{3}J=7.8	6.35 (br s)	n.o.[c]

[a] *meso* (78%); [b] *d,l* (22%); [c] n.o. = not observed; [d] Assuming that $^{5}J_{HOCCOH}$ = 0.00 Hz.

Table 4. ^{13}C NMR chemical shifts (δ/ppm) in DMSO-d_6 of **1**, **2**, **3** and **4**

Comp.	C2	C3	C3a	C4	C5	C6	C7	C7a	CH
1 *major*[a]	-----	-----	145.5	119.3	124.3	127.6	111.6	132.2	82.2
1 *minor*[b]	-----	-----	145.1	119.0	124.1	127.4	111.6	131.7	83.0
2 *major*	-----	138.8	-----	105.4	129.0	-----	-----	-----	83.7
2 *minor*	-----	138.7	-----	105.2	128.4	-----	-----	-----	84.2
3 *major*	136.1	-----	-----	128.1	117.0	-----	-----	-----	80.8
3 *minor*	135.7	-----	-----	127.9	116.9	-----	-----	-----	81.0
4 *major*	142.8	-----	143.8	119.4	122.3	121.8	112.2	132.8	79.9
4 *minor*	142.0	-----	143.1	119.2	122.2	121.6	111.5	132.7	80.1

[a] *meso* (78%); [b] *d,l* (22%).

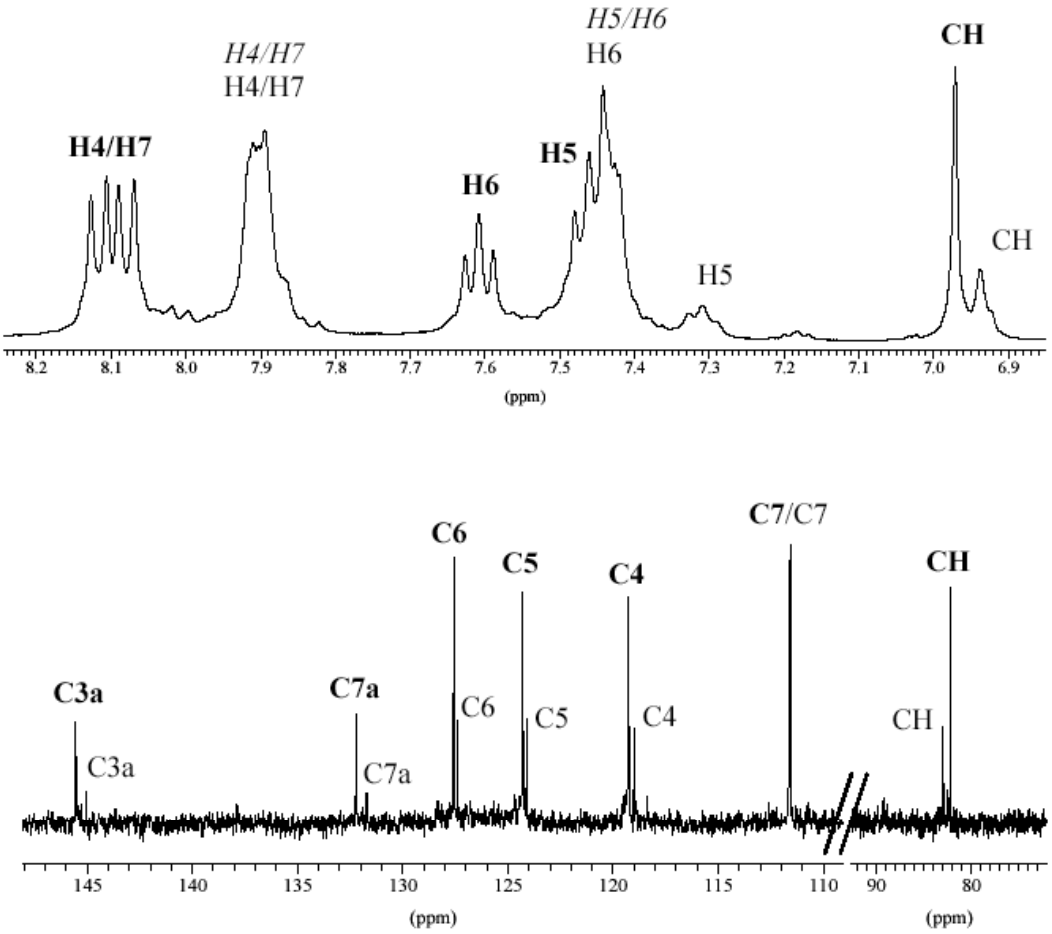

Figure 4. ^{1}H and ^{13}C NMR spectra signals of **1** in DMSO-d_6, showing the presence of the *major* form (boldface), the *minor* form (regular) and benzotriazole (**5**, italics).

In the ^{1}H NMR spectrum of 1,2-di(pyrazol-1-yl)ethane-1,2-diol (**2**) in DMSO-d_6 a mixture of stereoisomers and unreacted pyrazole is observed (Figure 5). The ^{1}H (Table 3) and ^{13}C (Table 4)

chemical shifts of the *major* and *minor* isomers (methine CH) show similar differences as in the case of benzotriazole **1** (+0.04 *vs*. +0.03 ppm and –0.5 *vs*. –0.8 ppm). Therefore, we conclude that also in the case of **2** the *major* isomer is the *meso* and the *minor*, the *d,l*. The signals appear duplicated in the ^{13}C NMR spectrum in DMSO-d_6 solution for **2** (Table 4 and Figure 5).

The coupling constants corresponding to the CH and OH groups of the *major* and *minor* isomers of compound **2** can be analyzed as an AA'XX' spectrum. For the HCCH couplings we have used a modified Karplus equation that takes into account two N and two O substituents:

$$^3J_{HCCH} = 4.9 \cos^2 \theta + 1.4 \quad (1)^{13}$$

We have modified the Karplus equation for a HCOH coupling

$$^3J_{HCOH} = 10.4 \cos^2 \theta - 1.5 \cos \theta + 0.2 \quad (2)^{13}$$

taking into account the presence of an N substituent:

$$^3J_{HCOH} = 8.4 \cos^2 \theta - 0.8 \cos \theta + 0.7 \quad (3)$$

We are aware that a 1-pyrazolyl substituent is not a standard amino group, nevertheless, we have applied eqs. (1) and (3) to the calculated conformations (see later).

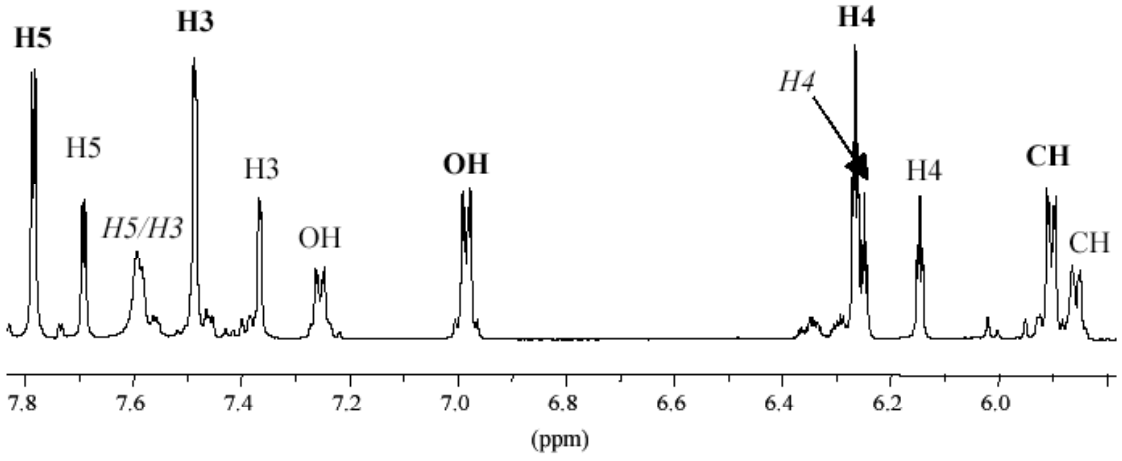

Figure 5. ^{1}H NMR spectrum signals of **2** in DMSO-d_6, showing the presence of *meso* form (boldface), *d,l* form (regular) and pyrazole (**6**, italics).

Using the ^{1}H CH signals of the bridge (Table 3) the following proportions of the *major* and

minor diastereoisomers were found: **1** 78/22; **2** 67/33; **3** 69/31; **4** 75/25. To these ratios correspond $\Delta G^{298.15}$ (in kJ mol^{-1}) of: **1** –3.1; **2** –1.8; **3** –2.0; **4** –2.7, that is, –2.4 kJ mol^{-1} on average, always in favor of the *meso* isomers.

Theoretical results

We have carried out B3LYP/6-31G* calculations (see experimental part) for derivatives **1** and **2**. The results are reported in Tables 5 and 6.

Table 5. Energies (hartree) and relative energies (kJ mol^{-1}) for bisadducts **1** *meso* and **1** *d,l*

Benzotriazole adducts	*meso* [gas]	*d,l* [gas]	diff. [gas]	*meso* [DMSO]	*d,l* [DMSO]	Diff. [DMSO]
(**1**)	–1019.59803	–1019.60133	+8.6	–1019.62362	–1019.62201	–4.2

Table 6. Energies (hartree) and relative energies (kJ mol^{-1}) for different bisadducts **2** *meso* and **2** *d,l*. The values between parentheses are relative values within the *meso* compounds

Pyrazole adducts	*meso* [gas]	*d,l* [gas]	Diff. [gas]	*meso* [DMSO]	*d,l* [DMSO]	Diff. [DMSO]
(**2a**)	–680.26536	-------	16.7 (0.0)	–680.28364	-------	4.4
(**2b**)	–680.25837	-------	35.0 (18.4)	–680.27612	-------	24.1 (19.7)
(**2c**)	–680.25484	-------	44.3 (27.6)			
(**2d**)	–680.25284	-------	49.6 (32.9)			
(**2e**)	-------	–680.25714	38.2			
(**2f**)	-------	–680.25811	35.7			
(**2g**)	-------	–680.27171	**0.0**	-------	–680.28531	**0.0**
(**2h**)	-------	–680.25654	39.8	-------		

A negative value of the difference means that the *meso* is more stable; a positive one corresponds to the *d,l* being more stable. For compound **1**, according to the calculations, the *d,l* is the most stable in absence of solvents (+8.6 kJ mol^{-1}) and the *meso* when a continuum model is used to simulate DMSO (the –4.2 kJ mol^{-1} value corresponds to ΔH). This last value agrees reasonably well with the experimental result, since in DMSO, the ratio 78/22 corresponds to $\Delta G^{298.15} = -3.1$ kJ mol^{-1}.

In the case of **2** we have carried out a wider study because in this case we know some coupling constants of the CHOH-CHOH fragment that can be used in defining the conformations. We have calculated four *meso* forms and four *d,l* ones. In Fig. 6 we also added the coupling constants calculated with eqs. (1) for θ and (3) for ϕ. When there are two values for dihedral angle ϕ, we have calculated a $^3J_{HCOH}$ coupling corresponding to the average. See Figure

7 for the calculated minimum energy conformations.

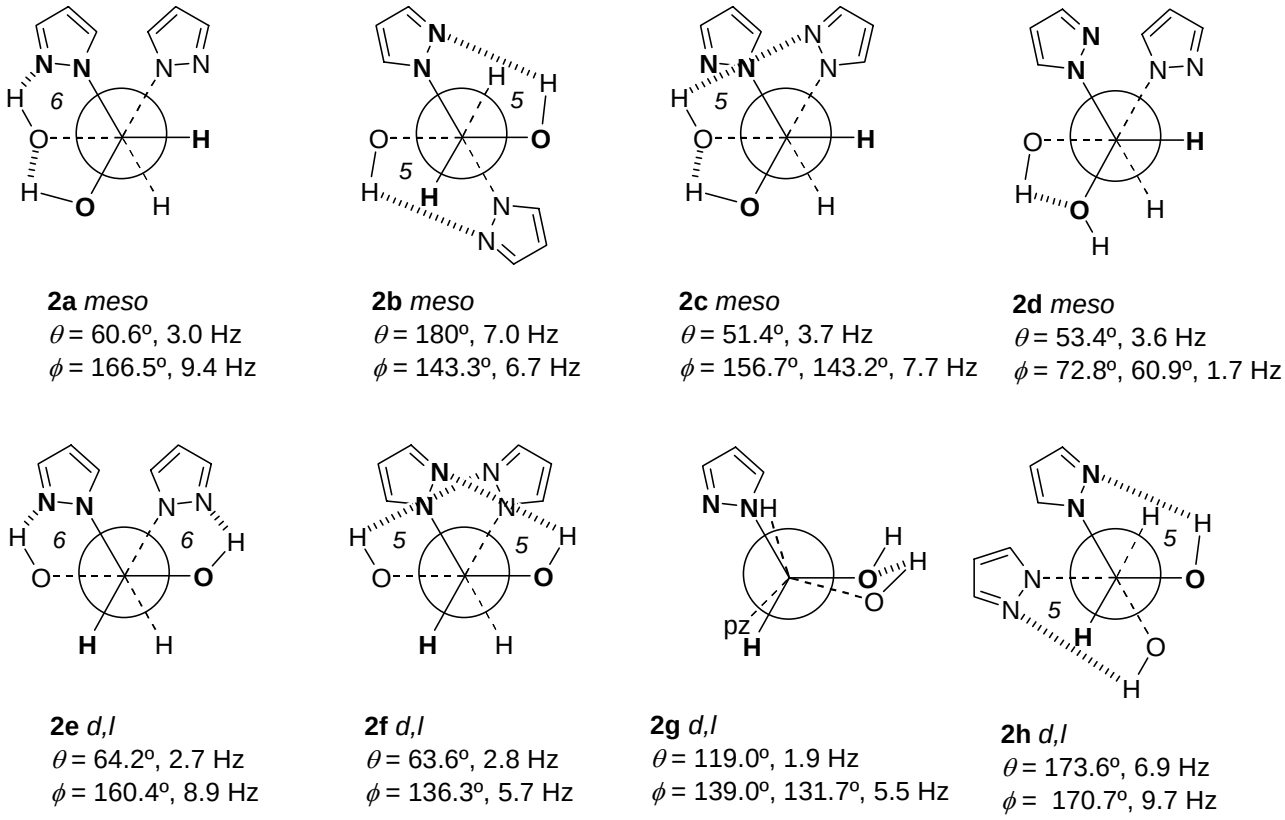

Figure 6. The eight calculated conformations of **2** (Table 6).

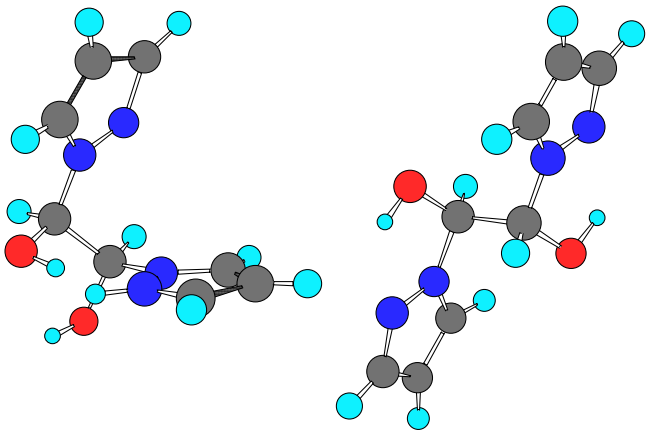

Figure 7. 2a (left) and **2b** (right) *meso* minimum energy conformations.

The *meso* isomer has coupling constants of $^3J_{HCCH}$ = 6.90 and $^3J_{HCOH}$ = 6.43 Hz, that correspond to **2b**. The *d,l* isomer has coupling constants of $^3J_{HCCH}$ = 5.25 and $^3J_{HCOH}$ = 6.70 Hz, that could correspond to a mixture of **2g** and **2h**.

The calculated relative energies of Table 6 (only the most stable have been calculated in DMSO) are: **2g** (*d,l*) 0.0 < **2a** (*meso*) 4.4 < **2b** (*meso*) 24.1 kJ mol^{-1}. The experimental value is –1.8 kJ mol^{-1} (67/33 in favor of the *meso*) that, according the coupling constants, is **2b**.

Conclusions

We have shown that the reactions of double addition of azoles to glyoxal are never complete and that the more basic the pyrazole is, the less complete the addition. The pyrazole derivative **2** has been characterized by NMR in what concerns the *meso vs*. *d,l* isomerism. Computational results are in accordance with the experimental data for benzotriazole **1**, but only partly to pyrazole adducts. It is possible that DMSO (calculated as a continuum) may break down the O–H···O HB of **2a** and **2g** destabilizing it with regard to **2b** and **2h** (both with two pseudo-five membered rings) having strong N–H···N HBs.

Experimental Section

General procedures for the synthesis of 1, 2, 3, and 4

A) Azole, sulfuric acid, and acetic acid were stirred at 75 ºC, and a 40% aqueous solution of glyoxal, was added. The mixture was kept at room temperature for 24 h, whereupon the solid was filtered off, washed with first with acetic acid, then twice with water and dried.[8]

B) A mixture of azole, 40% aqueous solution of glyoxal and acetic acid in water was allowed to stand overnight at room temperature. The resulting precipitate was collected by filtration, washed with water and dried.[9] This work-up corresponds to benzotriazole **1** and pyrazole **2** derivatives. In the case of imidazole and benzimidazole (adducts **3** and **4**) the final acid solution was evaporated and the resulting oil was washed with a small amount of cold 1:1 ethanol-water mixture, and then analyzed by NMR. Even in the case of solids, **1** and **2**, the melting point is meaningless because they are ternary mixtures of *meso*, *d,l* and starting azoles (**5**, **6**).

C) A solution of pyrazole (**6**, 1.13 g, 16.65 mmol) and 1,4-dioxane-2,3-diol (DODO, 1g, 8.33 mmol) in 3 mL of anhydrous DMF was heated under an Ar atmosphere at 70º C for 1 h 30 min. After cooling, the precipitate was filtered and washed with dichloromethane.

Even in the case of solids, **1**, **2**, **3** and **4**, the melting point is meaningless because they are ternary mixtures of *meso*, *d,l* and starting azoles (**5**, **6**, **7** and **8**).

NMR Experiments. ^{1}H (400.13 MHz) and ^{13}C (100.61 MHz) spectra in solution were obtained with a Bruker DRX-400 instrument at 300 K. Chemical shifts (δ in ppm) are given from internal solvents, THF-d_8 (3.58 ppm) and DMSO-d_6 (2.49 ppm) for ^{1}H NMR; THF-d_8 (67.4 ppm) and DMSO-d_6 (39.5 ppm) for ^{13}C NMR. Typical parameters for ^{1}H NMR spectra were spectral width 5000 Hz, pulse width 7.5 μs at an attenuation level of 0 dB and resolution 0.63-0.27 Hz

per point. Typical parameters for ^{13}C NMR spectra were spectral width 20500 Hz, pulse width 10.6 μs at an attenuation level of -6 dB and resolution 0.63 Hz per point; WALTZ-16 was used for broadband proton decoupling; the FIDS were multiplied by an exponential weighting (lb = 1 Hz) before Fourier transformation. 2D inverse proton detected heteronuclear shift correlation spectra, ^{1}H-^{13}C gs-HMQC, were carried out with the standard pulse sequences.[14] Attempts to differentiate *meso* and *d,l* isomers in the case of **2** in DMSO-d_6 solution (the compound is very insoluble in $CDCl_3$) failed both with chiral LSR [Eu(hfc)$_3$] and with Pirkle's alcohol.

Computational details. The geometry of the molecules has been optimized at the B3LYP/6-31G* computational level[15,16] within the Gaussian-03 package.[17] The minimum nature of the structures has been confirmed by frequency calculation at the same computational level. The solvent continuum model PCM has been used with the parameters defined for DMSO to model the solvation effect on the conformational energy.[18]

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