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Full Paper

Oximes in the Isoxazolone, Pyrazolone, and 1,2,3-Triazolone Series: Experimental and Computational Investigation of Energies and Structures of *E*/*Z* Isomers of α-Oxo-Oximes in the Gas Phase and in Solution

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The structures of a series of heterocyclic α-oxo-oximes, viz. 4-oximinoisoxazolone-5(4*H*)-ones **1** and **2**,4-oximino-5(4*H*)-pyrazolones **3**–**5**, and 4-oximino-1-phenyl-1,2,3-triazol-5(4*H*)-one **6**, were investigated experimentally and computationally. Whereas the intramolecularly H-bonded *ZZ* isomers of these oximes are usually the most stable in the gas phase, this preference is overcome by intermolecular H-bonding to a solvent or another molecule. For 1,3-dimethyl-4-oximino-5(4*H*)-pyrazolone **3b** a turnaround is seen when going from the solid (predominantly *Z* isomer) to DMSO solution (predominantly *E* isomer), which can be ascribed to an intermolecular H-bond between the oxime OH function and a DMSO molecule. Such isomerization is not seen in $CDCl_3$, where intermolecular H-bonding is unimportant. The *Z*/*E*-isomerization in DMSO solution is accelerated by photolysis. Calculations of the energies of different conformers, and of ^{13}C NMR data at the GIAO-ωb97xD/6-31G(d)//M06-2X/6-311++G(d,p) level permit a clear-cut correlation of conformer structures with observed ^{13}C NMR spectra.

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Introduction

Although the structures and properties of oximes have been investigated for over 130 years,[1] there are still important questions, such as which isomer, *E* or *Z*, is the most stable, and how do we determine this from spectroscopic data? *E*/*Z* isomerization in aldoximes was formerly called *syn*/*anti* isomerization, which was defined with respect to the orientation of the imine CH (or the smallest group in ketoximes); thus, in many cases *E* corresponds to *syn* (Chart 1).

Four structures are required in order to specify the orientation of the hydrogen atom in the N–OH function, for example the structures *ZZ*, *ZE*, *EE*, and *EZ* shown for α-oximinoketones (monoximes of α-diketones) in Chart 1. It can be important to distinguish these because, as discussed in this paper, the *ZZ* isomer can form intramolecular H-bonds to the C=O groups, but the other three can form intermolecular H-bonds, which may be more important and thus influence the relative energies and spectroscopic properties.

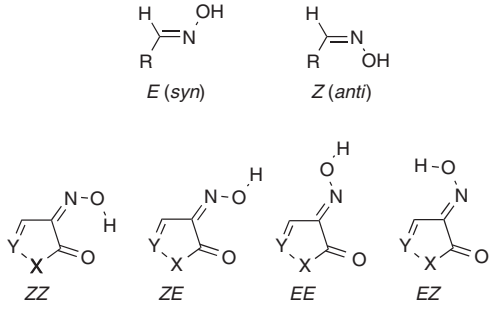


Chart 1. Oxime structure notations.

While the absolute structure of a crystalline oxime may be determined by X-ray crystallography, this does not necessarily reveal anything about the structure in solution, because some oximes have the tendency to crystallize in a form not expected from thermodynamic considerations. This can be ascribed to crystal lattice forces overcoming the usually small *E*/*Z* energy difference. Thus, acetaldoxime crystallizes as the *Z* isomer at 0°C,[2] but this material equilibrates in solution to give an *E*/*Z* ratio of ~40 : 60, corresponding to a free energy difference of 0.27 kcal mol^{-1} in favour of *Z* at 40°C.[3]

Reva and co-workers were able to vaporize the *Z* isomer from the crystalline acetaldoxime, isolate it in an Ar matrix, and obtain the IR spectrum. If the sample was first melted, *Z*/*E* equilibration occurred, and the resulting *Z*/*E* mixture was observed in the IR spectrum. When a liquid sample was frozen, the vapour over this solid was enriched in the *E* isomer.[4]

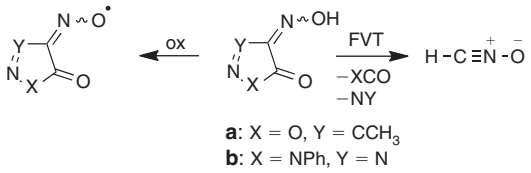
Phenylacetaldoxime also crystallizes as the *Z* isomer, which is therefore obtained initially on dissolution of the solid, but this

solution changes to predominately the thermodynamically preferred *E* isomer in the course of two days in benzene solution at room temperature, giving an *E*/*Z* ratio of 54 : 46, corresponding to a free energy difference of 0.1 kcal mol^{-1} in favour of *E*.[3]

Calculated barriers for pure, intramolecular *E*/*Z* isomerization in oximes in the gas phase are substantial, of the order of 55–60 kcal mol^{-1}, and they take place by nitrogen inversion,[5] but in the liquid state and in solution they are highly dependent on solvent polarity, acids and bases, and association.[4,6–8] Therefore, dramatically lower apparent activation barriers may be observed in solution. This makes it even more difficult to determine the preferred structures in solution. In the ^{1}H NMR spectrum of acetaldoxime, $CH_3C(H)$=N–OH, the quartet due to the methine proton of the *E* isomer resonates at higher field than that of the *Z* form in the neat liquid or in benzene solution,[3] but the opposite is observed in D_2O solution.[7] The enthalpy of activation for *E*/*Z* interconversion was determined as 13 kcal mol^{-1} in D_2O and about 16 kcal mol^{-1} in CCl_4.[7] The energy difference between the *Z* and *E* isomers was determined to be less than 1 kcal mol^{-1} (*E*/*Z* = 0.5–0.8 for various solvents, concentrations, and temperatures) and the preponderance of the *Z* isomer was ascribed not to its lower intrinsic energy but to preferential self-association of this isomer by intermolecular H-bonding. The lowest and highest *E*/*Z* ratios (0.5 and 0.8) were found in heptane and water, respectively. In the former, self-association is the most important; in the latter, intermolecular H-bonding with the solvent becomes important.[8]

In the ^{13}C NMR spectra, a *Z*-methyl group in acetone oxime, $(CH_3)_2C$=N–OH, resonates at higher field (6.5 ppm higher than the *E*-methyl), and this was ascribed to a screening effect of the *Z*-OH group.[9] In the acetophenone oxime, $Ph(CH_3)C$=N–OH, the *E(syn)*-CH_3 group appears at a 9 ppm higher field than the *Z(anti)*-CH_3 in $CDCl_3$ solution.[10] The imine carbon of the *E* isomer appears at lower field than that of the *Z* isomer. In isatin-3-oximes (isatoximes) and isatoxime ethers, the *E*-imine carbon again resonates at the lower field (147 versus 145 ppm), and the carbonyl group (C2) in the *E* isomer also appears at lower field (163 versus 157 ppm).[11] These oxime derivatives are reasonably stable configurationally, so that X-ray crystal structures can be used to aid the analysis of solution NMR data. In the case of 1,2-naphthoquinone 2-oxime, *Z*/*E* isomerization barriers of 49–52 kcal mol^{-1} (in the gas phase) were calculated at B3LYP and MP2 computational levels, and the lower-field C=O and C=N signals in the ^{13}C NMR spectrum (181 and 147 ppm, respectively) were assigned to the *EE* isomer based on calculations.[12] In a similar study, Ivanova et al. also concluded that the *EE* form was the major constituent, with a minor amount of the *ZZ* isomer postulated.[13] Here, the ^{13}C=O signal was shifted upfield by 1.3 ppm in the *ZZ* isomer. Both studies[12,13] emphasized the importance of inclusion of solvent effects (polarizable continuum model (PCM)) or the explicit inclusion of a DMSO molecule in the calculations in order to obtain correct relative energies in solution. In the cases of phenalene-1,2,3-trione 2-oxime and indane-1,2,3-trione 2-oxime, the lower field CO resonances were assigned to the *ZZ* structures for no obvious reason and probably erroneously; here, the two isomers equilibrated at 360 K in DMSO solution.[14] These examples demonstrate the need for great care in deducing structures of oximes from NMR spectra and in deciding on preferred isomer structures based on energy calculations.

Our interest in the chemistry of isoxazolones and related heterocycles,[15] in particular the very practical synthesis of fulminic acid, HCNO, by flash vacuum thermolysis of 4-oximino derivatives of isoxazol-5(4*H*)-ones,[16] pyrazolones and 1,2,3-triazol-5(4*H*)-ones[17] as well as the iminoxyl radicals generated by oxidation (Eqn 1) caused us to examine the nature of this type of oximes more closely. The results are reported herein.



(1)

Results and Discussion

The oximes examined here are shown in Chart 2. The compounds were examined by ^{1}H and ^{13}C NMR spectroscopy. In addition, their geometries were optimized at the M06-2X/6-311++G(d,p) level of theory both in the gas phase and in a simulated DMSO solvent field; the respective relative energies are given in Table 1.

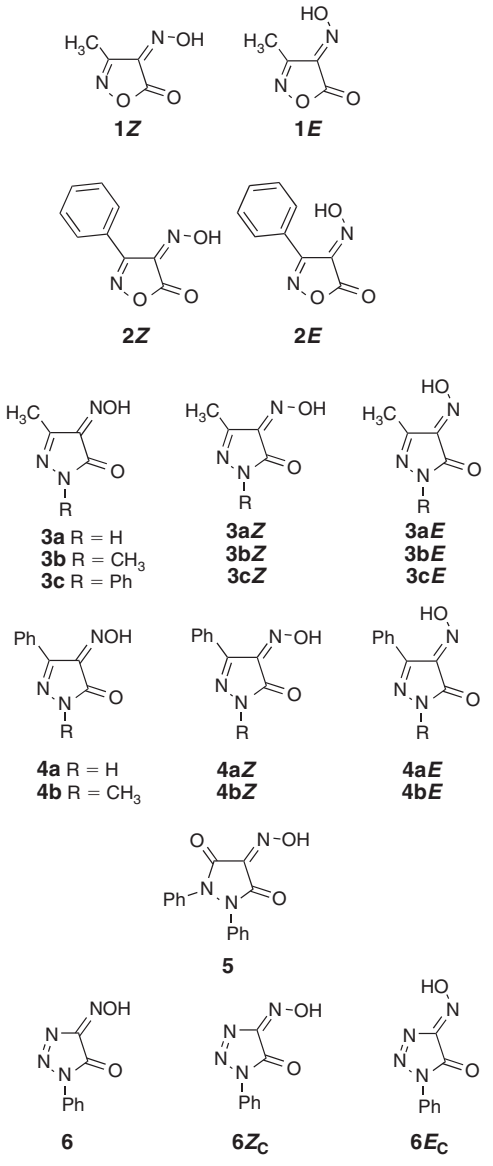


Chart 2. Oximes investigated in this paper. For compound **6** the same *Z*/*E* convention as for **1**–**5** is applied; this is indicated by the symbols Z_C and E_C, indicating that the stereochemistry is defined with respect to the C=O group.

NMR spectroscopic data were calculated at the GIAO-PCM-ωb97xD/6-31G(d)//PCM-M06-2X/6-311++G(d,p) level, which has proved its reliability in an extensive test of methods for the NMR calculation of heterocycles.[18] Calculations at the B3LYP/6-31G(d) level were also performed for several of the compounds in the present study, but these did not yield any further insight and are therefore not included in this paper. The influence of simulated DMSO and $CDCl_3$ solvation on the energies and NMR chemical shifts was investigated using the PCM model. The data are presented in Table 2.

Table 1. Relative energies (kcal mol^{-1}) of gas phase and solvated isomers of compounds investigated herein (M06-2X/6-311++G(d,p))

Compound	Gas phase				DMSO			
	ZZ	*ZE*	*EE*	*EZ*	*ZZ*	*ZE*	*EE*	*EZ*
1	0	1.5	0.9	9.6	0	−1.3	−1.7	4.9
Isatin-3-oxime **7**	0	3.4	0.0	8.7	0	1.6	−1.9	4.8
2a	0	1.9	3.2	8.0	0	−1.2	−0.2	4.5
3a	0	3.2	2.5	10.4	0	0.6	0.0	5.9
3b	0	3.6	2.9	10.7	0	0.9	0.3	6.2
3b ($CDCl_3$)[A]					0	1.7	1.1	7.7
3c	0	3.5	2.8	15.0	0	0.7	0.1	8.2
4a	0	3.8	4.9	9.2	0	0.6	1.4	5.6
4b	0	4.2	4.7	9.0	0	1.3	1.2	5.2
5	*Z* 0	–	*E* 2.3	–	*Z* 0	–	*E* 0.1	–
6[B]	0	1.5	1.1	1.6	0	−0.7	−1.7	0.2

[A]Energies for $CDCl_3$ instead of DMSO solution.
[B]For compound **6** the same *Z*/*E* convention as for **1**–**5** is applied, i.e. the stereochemistry is defined with respect to the C=O group (see caption for Chart 2).

In the case of 3-methyl-4-oximinoisoxazolone **1** both the *Z* and the *E* form of the oxime are observable by ^{13}C NMR spectroscopy, and the *E* isomer dominates. The structural assignments were made on the basis that the CH_3 group of the *Z* isomer appears at the higher field in both the ^1H NMR spectrum (2.2 ppm) and the ^{13}C NMR (10.7 ppm). C=O functions in *Z*-oxime isomers are expected to be shifted significantly upfield; for **1*Z*** to 159 ppm compared with 165 ppm for **1*E***. The upfield shifts of the *Z*-C=O groups in isatin-3-oxime derivatives, where secure X-ray structures are available,[11] are important points of reference.

The initial *E*/*Z* ratio for **1** measured shortly after dissolution in DMSO-d_6 was 94 : 6. After 48 h the *E*/*Z* ratio had fallen to 80 : 20. Therefore, it can be concluded that the solid oxime exists largely in the *E* form, but equilibration of the two isomers occurs in solution at room temperature. The changing *E*/*Z* ratio allows a straightforward correlation of ^1H and ^{13}C NMR spectra.

Phenomenologically the upfield shift of the *Z*-C=O group can be rationalized by noting that intramolecular (chelating)

Table 2. Experimental and computed ^{13}C NMR chemical shifts (in ppm, relative to TMS, for DMSO-d_6 solutions)

Compound	Experimental data[A]	Computed data
1*ZZ*		12.8, 137.7, 155.7 (CO), 158.2 (C(N)–Me)
1*ZE*	10.7, 139.6, 156.6, 159.8	13.3, 136.4, 150.0 (CO), 157.9 (C(N)–Me)
1*EE*	15.0, 139.0, 153.6, 165.0	17.2, 136.1, 151.1 (C(N)–Me), 159.0 (CO)
1*EZ*		15.0, 135.2, 147.7 (C(N)–Me), 158.3 (CO)
1*ZE*·DMSO[B]		13.4, 134.2, 150.8, 158.4
1*EE*·DMSO[B]		17.3, 133.9, 150.8, 160.9
1*EE*·DMSO·H[C]		16.6, 131.7, 153.2, 174.2
7*ZZ*		26.5, 5 C_{arom}, 139.8, 141.0, 156.3
7*ZE*		26.6, 5 C_{arom}, 140.4, 140.8, 151.1
7*EE*	25.6, 5 C_{arom}, 142.7, 143.2, 163.9	26.9, 5 C_{arom}, 141.6, 142.3, 157.8
7*EZ*		27.9, 5 C_{arom}, 141.0, 142.0, 157.2
2*ZZ*		6 C_{arom}, 136.8, 156.1, 157.4
2*ZE*	4 C_{arom}, 139.3, 155.5, 158.4	6 C_{arom}, 135.4, 150.2, 157.3
2*EE*		6 C_{arom}, 133.6, 153.2, 158.9
2*EZ*		6 C_{arom}, 133.9, 150.9, 158.3
3b*ZZ*	12.1, 30.4, 143.8, 146.0, 152.3	14.2, 33.5, 142.9, 144.6, 152.2
3b*ZE*		14.6, 33.9, 141.6, 143.1, 147.4
3b*EE*	16.0, 30.8, 139.5, 143.6, 160.4	19.1, 34.0, 136.3, 141.5, 155.7
3b*EZ*		16.9, 34.1, 132.2, 140.5, 155.3
5*Z*	6 C_{arom}, 141.5, 152.0, 158.4	12 C_{arom}, 136.2, 150.1, 151.8
5*E*		12 C_{arom}, 134.8, 146.0, 151.9
6*ZZ*[D]		5 C_{arom}, 132.2, 150.4 (CO), 151.1 (CN)
6*ZE*		5 C_{arom}, 133.0, 145.7 (CO), 149.0 (CN)
6*EE*	3 C_{arom}, 136.3 (C1-aryl), 145.8 (CN), 160.3 (C=O)	5 C_{arom}, 130.6, 143.3 (CN), 154.2 (CO)
6*EZ*		5 C_{arom}, 130.2, 146.5 (CN), 153.2 (CO)

[A]Assignment of experimental data to an isomer is based on the calculated relative energies.
[B]A DMSO molecule is coordinated to the oxime OH-group (see text).
[C]A proton has been placed at a fixed distance of 1.45 Å from the C=O group oxygen (see text).
[D]For the stereochemical notation for compound **6** see caption for Chart 2.

H-bonding in β-dicarbonyl compounds also leads to an upfield shift of the H-bonded carbonyl carbon atom.[19] However, following the work of Caldeira and Gil,[8] the effect may be due to self-association and/or H-bonding with the solvent rather than intramolecular H-bonding. Therefore, experimentally we can only determine whether the compounds are *E* or *Z*; calculations are required to determine the relative importance of *ZZ*, *ZE*, *EE*, and *EZ* isomers.

For calculations of the gas-phase structures, the *ZZ* isomer with an intramolecular H-bond between the OH and C=O group is always the lowest energy. In all cases, solvation increases the relative energy of the *ZZ* conformer by 2–3 kcal mol^{-1}, as the intramolecular H-bonds become less important. For **1**, M06-2X predicts *EE* to be the most stable, followed by *ZE* lying 0.4–0.5 kcal mol^{-1} higher, in both $CDCl_3$ and DMSO, in excellent agreement with the experimental data. Explicit solvation with an additional DMSO molecule coordinating at the OH moiety also favours the *EE* form, and its preference over **1*ZZ*** remains unchanged (see Table S1, Supplementary Material).

It is striking that none of the computational approaches gave a value close to the experimental value of 165 ppm for the carbonyl carbon in **1*EE***. The deviations are 5–10 ppm, resulting in too small chemical shifts. Similar trends are observed for most of the other investigated compounds. However, when a proton is placed near the carbonyl oxygen atom at a typical H-bond distance (O···H = 1.45 A), simulating H-bond donation from another oxime molecule, the C=O carbon shifts to lower field at ~174 ppm (see Table 2). This indicates the importance of intermolecular H-bonds in **1*EE*** due to either self-association or solvation (although explicit DMSO solvation does not lead to significant changes in the ^{13}C chemical shifts). In general, the calculated spectra for **1*EE*** and **1*ZE*** agree quite well with the experimental data.

For the reference compound isatin-3-oxime **7** (Chart 3) the relative energy calculated for the *EE* isomer (in DMSO) is the lowest, and the simulated NMR data agree well with this finding.[20]

It is observed that the C=O signal in the *ZE* isomer is shifted upfield by about 5 ppm compared with all other conformers, regardless of the computational method and the investigated molecule. This is probably due to a shielding effect of the neighbouring HO lone pair, which is closest to the C=O group in this isomer.

In 3-phenyl-4-oximinoisoxazolone **2**, steric hindrance has the result that only the *Z* isomer was detected by ^{13}C NMR spectroscopy as judged by the upfield chemical shift of the C=O group (158 ppm). This is in agreement with the calculations, which predict the *ZE* isomer to have the lowest energy in DMSO (*ZZ* is most stable in the gas phase). There is also good agreement between the measured and the simulated NMR data (both for DMSO solution).

Both *E* and *Z* isomers of the 3-methyl-4-oximinopyrazolones **3** are observable by NMR spectroscopy. In the case of **3a** the *E* isomer dominates, analogously with the situation for the isoxazolone **1**. In the case of 1,3-dimethyl-4-oximinopyrazolone **3b** the *E*/*Z* ratio is dependent on the solvent used for crystallization as well as the solvent used for the NMR measurement. The *E*/*Z* ratio changes from an initial excess of the *Z* isomer to an excess of the *E* isomer in the course of 5 days in DMSO-d_6 solution at room temperature – but it stays largely unchanged in $CDCl_3$. We ascribe this phenomenon to intermolecular H-bonding to DMSO, favouring the *E* isomer. Moreover, UV-irradiation of a DMSO-d_6 solution of **3b** for 2 h using a 75 W low-pressure Hg lamp causes a change of the *E*/*Z* ratio from 18 : 82 to 60 : 40, and it then stays at this value for at least 48 h in the dark at room temperature. Similar irradiation of a $CDCl_3$ solution had no such effect. Presumably, population of the excited state of the oxime facilitates isomerization from *Z* to *E* in DMSO solution, but any such isomerization would be thermally reversed in $CDCl_3$ solution, where the *Z* isomer is the most stable.[21] Our calculations predict the *ZZ* form to be preferred by about 3 kcal mol^{-1} in the gas phase. In a simulated chloroform environment, it remains the most stable isomer by 1.1–1.7 kcal mol^{-1}, in agreement with the unchanged *E*/*Z* ratio in $CDCl_3$. Inclusion of DMSO solvation in the calculations leads to nearly equally stable *EE* and *ZZ* isomers of **3b**, in line with the observed ratio. Thus, this is another example of an oxime that crystallizes in the intramolecularly H-bonded *ZZ* form but changes (in part) to the solvent-stabilized *EE* form in DMSO solution (Scheme 1).

Compound **3c** was similar to **3a** and **1**, affording an *E*/*Z* ratio of ~75 : 25 immediately upon dissolution in DMSO, but this changed to ~30 : 70 in 7 days at room temperature. The *EE* and the *ZZ* forms are predicted to have similar stabilities.

In the oximopyrazolones **4**, the *Z* forms remain more stable even in solution, according to the calculations. As in the case of **2**, steric hindrance by the phenyl group disfavours *E* isomers. The large chemical shifts of the OH peaks in the experimental ^1H NMR spectra point to the presence of the most stable *ZZ* form (see the Supplementary Material for details of ^1H NMR calculations). 1,2-Diphenyl-4-oximinopyrazolidin-3,5-dione **5** exists only in one *E* or *Z* conformation due to its symmetry (*ZZ* = *EZ* and *EE* = *ZE*). The calculations predict both forms to be equally stable in DMSO; the simulated NMR data fit the *Z* form better.

In the case of the oximinotriazole **6** the calculations predict the lowest energy for the *ZZ* form in the gas phase (for compound **6** we have applied the same *Z*/*E* convention as for **1**–**5**; see caption for Chart 2). This ordering is – again – reversed in DMSO solution. In agreement with this, the computed NMR data clearly indicate that the *EE* conformer is the observed form in DMSO-d_6.

Conclusion

The preferred configurations of α-oxo-oximes can be understood on the basis of steric hindrance (at C3, disfavouring *E* isomers), lone-pair repulsion between C=O and OH groups

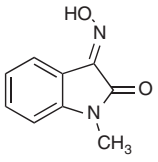
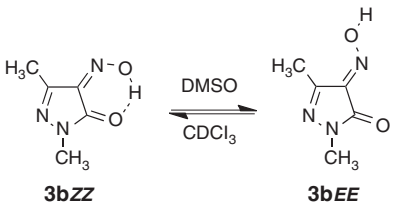


Chart 3. Isatin-3-oxime **7**.



3b*ZZ* **3b*EE***

Scheme 1. Solvent-dependent interchange of **3b*ZZ*** and **3b*EE*** isomers.

(disfavouring *ZE* isomers), and, most importantly, intramolecular H-bonding (favouring *ZZ* isomers) and intermolecular H-bonding (favouring *EE* isomers). Thus, for example, 3-methyl-4-oximinoisoxazolone **1** exists predominantly in the *EE* configuration, but the larger phenyl group causes oxime **2** to exist almost exclusively in the *ZE* configuration. The dimethyloximinopyrazolone **3b** crystallizes to give a preponderance of the intramolecularly H-bonded *ZZ* isomer, which is therefore observed as the major isomer by NMR spectroscopy in either $CDCl_3$ or DMSO-d_6 solution immediately upon dissolution, but it changes to an excess of the *EE* isomer in the course of 5 days in DMSO solution. This process is accelerated by photolysis in DMSO, but not in $CDCl_3$ solution and is ascribed to intermolecular H-bonding of the *EE* isomer with DMSO molecules.

Experimental

Note: as described in the text, NMR spectroscopy can only determine the presence of *Z* or *E* isomers, and their ratio. The NMR calculations are required in order to assign spectra to *ZZ*, *ZE*, *EE*, and *EZ* structures. The results of such analyses are presented in Table 2.

*3-Methyl-4-oximinoisoxazol-5(4*H*)-one* **1** was prepared in 84 % yield according to the literature method[22] and obtained as a white solid, mp 139–141°C (lit.[22] 141–142°C). δ_H (DMSO-d_6) *E*-isomer (major): 2.38 (s, 3H); *Z*-isomer (minor): 2.20 (s, 3H); both isomers: 10.4 (br s, 1H); *E*/*Z* ratio 30 min after dissolution: 94 : 6. *E*/*Z* ratio 48 h after dissolution: 80 : 20. δ_C (DMSO-d_6) *E*-isomer (major): 15.0, 139.0, 153.6, 165.0; *Z*-isomer (minor): 10.7, 139.6, 156.6, 159.8. λ_{max} (KBr)/cm^{-1} 3540–2400 (broad; maximum at 3220), 1755 vs, 1430 s, 1210 s, 1080 s, 1035 s, 855 s. *m*/*z* 128 (M^+, 5 %), 100 (3), 70 (8), 67 (4), 44 (99), 43 (75), 41 (100), 40 (55).

*3-Phenyl-4-oximinoisoxazol-5(4*H*)-one* **2** was prepared in 75 % yield according to the literature method[23] and obtained as yellow crystals, mp 143°C (lit.[23] 143°C). δ_H (DMSO-d_6) 7.4–7.7 (m, 5H), 9.8 (br s, 1H). δ_C (DMSO-d_6) (Z-isomer) 125.4, 127.0, 127.8, 131.7, 139.3, 155.5, 158.4. λ_{max} (KBr)/cm^{-1} 3200–2800 (broad; maxima at 3120 and 2830), 1785 vs, 1460 s, 1380 m, 1165 m, 1045 vs, 950 m, 880 s, 755 m, 735 m, 680 m, 660 m. *m*/*z* 190 (M^+, 3 %), 103 (100), 77 (14), 76 (33), 51 (10), 50 (14), 45 (32), 44 (18). Anal. Calc. for $C_9H_6N_2O_2$: C 256.85, H 3.18, N 14.73. Found: C 57.10, H 3.54, N 14.75.[21]

*3-Methyl-4-oximinopyrazol-5(4*H*)-one* **3a** was prepared in 84 % yield by the literature method;[24] mp 234–235°C (lit.[24] 230°C). δ_H (DMSO-d_6) *Z*-isomer: 2.06 (s, 3H), 11.34 (br s, 1H); *E*-isomer: 2.24 (s, 3H), 11.39 (br s, 1H); *E*/*Z* ratio immediately after dissolution: 70 : 30. λ_{max} (KBr)/cm^{-1} 3500–2800 (broad), 1695 s, 1610 s, 1275 s, 1045 s, 1020 s, 970 s, 730 s.

*1,3-Dimethyl-4-oximinopyrazol-5(4*H*)-one* **3b** was prepared from 1,3-dimethylpyrazol-5(4*H*)-one (4.5 g; 0.08 mol) and $NaNO_2$ by the method of Knorr[25] and obtained as a yellow solid (8.58 g; 76 %), recrystallized from either CCl_4 or H_2O, mp 144–145°C; λ_{max} (KBr)/cm^{-1} 3160 s (broad), 3000 s (broad), 2860 s (broad), 1675 s, 1615 m, 1455 m, 1030 s, 770 m. δ_H (DMSO-d_6) *E*-isomer (minor): 2.26 (s, 3H), 3.21 (s 3H); *Z*-isomer (major): 2.08 (s 3H), 3.19 (s, 3H); both isomers: 15.3 (br s). δ_H ($CDCl_3$) *E*-isomer (minor): 2.40 (s, 3H), 2.37 (s, 3H); *Z*-isomer (major): 2.26 (s 3H), 3.39 (s, 3H); both isomers: 15.5 (br s). The *E*/*Z* ratio is dependent on the solvent used for crystallization as well as the solvent used for NMR measurement. Compound **3b** recrystallized from CCl_4, measured immediately after dissolution, in DMSO-d_6: *E*/*Z* = 18 : 82; in $CDCl_3$: *E*/*Z* = 12/88. Compound **3b** recrystallized from H_2O, measured immediately after dissolution, in DMSO-d_6: *E*/*Z* = 31 : 69; in $CDCl_3$: *E*/*Z* = 18/82; after 5 d at room temperature: in DMSO-d_6: *E*/*Z* = 64 : 36; in $CDCl_3$: *E*/*Z* = 23/77. δ_C (DMSO-d_6) *Z*-isomer: 12.1, 30.4, 143.8, 146.0, 152.3; *E*-isomer: 16.0, 30.8, 139.5, 143.6, 160.4.

*3-Methyl-4-oximino-1-phenylpyrazol-5(4*H*)-one* **3c** was prepared according to Knorr[25] from 3-methyl-1-phenylyrazol-5(4*H*)-one (5.30 g; 0.031 mol) and sodium nitrite and obtained as a yellow solid (5.23 g; 83 %), mp 153–157°C from acetic acid (lit.[25] 157°C). λ_{max} (KBr)/cm^{-1} 3260 s (broad), 1695 s, 1615 m, 1585 m, 1495 m, 1420 m, 1360 m, 1305 m, 1030 s, 995 m, 990 m, 750 m. δ_H ($CDCl_3$) *E*-isomer (major): 2.60 (s, 3H), 7.4–8.3 (m, 5H); *Z*-isomer (minor): 2.42 (s 3H), 7.4-8.3 (m, 5H); *E*/*Z* ratio measured immediately after dissolution: 75 : 25, and similar in DMSO-d_6. δ_C (DMSO-d_6) 12.4, 151.4 (*Z*); 17.3, 159.4 (*E*); *E* and *Z* isomers 118.1, 125.0, 128.9, 137.7, 141.9, 144.0, 148.0.

*4-Oximino-3-phenylpyrazol-5(4*H*)-one* **4a** was prepared according to Ponzio and Ruggeri[26] and obtained as a yellow-orange solid, mp 177–182°C (with mild decomposition) (lit.[26] 180°C); λ_{max} (KBr)/cm^{-1} 3500 m (broad), 3230 s (broad), 2960 m (broad), 2900 m (broad), 1695 s, 1650 s, 1600 m, 1455 m, 1035 s, 915 s, 755 s, 740 s, 655 m. δ_H (DMSO-d_6) (only one isomer present): 7.46 (m, 3H), 7.94 (m, 2H), 11.90 (br s).

*1-Methyl-4-oximino-3-phenylpyrazol-5(4*H*)-one* **4b** was prepared according to Michaelis[27] and obtained as a yellow-orange solid, mp 157–164°C (subl. >75°C) (lit.[27] 162°C), λ_{max} (KBr)/cm^{-1} 3120 s (broad), 2970 s (broad), 2820 s (broad), 1660 s, 1600 m, 1455 s, 1395 m, 1030 s, 965 m, 890 s, 740 s, 680 m, 660 m, 640 m. δ_H (DMSO-d_6) (only one isomer present): 3.34 (s, 3H), 7.46 (m, 3H), 7.92 (m, 2H), 14.60 (br s).

1,2-Diphenyl-4-oximinopyrazolidin-3,5-dione **5** was prepared as described by Tsumaki[28] and obtained as a yellow-orange solid containing crystal water, mp 96–99°C. The monohydrate melts at 103°C.[29] The red, anhydrous compound melts at 163–164°C.[27] λ_{max} (KBr)/cm^{-1} 3420 m (broad), 2830 m (broad), 1755 s, 1720 vs, 1500 s, 1310 s, 1050 s, 770 m, 750 m. δ_C (DMSO-d_6) 123.4, 123.7, 125.9, 128.7, 135.3, 137.1, 141.5, 152.0, 158.4. For other spectroscopic properties, see Mondelli.[30]

*4-Oximino-1-phenyl-1,2,3-triazol-5(4*H*)-one* **6**[31] is light-sensitive and should be shielded from light during preparation and storage. It was prepared by nitrosation of 1-phenyl-5-oxo-1,2,3-triazole-4-carboxylate (0.02 mol) with $NaNO_2$ in alkaline solution. As described by Dimroth and Taub,[31] the initially formed red-blue dissolved product (probably the isomeric diazo-nitrosoacetanilide) precipitates on acidification as the oxime **6** in the form of a yellow powder (4 g; 97 %) with mp 130–190°C, whereby decomposition occurs at 190–210°C with a colour change from yellow over green to brown. The IR spectrum (KBr) of the yellow solid (oxime form) shows broad absorptions with maxima at 3460 and 2640 cm^{-1} and a strong C=O band at 1720 cm^{-1}. The compound is soluble in $CHCl_3$ and diphenyl ether without change. It is sparingly soluble in acetone and ethanol with complete transformation into the blue-green 4-nitroso-1,2,3-triazol-5-one isomer. The IR spectrum of the blue-green solid from acetone shows only a weak, broad absorption at 3320 cm^{-1} (NH) and a strong absorption at 1655 cm^{-1}. The blue-green compound was not obtained in a pure state, and it decomposes above 40°C. The yellow solid dissolves in DMSO with intense green colour, presumably as a mixture of the yellow oxime and the blue nitroso compound, but the dissolved material decomposes at room temperature in the course of a few hours with a colour change to yellow-orange.

Yellow (oximino-triazolone), red (diazo-nitrosoacetanilide), and green (nitroso-triazolone) salts, and yellow (oxime) and red (diazo) acyl derivatives of **6** have also been described.[32]

δ_H (DMSO-d_6) of compound **6** 7.21–7.60 (m, 3H), 7.78–7.89 (m, 2H). δ_C (DMSO-d_6) of compound **6** 119.5 (CH), 126.3 (CH), 129.2 (CH), 136.3 (C1-aryl), 145.8 (CN), 160.3 (C=O).

Computational Methods

Calculations were performed with the program package *Gaussian 09*.[33] Structures were optimized using the global hybrid functional M06-2X[34] with the 6-311++G(d,p)[35] basis set. In additional optimizations, solvent effects were included via the PCM[36] with a dielectric constant of 46.826 (DMSO) and 4.7113 (chloroform). Chemical shifts based on the PCM(DMSO) geometries were computed by using the gauge invariant atomic orbital method[37–39] (GIAO) and the dispersion corrected ω-B97xD functional[40] with the 6-31G(d) basis set.[41–43] Again, a simulated DMSO solvent field was applied. The PCM calculations were performed with the default settings for the respective solvent (see Supplementary Material for details).

Supplementary Material

Calculated ^{1}H and ^{13}C NMR data, absolute energies, and Cartesian coordinates of all computed structures and details of PCM parameters are available on the Journal's website.

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References

[1] (a) V. Meyer, A. Janny, *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 1164. doi:10.1002/CBER.188201501257
(b) V. Meyer, A. Janny, *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 1324. doi:10.1002/CBER.188201501285
(c) M. Yamane, K. Narasaki, in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations* (Ed. A. Padwa) **2004**, Vol. 27, Ch. 27.15, pp. 605–648 (Thieme: Stuttgart).
(d) *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids* (Eds Z. Rappoport, J. F. Liebman) **2009** (Wiley: Hoboken, NJ).

[2] R. E. Gawley, T. Nagy, *Tetrahedron Lett.* **1984**, *25*, 263. doi:10.1016/S0040-4039(00)99856-3

[3] G. J. Karabatsos, R. A. Taller, *Tetrahedron* **1968**, *24*, 3347. doi:10.1016/S0040-4020(01)92633-X

[4] A. Andrzejewska, L. Lapinski, I. Reva, R. Fausto, *Phys. Chem. Chem. Phys.* **2002**, *4*, 3289. doi:10.1039/B203240F

[5] R. D. Bach, G. J. Wolber, *J. Org. Chem.* **1982**, *47*, 245. doi:10.1021/JO00341A013

[6] R. Glaser, A. Streitwieser, *J. Am. Chem. Soc.* **1989**, *111*, 7340. doi:10.1021/JA00201A010

[7] C. E. Holloway, C. P. J. Vuik, *Tetrahedron Lett.* **1979**, *20*, 1017. doi:10.1016/S0040-4039(01)87178-1

[8] M. M. Caldeira, V. M. S. Gil, *Tetrahedron* **1976**, *32*, 2613. doi:10.1016/0040-4020(76)88037-4

[9] (a) G. C. Levy, G. L. Nelson, *J. Am. Chem. Soc.* **1972**, *94*, 4897. doi:10.1021/JA00769A017
(b) N. Gurudata, *Can. J. Chem.* **1972**, *50*, 1956. doi:10.1139/V72-310

[10] G. W. Buchanan, B. A. Dawson, *Can. J. Chem.* **1978**, *56*, 2200. doi:10.1139/V78-361

[11] (a) NMR and X-ray studies of isatin derivatives: N. Sin, B. L. Venables, X. Liu, S. Huang, Q. Gao, A. Ng, R. Dalterio, R. Rajamani, N. A. Meanwell, *J. Heterocycl. Chem.* **2009**, *46*, 432. doi:10.1002/JHET.84
(b) NMR: W. Holzer, Z. Gyorgydeak, *J. Heterocycl. Chem.* **1996**, *33*, 675. doi:10.1002/JHET.5570330326
(c) X-ray (*EE* structure): Y. Miao, X. Zhang, C. Liu, J. You, *Acta Crystallogr. Sect. E: Struct. Rep. Online* **2011**, *67*, o1291. doi:10.1107/S1600536811015418

[12] A. Krzan, J. Mavri, *Chem. Phys.* **2002**, *277*, 71. doi:10.1016/S0301-0104(02)00282-3

[13] G. Ivanova, V. Enchev, *Chem. Phys.* **2001**, *264*, 235. doi:10.1016/S0301-0104(01)00245-2

[14] V. Enchev, G. Ivanova, A. Ugrinov, G. D. Neykov, S. Minchev, N. Stoyanov, *J. Mol. Struct.* **1998**, *440*, 227. doi:10.1016/S0022-2860(97)00268-8

[15] (a) G. I. Yranzo, J. Elguero, R. Flammang, C. Wentrup, *Eur. J. Org. Chem.* **2001**, 2209. doi:10.1002/1099-0690(200106)2001:12<2209::AID-EJOC2209>3.0.CO;2-X
(b) H. S. Rzepa, C. Wentrup, *J. Org. Chem.* **2013**, *78*, 7565. doi:10.1021/JO401146K

[16] (a) C. Wentrup, B. Gerecht, H. Briehl, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 467. doi:10.1002/ANIE.197904671
(b) B. Winnewisser, P. Jensen, *J. Mol. Spectrosc.* **1983**, *101*, 408. doi:10.1016/0022-2852(83)90145-5
(c) T. Pasinszki, N. Kishimoto, K. Ohno, *J. Phys. Chem. A* **1999**, *103*, 6746. doi:10.1021/JP991394N
(d) G. Schulze, O. Koja, B. P. Winnewisser, M. Winnewisser, *J. Mol. Struct.* **2000**, *517–518*, 307. doi:10.1016/S0022-2860(99)00260-4
(e) W. Feng, J. F. Herschberger, *J. Phys. Chem. A* **2012**, *116*, 10285. doi:10.1021/JP306788R

[17] H. Müller-Starke, *Thermische Reaktionen von (4H)-Isoxazol-5-on-Derivaten und ESR-spektroskopische Untersuchungen an Radikalen aus 4-Oximino-(4H)-Isoxazol-5-onen und strukturverwandten Heterocyclen, Diplomarbeit* **1979**, Universität Marburg, Marburg, Germany.

[18] A. Buß, *Evaluation theoretischer Methoden zur Berechnung NMR-chemischer Verschiebungen von Heterocyclen, Bachelorarbeit* **2012**, Universität Oldenburg, Oldenburg, Germany. In this thesis, the level of theory employed in the current work (ωb97xD/6-31G(d)//M06-2X/6-311++G(d,p)) has proved to reliably reproduce the ordering of the chemical shifts.

[19] (a) J. B. Stothers, P. C. Lauterbur, *Can. J. Chem.* **1964**, *42*, 1563. doi:10.1139/V64-240
(b) J. H. Billman, S. A. Sojka, P. R. Taylor, *J. Chem. Soc., Perkin Trans. 2* **1972**, 2034. doi:10.1039/P29720002034
(c) H.-O. Kalinowski, S. Berger, S. Braun, *^{13}C-NMR Spectroscopy* **1991** (Wiley: Hoboken, NJ).

[20] There are two experimental sets of ^{13}C NMR data reported, one in $CDCl_3$ and one in DMSO. However, the two sets differ significantly in one value: while the third-largest shift in $CDCl_3$ is at 132.7 ppm, it is 142.7 ppm in DMSO. All our calculations predict this value to be around 141 ppm, so we assume that the number reported for the $CDCl_3$ measurement is erroneous due to a typing error.

[21] Examples of photoisomerization of oximes: (a) R. J. Olsen, *J. Photochem. Photobiol. A* **1997**, *103*, 91. doi:10.1016/S1010-6030(96)04482-6
(b) A. Olszanowski, E. Krzyzanowska, K. Alejski, *J. Chem. Technol. Biotechnol.* **1997**, *68*, 236. doi:10.1002/(SICI)1097-4660(199702)68:2<236::AID-JCTB642>3.0.CO;2-E

[22] L. Bouveault, A. Wahl, *Ber. Dtsch. Chem. Ges* **1905**, *38*, 928.

[23] L. Claisen, W. Zedel, *Ber. Dtsch. Chem. Ges* **1891**, *24*, 140. doi:10.1002/CBER.18910240124

[24] (a) T. Curtius, R. Jay, *J. Prakt. Chem.* **1889** [2], *39*, 52.
(b) T. Curtius, *J. Prakt. Chem.* **1894** [2], *50*, 512.
(c) M. Betti, *Gazz. Chim. Ital.* **1904**, *34I*, 211.

[25] L. Knorr, *Justus Liebigs Ann. Chem.* **1887**, *238*, 137 (185). doi:10.1002/JLAC.18872380107

[26] G. Ponzio, G. Ruggeri, *Gazz. Chim. Ital.* **1926**, *56*, 741.

[27] A. Michaelis, H. Dorn, *Justus Liebigs Ann. Chem.* **1907**, *352*, 152 (167). doi:10.1002/JLAC.19073520110

[28] T. Tsumaki, *Bull. Chem. Soc. Jpn.* **1931**, *6*, 1. doi:10.1246/BCSJ.6.1

[29] C. Cardani, L. Merlini, E. Boeri, *Gazz. Chim. Ital.* **1966**, *96*, 973.

[30] R. Mondelli, *Gazz. Chim. Ital.* **1965**, *95*, 1371.

[31] O. Dimroth, L. Taub, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 3915.
[32] O. Dimroth, O. Dienstbach, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 4055. doi:10.1002/CBER.190804103111
[33] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, Rev. B01* **2009** (Gaussian, Inc.: Wallingford, CT).
[34] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215. doi:10.1007/S00214-007-0310-X
[35] (a) A. D. McLean, G. S. Chandler, *J. Chem. Phys.* **1980**, *72*, 5639. doi:10.1063/1.438980
(b) R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, *J. Chem. Phys.* **1980**, *72*, 650. doi:10.1063/1.438955
(c) M. J. Frisch, J. A. Pople, J. S. Binkley, *J. Chem. Phys.* **1984**, *80*, 3265. doi:10.1063/1.447079
[36] (a) S. Miertus, E. Scrocco, J. Tomasi, *Chem. Phys.* **1981**, *55*, 117. doi:10.1016/0301-0104(81)85090-2
(b) S. Miertus, J. Tomasi, *Chem. Phys.* **1982**, *65*, 239. doi:10.1016/0301-0104(82)85072-6
(c) J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999. doi:10.1021/CR9904009
[37] F. London, *Naturwissenschaften* **1927**, *15*, 187. doi:10.1007/BF01505037
[38] F. London, *J. Phys. Radium* **1937**, *8*, 397. doi:10.1051/JPHYSRAD:01937008010039700
[39] R. Ditchfield, *Mol. Phys.* **1974**, *27*, 789. doi:10.1080/00268977400100711
[40] J. D. Chai, M. Head-Gordon, *J. Chem. Phys.* **2008**, *128*, 84106. doi:10.1063/1.2834918
[41] R. Ditchfield, W. J. Hehre, J. A. Pople, *J. Chem. Phys.* **1971**, *54*, 724. doi:10.1063/1.1674902
[42] W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257. doi:10.1063/1.1677527
[43] P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta* **1973**, *28*, 213. doi:10.1007/BF00533485