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Synthesis and structural study of tetrahydroindazolones

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Abstract—Multinuclear magnetic resonance spectroscopy allowed us to characterize four 1(2),5,6,7-tetrahydro-4*H*-indazol-4-one derivatives (**1**–**4**) and establish the most stable tautomer in each case. The crystal structure of 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) (orthorhombic space group *P*2(1)2(1)2(1), *a*=10.1243(8), *b*=21.526(2), *c*=24.992(2) Å, *Z*=4, 293 K) presents two different trimers, bonded through N–H···N hydrogen bonds involving tautomers 1*H* and 2*H*. In crystalline 3,6,6-trimethyl-2,5,6,7-tetrahydro-4*H*-indazol-4-one (**4**) (monoclinic space group *P*2(1)/*c*, *a*=5.9827(7), *b*=16.494(2), *c*=11.012(1) Å, *β*=93.464(2)°, *Z*=4, 293 K) only tautomer 2*H* exists forming a hydrogen-bonded network through the 4-oxo group and a water molecule.

1. Introduction

The main difference between pyrazoles **I** and their benzo derivatives, indazoles **II** (Fig. 1) is related to their annular tautomerism.[1] In pyrazoles **I**, although the tautomeric equilibrium constant depends on the nature of R^3 and R^5, it is always not very different from 1. Substituent R^4 (symmetric with regard to N1 and N2) exerts its effect through interactions with R^3 and R^5. In the case of indazoles **II**, the aromaticity of the benzene ring strongly favors the N(H)1 tautomer and only in very special cases tautomer N(H)2 becomes stable.[2]

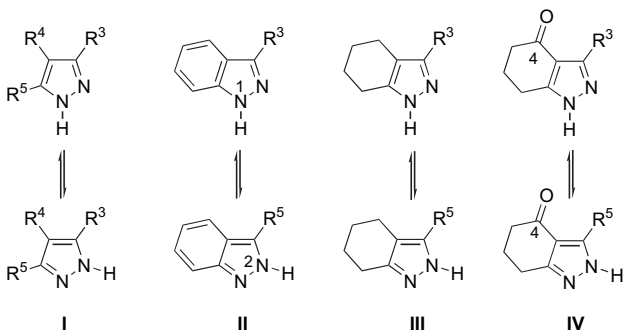

Figure 1. Structural relationships between derivatives **I**–**IV**.

If the six-membered ring is saturated, the resulting 4,5,6,7-tetrahydroindazoles **III** become again like pyrazoles [3(5),4-tetramethylenepyrazoles], both tautomers being again of similar energy.[3] The compounds that interest us now are 4-oxo derivatives **IV** of tetrahydroindazoles and therefore it is expected that, in what annular tautomerism is concerned, both tautomers would be of comparable stability.

Both pyrazoles[4,5] and indazoles[6,7] are frequently found in medicinal chemistry. Compounds **IV** have a structure intermediate between **II** and **III** because, even if the 4-hydroxy tautomer is energetically disfavored, the sp^2 hybridization at position 4 should modify the conformation of the six-membered ring.

The purpose of the present paper is twofold: (i) study the structure and tautomerism of compounds **1**–**4** belonging to the **IV** series; (ii) prepare new compounds related to indazoles for future studies as NOS inhibitors.[8–11] With these objectives, we have synthesized and characterized four 1(2),5,6,7-tetrahydro-4*H*-indazol-4-one derivatives shown in Figure 2, where the two main tautomeric forms are represented.

To approach the study of the interaction between new inhibitors and the heme catalytic domain of the endothelial isoform of NOS (eNOS),[12] it is crucial to elucidate in which tautomeric form the entitled compounds will exist. Thus, we have performed a structural study of compounds **1**–**4** to know the predominant, or the unique tautomer, by

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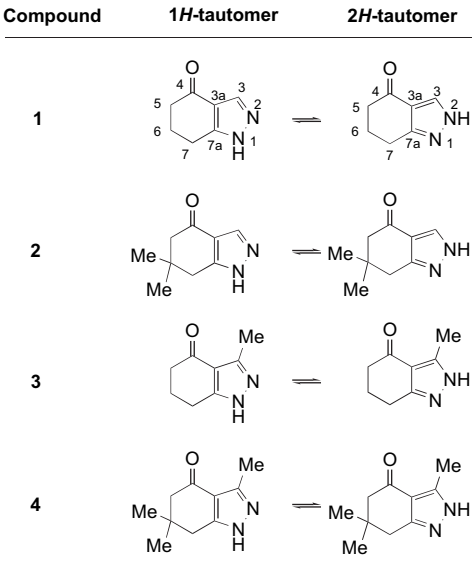


Figure 2. The four tetrahydroindazolones.

multinuclear NMR spectroscopy in solution and in solid state. Besides, in the cases of tetrahydroindazolones **2** and **4** the X-ray crystal structure was determined.

2. Results and discussion

2.1. Chemistry

4,5,6,7-Tetrahydroindazoles [3(5),4-tetramethylenepyrazoles] are usually prepared from cyclohexanone and its derivatives.[13,14] If instead of cyclohexanones, 1,3-cyclohexanediones are used, 1(2),5,6,7-tetrahydro-4*H*-indazol-4-ones are obtained.[15,16] These compounds (Fig. 3) have a rich reactivity with not less than four reactive positions that make them interesting scaffolds in medicinal chemistry.[17]

Known from a long time,[17–22] their chemistry was extensively studied by Sucrow et al. in 1970s and 1980s (see Ref. 24 for their reactivity)[23–29] with other significant contributions by Strakova and Gudriniece,[30] Akhrem (or Achrem),[31,32] Nunn and Rowell,[33] Schenone et al.,[34] Dalla Croce and La Rosa,[35] Le Tourneau and Peet,[36] Anderson-McKay et al.,[37] and Molteni et al.[38]

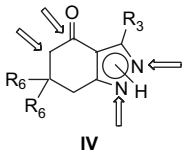
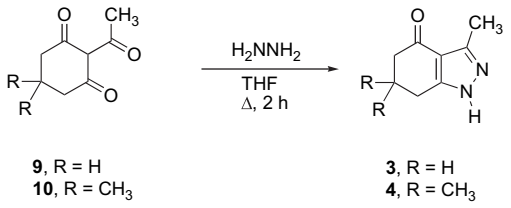


Figure 3. Reactivity of 6,6-disubstituted tetrahydroindazolones.

1(2),5,6,7-Tetrahydro-4*H*-indazol-4-one (**1**) and 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) (Scheme 1) were prepared according to the literature[38] starting from 1,3-cyclohexanedione (**5**) and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**6**), respectively, through the corresponding dimethylaminomethylene derivatives **7** and **8**.[34] Yields were moderate and their purification was achieved by column chromatography.

Similarly, 3-methyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**3**) and 3,6,6-trimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**4**) (Scheme 2) were synthesized[37] from 2-acetyl-1,3-cyclohexanedione (**9**) and 2-acetyldimedone (**10**) with satisfactory yields and their purification was straightforward (see Section 4).

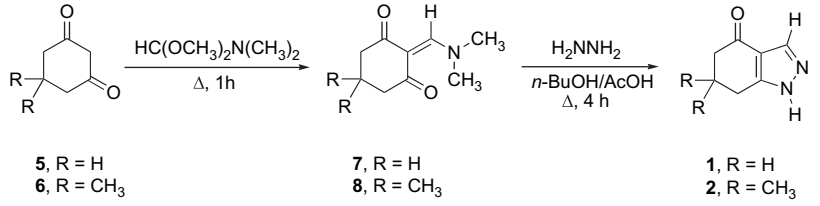


Scheme 2. Synthesis of compounds **3** and **4**.

Of the four compounds, only **2** was not previously reported. Since there are some discrepancies amongst the melting points (ours being measured by DSC) it is worth to recapitulate them here: compound **1** 163.8 °C (DSC), lit. 164–165 °C;[38] compound **2** 132.1 °C (DSC, new); compound **3** 160.3 °C (DSC), lit. 155 °C,[32] 152–154 °C;[35] compound **4** 101.4 °C (DSC), lit. 101–103 °C,[30] 101–102 °C,[31] 100.3–102.4 °C.[37]

2.2. Computational studies

On excluding OH-tautomers that are much less stable than the oxo forms,[39] the tautomerism of tetrahydroindazolones reduces, as in pyrazoles, to 1*H*- and 2*H*-tautomers. We already carried out computational studies (ab initio HF/6-31G*, HF/6-31G**, and DFT B3LYP/6-31G**)[39] establishing that in the gas phase tautomer 2*H* is the most stable one in all the four cases (B3LYP/6-31G**). On the other hand, according to HF/6-31G* and HF/6-31G** calculations, for derivatives **1** and **2**, tautomer 1*H* is more stable than 2*H* by about 0.65 kJ mol^{-1}, but for compounds **3** and **4** (with a methyl group at the 3-position) the 2*H* tautomer will be stabilized with respect to 1*H* by about 2 kJ mol^{-1}. The calculated dipole moments, by all methods, show that 1*H* tautomers have dipole moments nearly 2.5 times higher than 2*H* tautomers. Thus polar solvents will favor the 1*H* tautomer. In Table 1 we have summarized the results of



Scheme 1. Synthesis of compounds **1** and **2**.

Table 1. Energy differences in kJ mol^{-1} and dipole moments in brackets [Debye]

Compound	Methods	1*H*	2*H*
1	HF/6-31G**	0.0 [5.66]	0.45 [2.13]
	B3LYP/6-31G** (+ZPE)	1.18 [5.27]	0.0 [2.18]
2	HF/6-31G**	0.0 [5.65]	0.68 [2.12]
	B3LYP/6-31G** (+ZPE)	0.91 [5.26]	0.0 [2.17]
3	HF/6-31G**	2.03 [5.25]	0.0 [1.94]
	B3LYP/6-31G** (+ZPE)	3.64 [4.80]	0.0 [2.0]
4	HF/6-31G**	1.89 [5.24]	0.0 [1.94]
	B3LYP/6-31G** (+ZPE)	3.14 [4.79]	0.0 [2.0]

the calculations at the ab initio HF/6-31G** and density functional B3LYP/6-31G** levels for tautomers 1*H* and 2*H*.

2.3. NMR spectroscopy

In the following tables we report the NMR results concerning compounds **1**–**4**: Table 2 (^{1}H NMR), Table 3 (^{13}C NMR), and Table 4 (^{15}N NMR). Figure 4 illustrates the observation of the NH signals in ^{1}H NMR for compound **4**. Such clear observation of pyrazole tautomers is not at all usual,[40–42] in the present case it allows to determine the tautomeric equilibrium constants by simple integration of the ^{1}H NMR signals. The K_{eq} defined as [1*H*]/[2*H*] of 1.04 obtained for compound **3**, can be compared with that of 1.44 determined in 3-methyl-1(2),5,6,7-tetrahydroindazole,[43] allowing us to point out that a carbonyl group in position 4 favors the 2*H* tautomer.

The assignment of the signals has been achieved taking into account the chemical shift values, their multiplicity and, when necessary, 2D homonuclear and heteronuclear correlations were undertaken. Literature data concerning the ^{13}C NMR and ^{15}N NMR of pyrazoles have been of much use to assign the signals to each tautomer 1*H* and 2*H*.[44,45]

Table 2. Solution ^{1}H NMR chemical shifts (δ in ppm) of 1*H* and 2*H* tautomers with the indication of the equilibrium constants K_{eq} defined as [1*H*]/[2*H*]

Compound	%	K_{eq}	NH	H-3	H-5	H-6	H-7	CH_3(3)	CH_3(6)
1 (1*H*)[a]	65		13.15	7.74	2.35	2.01	2.82	—	—
1 (2*H*)[a]	35		13.24	8.19	2.35	2.01	2.74	—	—
1[a]		1.86							
1 (1*H*)[b]	63		12.61	7.73	2.37	2.06	2.87	—	—
1 (2*H*)[b]	37		12.69	8.16	2.37	2.06	2.77	—	—
1[b]		1.70							
2 (1*H*)[a]	57		13.14	7.75	2.27	—	2.68	—	1.00
2 (2*H*)[a]	43		13.14	8.19	2.27	—	2.68	—	1.00
2[a]		1.33							
2 (1*H*)[b]	55		12.75	7.76	2.28	—	2.77	—	1.06
2 (2*H*)[b]	45		12.83	8.21	2.28	—	2.67	—	1.06
2[b]		1.22							
3 (1*H*)[c]	51		14.32	—	2.40	2.05	2.87	2.45	—
3 (2*H*)[c]	49		14.34	—	2.40	2.05	2.82	2.53	—
3[c]		1.04							
4 (1*H*)[a]	44		12.72	—	2.22	—	2.65	2.28	1.00
4 (2*H*)[a]	56		12.86	—	2.22	—	2.56	2.39	0.98
4[a]		0.79							
4 (1*H*)[b]	42		12.56	—	2.24	—	2.71	2.32	1.03
4 (2*H*)[b]	58		12.75	—	2.24	—	2.60	2.45	1.03
4[b]		0.72							

[a] DMSO-d_6 at 300 K.
[b] THF-d_8 at 207 K.
[c] CD_2Cl_2 at 175 K.

Table 3. Solution ^{13}C NMR chemical shifts (δ in ppm) of 1*H* and 2*H* tautomers

Compound	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	CH_3(3)	CH_3(6)
1 (1*H*)[a]	136.7	117.9	192.4	37.8	23.2	20.4	150.3	—	—
1 (2*H*)[a]	128.7	117.9	193.8	38.6	23.5	22.4	155.8	—	—
2 (1*H*)[b]	137.7	118.1	193.5	52.8	36.5	34.8	149.9	—	28.5
2 (2*H*)[b]	129.4	118.1	191.9	53.3	36.0	37.2	156.0	—	28.5
3 (1*H*)[c]	148.0	114.9	194.8	37.9	22.5	20.9	151.2	13.4	—
3 (2*H*)[c]	141.9	114.5	196.0	38.5	23.1	23.3	156.7	11.1	—
4 (1*H*)[a]	146.8	113.9	192.4	52.3	35.4	34.2	150.0	13.2	27.9
4 (2*H*)[a]	140.8	113.5	193.8	52.7	34.9	36.5	155.3	10.5	27.9

[a] DMSO-d_6 at 300 K.
[b] THF-d_8 at 207 K.
[c] CD_2Cl_2 at 175 K.

In what concerns the ^{13}C NMR chemical shifts for each pair of tautomers the main conclusions from Table 4 are that in 1*H* tautomers δC-3 is downfield by about 7 ppm with respect to δC-3 of 2*H* tautomers, but on the contrary the δC-7a values for the 1*H* forms are upfield in approximately 5.5 ppm comparatively to those of tautomers 2*H*. The remaining signals have similar δ values and are not of use to distinguish between them.

In Table 4 are reported the chemical shifts of ^{15}N NMR of both tautomers for each compound, obtained by ^{1}H–^{15}N 2D inverse proton detection heteronuclear shift correlation experiments. The pyrrole N*H* was detected in all cases, but not so in the pyridine nitrogen, as no correlations could be observed in the experimental conditions tested.

The equilibrium constants in Table 2 should depend on the substituent at position 3 (0 if H and 1 if CH_3), the substituents at position 6 (0 if H and 1 if $(CH_3)_2$) and the solvent. For the solvent we have selected the SPP^N parameter.[46,47] A multiregression on the seven values leads to the following equation:

$$Ln\,K_{eq} = (0.109 \pm 0.018) - (0.519 \pm 0.003)\,\text{Pos 3} - (0.338 \pm 0.003)\,\text{Pos 6} + (0.510 \pm 0.020)\,SPP^N \qquad r^2 = 0.99994 \qquad (1)$$

The coefficients of Eq. 1 mean: the intercept corresponds to the unsubstituted compound **1** in the gas phase (SPP^N=0.00), i.e., in the gas phase there should be a slight excess of 1*H*-tautomer (53%). A methyl group at position 3 decreases

Table 4. Solution ^{15}N NMR chemical shifts (δ in ppm) of 1*H* and 2*H* tautomers

Compound	Solvent	N-1	N-2
1 (1*H*)	THF-d_8 at 207 K	−178.8	[a]
1 (2*H*)	THF-d_8 at 207 K	[a]	−175.1
2 (1*H*)	THF-d_8 at 207 K	−177.6	−79.2
2 (2*H*)	THF-d_8 at 207 K	[a]	−174.1
3 (1*H*)	CD_2Cl_2 at 175 K	−180.7	−102.6
3 (2*H*)	CD_2Cl_2 at 175 K	−110.1	−172.0
4 (1*H*)	THF-d_8 at 207 K	−183.2	[a]
4 (2*H*)	THF-d_8 at 207 K	[a]	−173.5

[a] No correlations were detected using gs-HMQC and gs-HMBC with various delays.

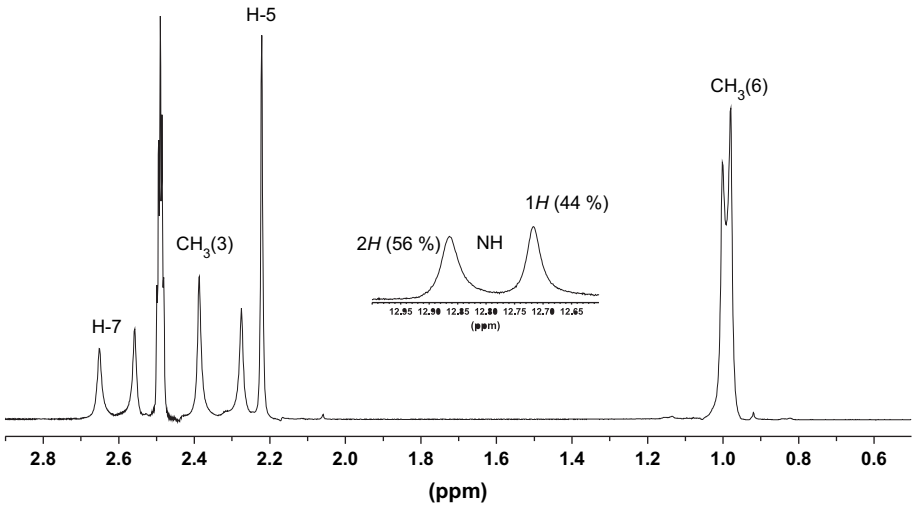


Figure 4. ^{1}H NMR spectrum of 3,6,6-trimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**4**) in DMSO-d_6 at 300 K.

the population of the 1*H*-tautomer probably due to a destabilizing interaction with the carbonyl oxygen (this will have consequences on the crystal structures of **2** and **4**). Although weaker, the same happens with a *gem*-dimethyl substitution at position 6 probably mediated by a conformational change of the six-membered ring. An increase of the solvent polarity favors the 1*H*-tautomer in agreement with the calculated dipole moments of Table 1.

Table 5 presents the NMR data, ^{13}C and ^{15}N chemical shifts, obtained for all compounds **1**–**4** in solid state. As the X-ray structures of derivatives **2** and **4** described in the next section of the present paper clearly show that 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) exists as a mixture of 2/3 of 1*H* and 1/3 of 2*H* tautomers (see Figs. 5 and 6 for the corresponding ^{13}C and ^{15}N CPMAS spectra) and 3,6,6-trimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one

Table 5. ^{13}C NMR and ^{15}N NMR chemical shifts (δ in ppm) in solid state of compounds **1**–**4**

Compound	N-1	N-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	Others
1	−172.1	−75.6	*138.1*	118.8	195.6	36.9	23.5	21.2	*151.5*	—
2	−111.7[a]		*132.2*	117.8	191.0	50.7	35.1	30.6	*150.1*	Me (6)
	−123.0[a]		*133.3*	118.6	192.0	51.8	36.0	32.2	*151.3*	25.6
	−139.7[a]		*135.0*	119.2	193.2				*151.9*	26.3
	−151.1[a]		*137.2*						*152.7*	27.7
	−165.0[a]									28.5
3	−178.5	−79.7	*146.2*	114.9	196.1	38.9	23.1	20.9	*152.3*	Me (3)
						40.1				14.8
4	−100.1	−163.2	*141.3*	113.3	196.9	53.2	36.0	36.0	*155.9*	Me (3)
										11.6
										Me (6)
										25.8, 30.9

[a] No assignment of the signals was made.

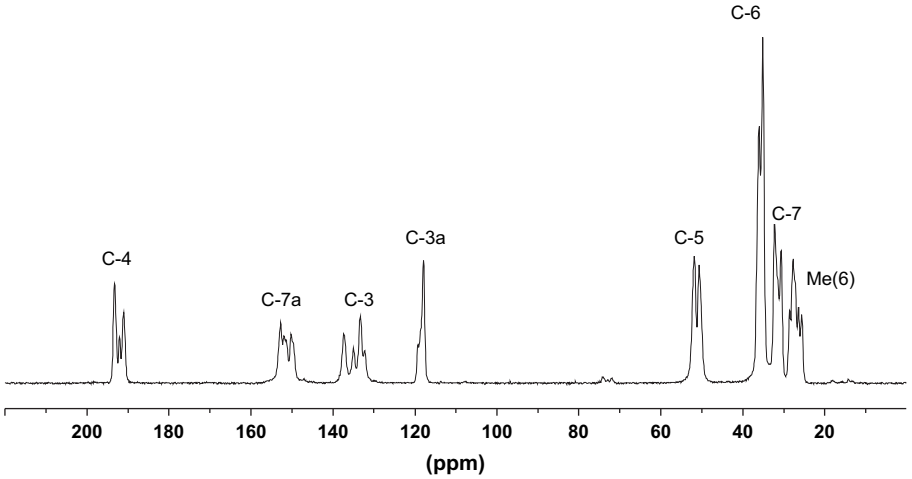


Figure 5. ^{13}C CPMAS NMR spectrum of 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) from dichloromethane/petroleum ether.

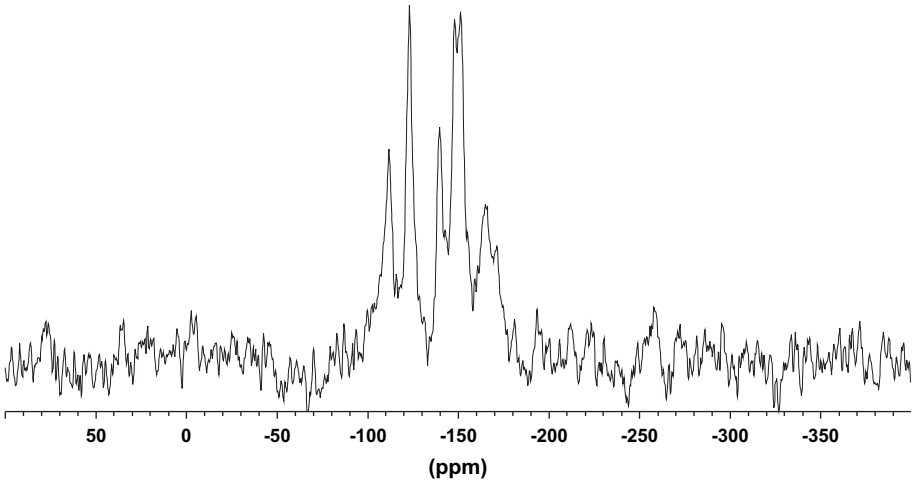


Figure 6. ^{15}N CPMAS NMR spectrum of 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) from dichloromethane/petroleum ether.

(**4**) only in the 2*H* form, in view of the CPMAS NMR data analysis we can conclude that derivatives **1** and **3** are 1*H* tautomers in solid state, confirming again that the predominating tautomer in solution is in most of the cases the one existing in solid state.[48]

2.4. X-ray crystal and molecular structures

Crystals of enough quality to be analyzed by X-ray diffraction were obtained only for compound **2** from dichloromethane/petroleum ether and for compound **4** from water.

Six crystallographic independent molecules bonded by strong hydrogen bonds were identified in the structural determination of 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**). All pyrazole rings are planar with distances and angles within the normal ranges.[49] Hydrogen bonds lead to trimers as shown in Figure 7 (Table 6).[50]

Table 6. Hydrogen bonds for compounds **2** and **4**, distances in Å, angles in °

Compound	D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	<(DHA)
2	N(11)–H(11)···N(12)	1.05	1.94	2.877(6)	147.3
	N(22)–H(22)···N(23)	1.06	1.76	2.802(6)	169.0
	N(13)–H(13)···N(21)	1.00	2.01	2.826(6)	137.5
	N(14)–H(14)···N(26)	0.99	1.92	2.891(7)	166.2
	N(16)–H(16)···N(15)	1.04	2.00	2.976(5)	154.5
	N(25)–H(25)···N(24)	0.94	1.83	2.765(7)	179.7
4	O(2)–H(2B)···O(1)	0.93	1.90	2.830(2)	172.5
	N(2)–H(2)···O(2)[a]	0.92	1.86	2.772(2)	170.4
	O(2)–H(2A)···N(1)[b]	0.94	1.89	2.822(2)	172.1

Symmetry transformations used to generate equivalent atoms.
[a] $-x+1, y-1/2, -z+1/2$.
[b] $x-1, -y+3/2, z-1/2$.

Additionally, weak hydrogen bonds (C33–H33···O11′ ($-x+2$, $y-1/2$, $-z+1/2$), *d*(C33···O11′)=3.234(7) Å <C33H33O11′=142°) and (C34–H34···O16″ ($-x+1$, $y-1/2$, $-z+1/2$), *d*(C34···O16″)=3.250(7) Å, <C34H34O16″=163.5°) form chains along the *b* axis. These chains exhibit weak

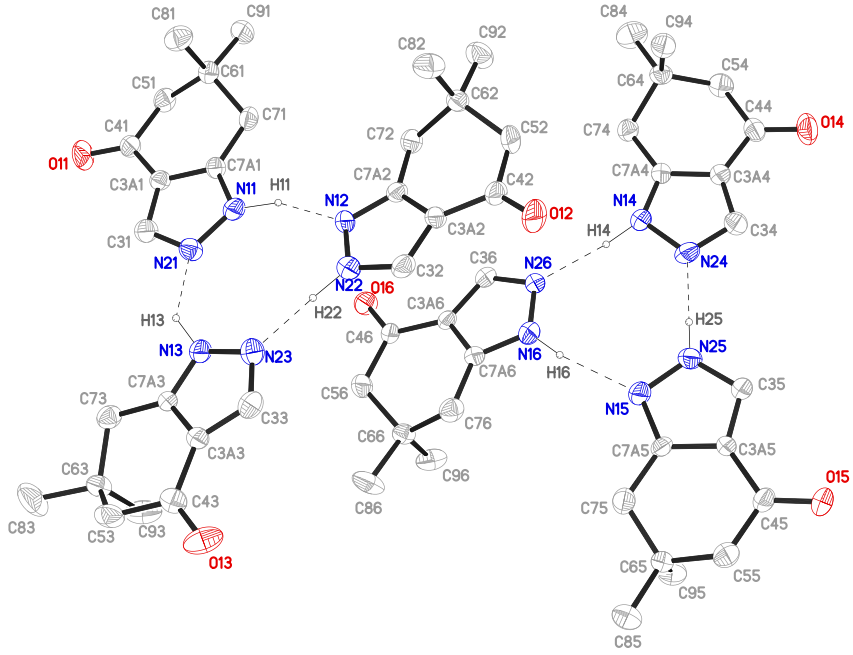


Figure 7. ORTEP view (35% probability) of the two trimers of **2**.

interactions (C96–H96···O13‴(−*x*+1, *y*, *z*), *d*(C96···O13‴)=3.306(7) Å, <C96H96AO16″=130°) piling up along the *a* axis (Fig. 8).

Figure 9 shows the asymmetric unit of 3,6,6-trimethyl-2,5,6,7-tetrahydro-4*H*-indazol-4-one (**4**), the crystal consists of molecules held together by water molecules involving three hydrogen bonds (Table 6 and Fig. 10). These features lead to a layer parallel to [10−2] plane and these layers are within van der Waals distances. As in previous compound **2**, distances and angles lie in the normal ranges.

Compound **2** crystallizes forming trimers, one of the secondary structures that pyrazoles and indazoles can adopt in the crystal.[50,51] Which is not common at all is that the trimer is formed by two different tautomers, two of them being 2*H* and the third one being 1*H*. The only precedent is the recently described example of a tetramer formed by two

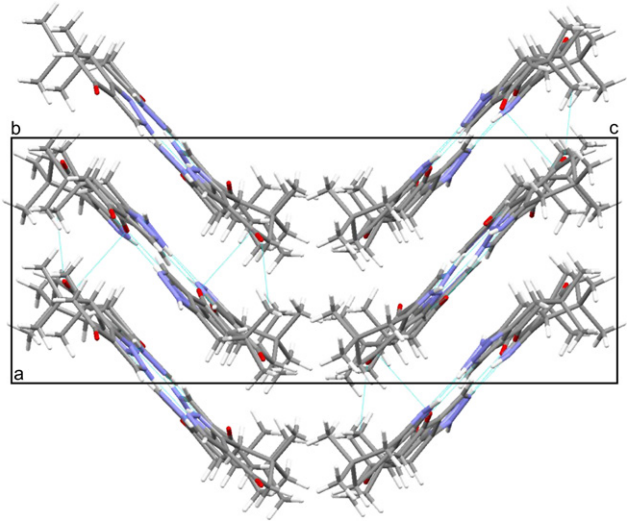


Figure 8. 2D network along the *b* axis in **2**.

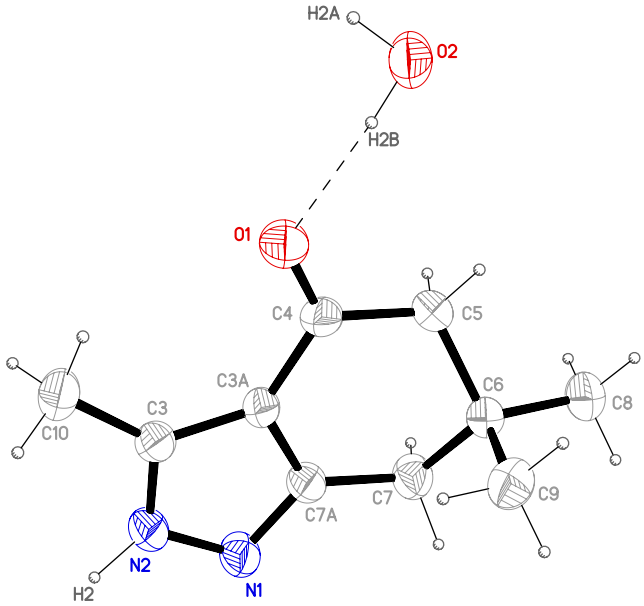


Figure 9. ORTEP view (40% probability) of the molecular structure of **4** plus one water molecule.

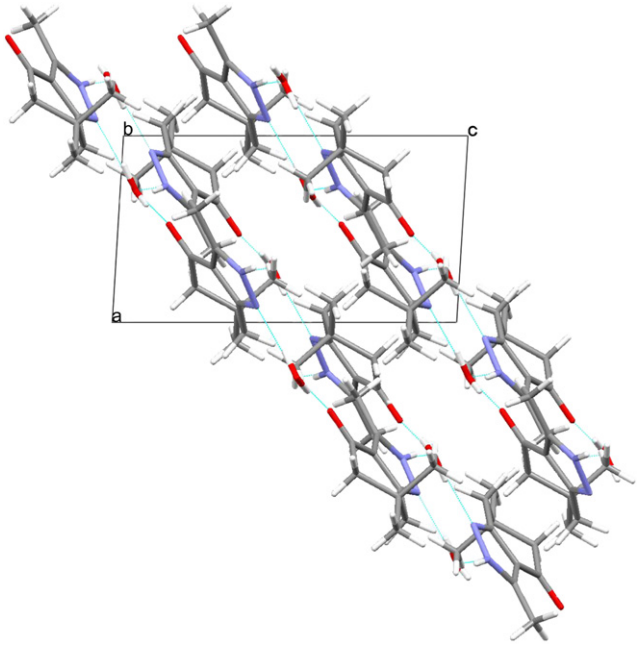


Figure 10. 2D network along the *b* axis in **4**.

tautomers in a 3:1 ratio (older examples were known but for balanced 2:2 tetramers).[42] This corresponds to two tautomers of almost the same energy (Table 2, compound **2**). The other unexpected result is that the hydrogen-acceptor (HBA) ability of the carbonyl oxygen is not used and thus Desiraju's principle of maximum saturation of HBs is not followed.[52–54]

On the other hand, compound **4** has a 2*H*-tautomer clearly more stable than the 1*H* (Table 2 and Eq. 1) and only this tautomer is present in the crystal forming chains, catemers, but using water molecules to saturate the HBA properties of the carbonyl group.

3. Conclusions

Computational calculations of 1(2),5,6,7-tetrahydro-4*H*-indazol-4-ones (**1**–**4**) conclude that the two main tautomeric forms 1*H* and 2*H* are very close in energy in the gas phase. Moreover, as tautomers 1*H* have dipole moments nearly 2.5 times higher than the 2*H* ones, polar solvents will favor the 1*H* forms.

In solution, tetrahydroindazolones **1**–**4** exist as mixtures of both tautomers with equilibrium constants K_{eq} defined as [1*H*]/[2*H*] varying in the following order **1** (1.70, THF-d_8 at 207 K)>**2** (1.22, THF-d_8 at 207 K)>**3** (1.04, CD_2Cl_2 at 175 K)>**4** (0.72, THF-d_8 at 207 K).

In the solid state 6,6,-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) forms trimers composed by 2/3 of 1*H* and 1/3 of 2*H* tautomers and 3,6,6-trimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**4**) gives rise to chains containing only 2*H* forms and water molecules, as X-ray diffraction analysis demonstrates. The CPMAS NMR data of 1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**1**) and 3-methyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**3**) are in agreement with the presence of 1*H* tautomers.

The four compounds will be tested as NOS inhibitors within the framework of a collaborative project with Professor C. S. Raman, Dr. Pierre Nioche (University of Texas Houston) and Professor Dario Acuña-Castroviejo (Universidad de Granada).

4. Experimental

4.1. Chemistry

The starting materials 1,3-cyclohexanedione 97% (**5**), dimedone 95% (**6**), and 2-acetyl-1,3-cyclohexanedione 98% (**9**) were commercially available from Aldrich and 2-acetyldimedone 98% (**10**) from Fluka and were used without further purification. Melting points for tetrahydroindazolones were determined by DSC on a Seiko DSC 220C connected to a Model SSC5200H Disk Station and for the other compounds a ThermoGalen hot stage microscope was used. Thermograms (sample size 0.003–0.0010 g) were recorded at a scanning rate of 2.0 °C min^{-1}. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh) and the R_f values were measured on aluminum baked TLC plates of silica gel 60 F254 (Merck, 0.2 mm) with the indicated eluent. Elemental analyses for carbon, hydrogen, and nitrogen were carried out by the Microanalytical Service of the Universidad Complutense of Madrid on a Perkin–Elmer 240 analyzer.

4.1.1. 2-(Dimethylaminomethylene)-1,3-cyclohexanedione (7). A solution of 1,3-cyclohexanedione (**5**) (0.50 g, 4.5 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (2 mL) was refluxed for 1 h. The excess acetal was distilled off under reduced pressure to obtain the pure product **7** as a dark solid (0.76 g, 100%). Mp: 117–119 °C (lit. mp:[34] 118 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.93 (2H, dt, ^3J=6.4 Hz, $CH_2CH_2CH_2$), 2.45 (4H, t, ^3J=6.4 Hz, CH_2CO), 3.16 (3H, s, NCH_3), 3.38 (3H, s, NCH_3), 8.04 (1H, s, =C*H*N).

4.1.2. 2-(Dimethylaminomethylene)-5,5-dimethyl-1,3-cyclohexanedione (8). A solution of 5,5-dimethyl-1,3-cyclohexanedione (**6**) (0.50 g, 3.6 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (2 mL) was refluxed for 1 h. The excess acetal was distilled off under reduced pressure to obtain the pure product **8** as a yellowish solid (0.70 g, 100%). Mp: 92–94 °C (lit. mp:[34] 93 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.05 (3H, s, $(CH_3)_2$), 2.35 (4H, s, CH_2), 3.18 (3H, s, NCH_3), 3.37 (3H, s, NCH_3), 7.99 (1H, s, =C*H*N).

4.1.3. 1(2),5,6,7-Tetrahydro-4*H*-indazol-4-one (1). A solution of 1 g of 2-(dimethylaminomethylene)-1,3-cyclohexanedione (**7**, 6.0 mmol), 0.35 g of 55% hydrazine hydrate (6.0 mmol), and 0.6 mL of acetic acid, in 15 mL of 1-butanol was heated under reflux in a round bottom flask for 4 h. The mixture is allowed to cool to room temperature and the solvent evaporated under reduced pressure to leave a dark solid. After column chromatography on silica using ethyl acetate/hexane 2:1 as eluent, pure product **1** was obtained as a white solid (0.24 g, 30%). Mp: 163.8 °C (DSC) (lit. mp:[38] 164–165 °C). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.4 (br s, C4), 153.2 (br s, C7a), 134.5 (vbr s, C3), 118.8 (s, C3a), 38.4 (t, ^1J=128.0 Hz, C5), 23.5 (t, ^1J=130.3 Hz, C6), 21.8 (t, ^1J=129.4 Hz, C7).

4.1.4. 6,6-Dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (2). One gram of 55% hydrazine hydrate (16.5 mmol) was added dropwise under stirring to a solution of 2-(dimethylamino-methylene)dimedone (**8**) (3 g, 15 mmol) and acetic acid (0.5 mL) in 45 mL of 1-butanol in a three necked round bottom flask. The resulting mixture was heated under reflux for 4 h and then allowed to cool to room temperature. After evaporation of the solvent, the residue was redissolved in dichloromethane and filtered (a yellowish solid was discarded). Evaporation of dichloromethane gave a yellowish solid that was purified by column chromatography (silica gel) with ethyl acetate/hexane 1:1 as eluent. Product **2** thus obtained, was crystallized from water (1 g, 41%). Mp: 132.1 °C (DSC). Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.61; H, 7.29; N, 16.79. ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.8 (t, ^2J=6.3 Hz, C4), 152.4 (m, C7a), 133.9 (d, ^1J=190.4 Hz, C3), 117.6 (s, C3a), 52.6 (tt, ^1J=127.3 Hz, ^3J=4.1 Hz, C5), 35.7 (m, ^2J=3.8 Hz, C6), 35.7 (tt, ^1J=129.6 Hz, ^3J=4.5 Hz, C7), 28.4 [q, ^1J=125.8 Hz, Me (6)].

4.1.5. 3-Methyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (3). To a solution of 0.5 g (3.2 mmol) of 2-acetyl-1,3-cyclohexanedione (**9**) in 20 mL of tetrahydrofuran, in a three necked round bottom flask, were added dropwise under stirring 0.21 g of 55% hydrazine hydrate (3.6 mmol). The mixture was refluxed for 2 h, allowed to cool to room temperature and filtered through Celite. The solution was evaporated under reduced pressure to leave a yellowish solid that was purified by column chromatography (silica gel) with diethyl ether/hexane 2:1 as eluent. This way pure product **3** was obtained (0.41 g, 85%). Mp: 160.3 °C (DSC) (lit. mp: 155 °C,[32] 152–154 °C.[35] Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.90; H, 6.58; N, 18.26. ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 195.2 (t, ^2J=6.1 Hz, C4), 154.7 (br s, C7a), 145.3 (br s, C3), 115.7 (s, C3a), 38.9 (tt, ^1J=127.6 Hz, ^2J=4.1 Hz, C5), 23.7 (tt, ^1J=130.3 Hz, H, ^2J=4.1 Hz, C6), 22.4 (t, ^1J=130.4 Hz, C7), 12.1 [q, ^1J=129.7 Hz, Me (3)].

4.1.6. 3,6,6-Trimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (4). In a three necked round bottom flask a solution of 0.72 g of 2-acetyldimedone (**10**) (4.0 mmol) in 20 mL of tetrahydrofuran was prepared to which 0.26 g of 55% hydrazine hydrate (4.5 mmol) were added dropwise and under stirring. The mixture was heated under reflux for 2 h and allowed to cool to room temperature. After evaporation of the solvent a yellowish solid was obtained, which was crystallized from ether and recrystallized from water to give product **4** (0.45 g, 63%). Mp: 101.4 °C (DSC) (lit. mp:[37] 100.3–102.4 °C). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.5 (t, ^2J=6.1 Hz, C4), 154.0 (t, ^2J=7.0 Hz, C7a), 145.0 (q, ^3J=6.8 Hz, C3), 114.6 (s, C3a), 53.0 (t, ^1J=127.3 Hz, C5), 36.2 (t, ^1J=129.8 Hz, C7), 35.5 (m, C6), 28.4 [q, ^1J=123.7 Hz, Me (6)], 11.9 [q, ^1J=129.8 Hz, Me (3)].

4.2. NMR parameters

Solution spectra were recorded on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C and

40.56 MHz for ^{15}N) spectrometer with a 5-mm inverse-detection H–X probe equipped with a *z*-gradient coil for ^{1}H, ^{13}C, and ^{15}N. Chemical shifts (δ in ppm) are given from internal solvents, $CDCl_3$ (7.26), CD_2Cl_2 (5.32), THF-d_8 (3.58), DMSO-d_6 (2.49) for ^{1}H and $CDCl_3$ (77.0), THF-d_8 (67.4), CD_2Cl_2 (54.0), DMSO-d_6 (39.5) for ^{13}C and nitromethane (0.00) for ^{15}N NMR was used as external reference. Typical parameters for ^{1}H NMR spectra were spectral width 6400 Hz, pulse width 7.5 μs at an attenuation level of 0 dB and resolution 0.39 Hz per point. Typical parameters for ^{13}C NMR spectra were spectral width 20,500 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 (^{1}H–^{1}H) gs-COSY and inverse proton detected heteronuclear shift correlation spectra, (^{1}H–^{13}C) gs-HMQC, (^{1}H–^{13}C) gs-HMBC, (^{1}H–^{15}N) gs-HMQC, and (^{1}H–^{15}N) gs-HMBC, were acquired and processed using standard Bruker NMR software and in non-phase-sensitive mode.[55] Gradient selection was achieved through a 5% sine truncated shaped pulse gradient of 1 ms. Variable temperature experiments were recorded on the same spectrometer. A Bruker BVT3000 temperature unit was used to control the temperature of the cooling gas stream and an exchanger to achieve low temperatures. Solid state ^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CPMAS NMR spectra were obtained on a Bruker WB 400 spectrometer at 300 K using a 4 mm DVT probe head. Samples were carefully packed in a 4-mm diameter cylindrical zirconia rotor with Kel-F end-caps. Operating conditions involved 3.2 μs 90° ^{1}H pulses and decoupling field strength of 78.1 kHz by TPPM sequence. The NQS (non-quaternary suppression) technique[55] to observe only the quaternary C-atoms was employed. ^{13}C spectra were originally referenced to a glycine sample and then the chemical shifts were recalculated to the Me_4Si (for the carbonyl atom δ (glycine)=176.1 ppm) and ^{15}N spectra to $^{15}NH_4Cl$ and then converted to nitromethane scale using the relationship: δ ^{15}N(nitromethane)=δ ^{15}N(ammonium chloride) −338.1 ppm. The typical acquisition parameters for ^{13}C CPMAS were spectral width 40 kHz, recycle delay 5 s, acquisition time 30 ms, contact time 2 ms, and spin rate 12 kHz. And for ^{15}N CPMAS spectral width 40 kHz, recycle delay 5 s, acquisition time 35 ms, contact time 6 ms, and spin rate 6 kHz.

4.3. X-ray data collection and structure refinement

Suitable crystals for X-ray diffraction experiments were obtained by crystallization from dichloromethane/petroleum ether (**2**) or water (**4**). Data collection were carried out at room temperature on a Bruker Smart CCD diffractometer using graphite-monochromated Mo Kα radiation (λ= 0.71073 Å) operating at 50 kV and 30 mA. In both cases, data were collected over a hemisphere of the reciprocal space by combination of three exposure sets, each exposure was of 20 s covering 0.3° in ω. The first 50 frames were recollected at the end of the data collection to monitor crystal decay. A summary of the fundamental crystal and refinement data are given in Table 7. The structures were solved by direct methods and refined by full-matrix least-square procedures on F^2 (SHELXL-97).[56] All non-hydrogen atoms were refined anisotropically. In both cases, all hydrogen atoms were included in their calculated positions and refined riding on the respective carbon atoms with the exceptions listed below. In the structure of **4** the hydrogen atoms bonded to N2 atom and the hydrogen atoms bonded to O2 (water) were located in a Fourier synthesis and refined riding on the respective bonded atoms. The same treatment was followed with the hydrogen atoms bonded to N11, N13, N14, N16, N22 and N25 in the structure of **2**. Largest peaks and holes in the final difference map were 0.194 and −0.204 e Å^{-3} for **2** and 0.196 and −0.147 e Å^{-3} for **4**. Final *R* (*Rw*) values were 4.83 (13.91) for **2** and 4.97 (15.26) for **4**. The flack parameter is 0.00, an indication of the correct determination of the crystalline absolute structure. Further crystallographic details for the structures reported in this paper may be obtained from the Cambridge Crystallographic Data Center, on quoting the depository numbers CCDC-608789 and CCDC-608790.

Table 7. Crystal data and structure refinement for 6,6-dimethyl-1(2),5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) and 3,6,6-trimethyl-2,5,6,7-tetrahydro-4*H*-indazol-4-one (**4**)

Crystal data	**2**	**4**
Identification code	CCDC-608790	CCDC-608789
Empirical formula	$C_9H_{12}N_2O$	$C_{10}H_{16}N_2O_2$
Formula weight	164.21	196.25
Wavelength (Å)	0.71073	0.71073
Crystal system	Orthorhombic	Monoclinic
Space group	*P*2(1)2(1)2(1)	*P*2(1)/*c*
Unit cell dimensions		
a (Å)	10.1243(8)	5.9827(7)
b (Å)	21.526(2)	16.494(2)
c (Å)	24.992(2)	11.012(1)
β (°)	—	93.464(2)
Volume (Å^3)	5446.6(7)	1084.7(2)
Z	24	4
Density (calculated) (Mg/m^3)	1.202	1.202
Absorption coefficient	0.081 (mm^{-1})	0.085 (mm^{-1})
F(000)	2112	424
Theta range (°) for data collection	1.25–25.0	2.23–28.72
Index ranges	$-12\le h\le 12$ $-20\le k\le 25$ $-29\le l\le 29$	$-8\le h\le 7$ $-20\le k\le 21$ $-14\le l\le 11$
Reflections collected	42,257	6842
Independent reflections	9572 [*R* (int)=0.1342]	2582 [*R* (int)=0.0712]
Data/restraints/ parameters	9572/0/688	2582/0/133
Goodness-of-fit on F^2	0.801	0.909
R[a] [$I>2\sigma$ (I)]	0.0484 (3204 obs. reflect.)	0.0497 (1374 obs. reflect.)
Rw_F[b] (all data)	0.1391	0.1526

[a] $\sum \|\|F_o\|-\|F_c\|\| / \sum |F_o|$.
[b] $\{\sum[w(F_o^2 - F_c^2)^2] / \sum[w(F_o^2)^2]\}^{1/2}$.

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