

Polymorphism vs. Desmotropy: The Cases of 3-Phenyl- and 5-Phenyl-1*H*-pyrazoles and 3-Phenyl-1*H*-indazole

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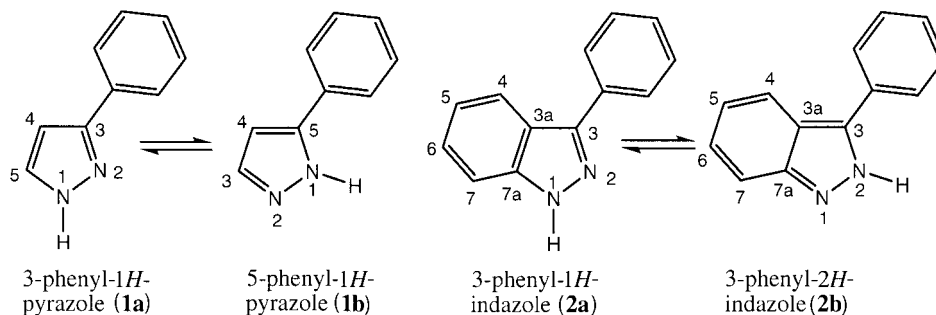
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Two desmotropes, 3-phenyl-1*H*-pyrazole (**1a**) and 5-phenyl-1*H*-pyrazole (**1b**) have been isolated and the conditions for their interconversion established. The X-ray structure of **1b** has been determined ($a = 10.862(1)$, $b = 5.7620(5)$, $c = 12.927(2)$ Å, $\beta = 111.435(2)^\circ$, space group $P2_1/c$), and both tautomers **1a** and **1b** were characterized by NMR in the solid state (^{13}C - and ^{15}N -CPMAS). In the case of 3-phenyl-1*H*-indazole (**2a**), two concomitant polymorphs have been analyzed by X-ray crystallography, and their NMR spectral properties were determined. The low-melting-point polymorph, at 106.7° , contains three molecules in the asymmetric unit ($a = 41.086(1)$, $b = 7.3860(2)$, $c = 23.391(1)$ Å, $\beta = 117.697(1)^\circ$, space group $C2/c$) and the high-melting-point one, 115.3° , six molecules ($a = 13.7818(4)$, $b = 13.7976(5)$, $c = 18.9445(5)$ Å, $\alpha = 94.300(3)$, $\beta = 95.131(3)$, $\gamma = 119.428(3)^\circ$, space group $P-1$). Here, too, it has been experimentally determined how to transform one form into the other. Density-functional-theory calculations at the B3LYP/6-31G** level have been performed in both examples to rationalize the stability of the different tautomers.

1. Introduction. – Tautomeric compounds, as other compounds, can present polymorphism (we refer here to true polymorphism, not to solvates, also called pseudopolymorphism), but, in addition, they can present desmotropy. The term polymorphism is a very well-known descriptor for tautomeric heterocycles [1–5]; the term desmotropy refers, more precisely, to the observation of crystallization of a compound in two different tautomers (there are no known examples of a compound that crystallize in three or more tautomeric forms). This term must not be used for crystals containing simultaneously two tautomers that, in general, but not always, are in a 1:1 ratio. Desmotropy is not very rare [6–9], but, in many cases, the examples are found under the headings 'tautomerism' and 'polymorphism' [10–16], even when desmotropic crystals are not polymorphs, since tautomers are two different compounds that isomerize rapidly in solution¹⁾. The studies of the transformation of a tautomer into another tautomer in the solid state are examples of dynamic desmotropy [13][15].

¹⁾ Some authors use the term 'tautomerizational polymorphism' [1] or 'tautomeric polymorphism' [17] instead of desmotropy. In our opinion, the distinction between polymorphism and isomerism cannot be based on the activation barrier separating two forms in solution, which would lead to similar problems as those concerning the terms conformation (alkanes) vs. configuration (alkenes). We advocate using the term polymorphism in situations where both forms are identical in terms of connectivity matrices, thus excluding tautomerism in situations where bonds are broken and created.

It is evident that, to have a reasonable probability to crystallize two tautomers, their intrinsic difference in energy should be rather low [18][19]. This is not generally the case in functional tautomerism (*e.g.*, oxo/hydroxy), but it is common for the annular tautomerism of azoles [20]. We will report in the present paper the case of two azoles, 3(5)-phenyl-1*H*-pyrazole (**1**) and 3-phenylindazole (**2**).

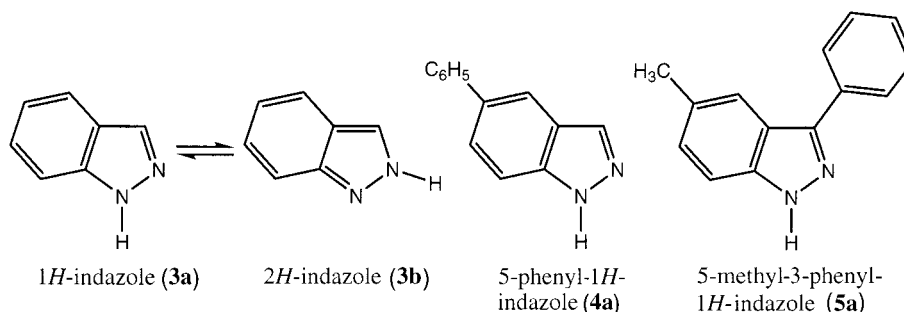


We have devoted several papers to the tautomerism of 3(5)-phenyl-1*H*-pyrazole **1** [20–24]. In solution (NMR) and in the gas phase (*ab initio* calculations), tautomer **1a** is the most stable (*ca.* 2 kJ mol^{−1}). But, in the solid state (¹³C-CPMAS-NMR), the chemical shifts correspond to the 5-phenyl tautomer **1b** [23]. In all publications and general books, this compound is reported to have a melting point of 78° [25–32] without any indication of peculiar behavior, and, so, the conclusion would be that this compound shows neither polymorphism nor desmotropy. However, in a review on the application of mass spectrometry to the analysis of tautomeric organic compounds, Terent'ev and Kalandarishvili [33] have stated on p. 346: 'The transformation of 3-phenylpyrazole into more stable 5-phenylpyrazole, which has a higher melting point, was described', with reference to [34]. However, careful reading of Kost and Grandberg's review [34] reveals nothing concerning compound **1**.

The case of 3-phenylindazole is different. In an authoritative review [35], it is stated (on p. 291): 'The existence of two forms of 3-phenylindazole has been taken to provide support for the equilibrium idea. On this basis, the two forms shown in the equilibrium **2a/2b**, in which the imino hydrogen atoms are on different nitrogen atoms, would correspond to the two forms of 3-phenylindazole. The two forms of 3-phenylindazole are interconvertible under various conditions. Similar interconversion of the two forms has been observed with certain 5-substituted indazoles. If these examples actually constitute pairs of isomers differing only in the location of the imino hydrogen, the double bond locations should differ. However, refractometric measurements indicate that both contain the benzene ring'. And then, on p. 323: '3-phenylindazole exists in two forms. The lower-melting (107–108°C), if maintained slightly above its melting point, resolidifies and then melts at 115–116°C. Both compounds give the same *N*-acetyl derivative, hydrolysis of which affords the low melting point. It has been suggested by von Auwers that the two compounds are desmotropes and differ in the location of the imino hydrogen (*N*–*H*), and that both exist in the melt'. These conclusions are based on Von Auwers' results [36–39]. When this compound has been reported in more recent

times, either the melting point is not reported [40][41], or a melting point of 106–107° is given [42][43].

Nevertheless, the intrinsic difference in stability between 1*H*-indazole (**3a**) and 2*H*-indazole (**3b**) is too high (17 kJ mol⁻¹ [44][45]) to easily accept that one of the compounds with a melting point of 108° or 116° could be **2b**. In the solid state, indazole crystallizes as **3a** [46], and other indazoles like 5-phenylindazole [47] and 3-phenyl-5-methylindazole also crystallize as 1*H*-tautomers, **4a** and **5a** [48], respectively.



2. Results and Discussion. – 2.1. *The Case of 3(5)-Phenyl-1*H*-pyrazole 1.* When this pyrazole was crystallized from petroleum ether, it was observed that, depending on the evaporation conditions and the solute/solvent ratio, a white form, or a pale yellow and more crystalline form of **1** was obtained. An NMR study in the solid state (see later) of both samples shows that the white variety was a mixture of **1a** and **1b**, while the yellow one contained exclusively **1a**. Therefore, the white solid is an example of concomitant desmotropy. To obtain exclusively one tautomer, we carried out a series of experiments, the more significant being: *i*) dissolving the crude compound in petroleum ether and slowly evaporating the solvent at room temperature afforded tautomer **1a** (pale yellow); *ii*) dissolving tautomer **1a** in EtOH and quickly removing the solvent *in vacuo* or recrystallizing **1a** in CH₂Cl₂ at 4° (freezer) afforded tautomer **1b**; *iii*) Solid **1a** on standing (several days) or by mechanical grinding was transformed into **1b**; *iv*) Melting transformed **1b** into **1a**.

NMR Spectroscopy in Solution. We have recorded the ¹H-, ¹³C-, and ¹⁵N-NMR spectra of compound **1** in (D₁₈)HMPA, [(CD₃)₂N]₃PO, a solvent known to slow the annular prototropic equilibria [18]. The spectra correspond to mixtures of 65% of tautomer **1a** and 35% of tautomer **1b**. The chemical shifts were summarized in Table 1, and the different signals were assigned through standard gs-HMQC and gs-HMBC experiments and by analogy with published results [22]. Note that the NH proton of tautomer **1b** is deshielded relative to that of **1a** by the nearby Ph ring; these signals were used to determine the ratio **1a/1b**.

¹³C- and ¹⁵N-CPMAS-NMR Spectroscopy in the Solid State. We have already noted that ¹⁵N chemical shifts are more sensitive to environmental effects, such as H-bonds, than to tautomerism [49]. On the other hand, ¹³C chemical shifts are very similar to those in solution and constitute a precise tool to identify and determine the purity (up to 10%) of these tautomers. The tautomer obtained by crystallization in CH₂Cl₂ at 4° (freezer) used to determine the X-ray structure corresponds to tautomer **1b**. In Fig. 1,

Table 1. NMR Chemical Shifts of 3(5)-Phenylpyrazole **1** in (*D*₁₈)HMPA at 300 K and in the Solid State

Nucleus	1	2	3	4	5	Ph Group
3-Phenyl-1 <i>H</i> -pyrazole (1a) 65%						
¹ H ^a)	12.85	–	–	–	–	–
¹³ C ^a)	–	–	150.44	101.54	135.35	135.35 (<i>ipso</i>), 125.63 (<i>ortho</i>), 128.73 (<i>meta</i>), 127.14 (<i>para</i>)
¹⁵ N ^a)	–171.9	–86.7	–	–	–	–
¹³ C ^b)	–	–	150.4	101.8	133.8	133.9 (<i>ipso</i>), 127.5 (<i>ortho</i>), 127.5 (<i>meta</i>), 127.5 (<i>para</i>)
¹⁵ N ^b)	–173.9	–84.4	–	–	–	–
5-Phenyl-1 <i>H</i> -pyrazole (1b) 35%						
¹ H ^a)	13.28	–	–	–	–	–
¹³ C ^a)	–	–	139.69	101.54	142.30	130.89 (<i>ipso</i>), 125.63 (<i>ortho</i>), 128.73 (<i>meta</i>), 129.33 (<i>para</i>)
¹⁵ N ^a)	–176.6	–76.3	–	–	–	–
¹³ C ^b)	–	–	143.0	101.6	142.9	129.7 (<i>ipso</i>), 125.8 (<i>ortho</i>), 129.4 (<i>meta</i>), 129.4 (<i>para</i>)
¹⁵ N ^b)	–176.8	–93.0	–	–	–	–

a) HMPA. b) CPMAS.

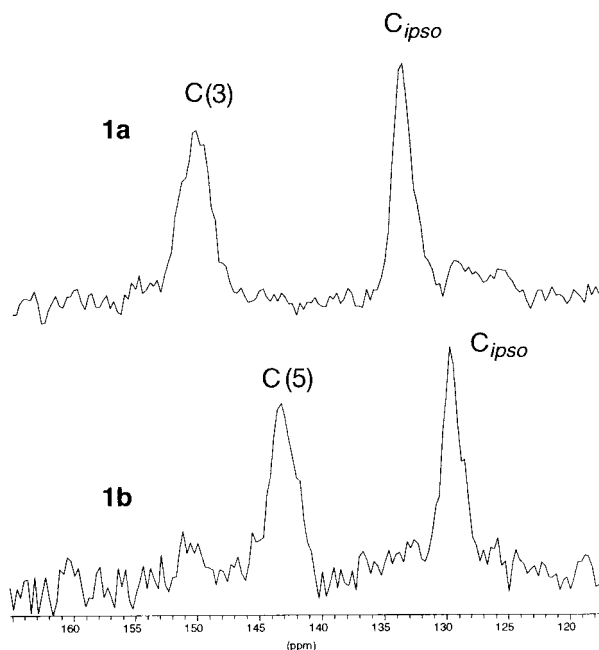
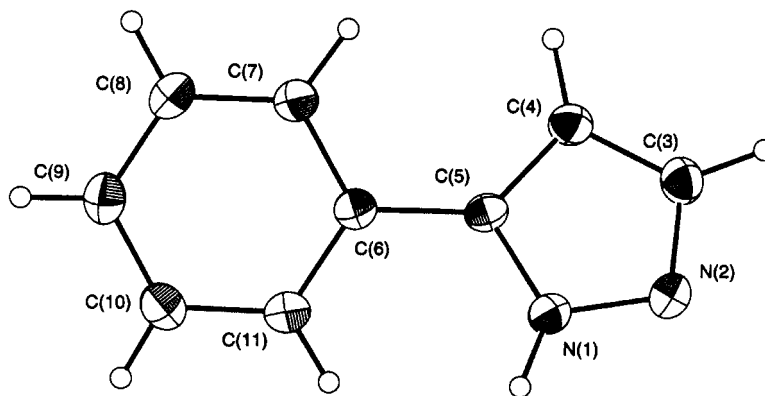
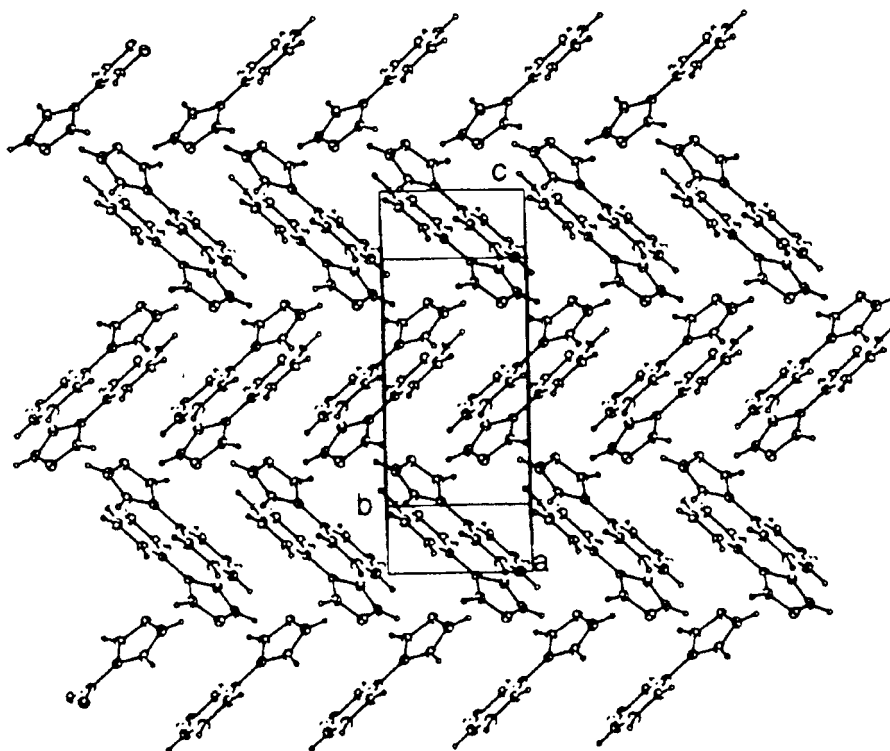


Fig. 1. Quaternary C-atoms obtained by means of the NQS sequence in ¹³C-NMR CPMAS for desmotropes **1a** and **1b**

we present the quaternary C-atoms C(3) and C_{ipso} for **1a**, and C(5) and C(*ipso*) for **1b**, in the solid state (see *Exper. Part*).

X-Ray-Crystal and Molecular Structure of 5-Phenyl-1*H*-pyrazole (1b**).** The crystals of **1a** obtained by slow evaporation in petroleum ether were not suitable for crystal-structure determination. Moreover, on standing, crystals of **1a** evolved to **1b**. On the

Fig. 2. Molecular structure of 5-phenyl-1H-pyrazole (**1b**)Fig. 3. Molecular packing for 5-phenyl-1H-pyrazole (**1b**)

other hand, those of **1b** proved suitable. Their main characteristics are reported in the *Exper. Part* and are depicted in *Figs. 2* and *3*.

The compound crystallizes as a chain of N–H···N H-bonded molecules (catemer), this being one of the typical motifs of NH-pyrazole crystals [50]. Phenylpyrazoles,

unless the two rings are in the same plane ($\theta = 0^\circ$) or are orthogonal ($\theta = 90^\circ$), present axial chirality, the rings adopting (*M*) (Minus) or (*P*) (Plus) conformations. These conformations, being separated by a very low barrier, are in rapid equilibrium in solution. The helices formed by these structures could crystallize in three structures: *i*) the helix contains both conformations in alternation ($(M,P)_n$; *ii*) in the same crystal, there are two adjacent helices, one ($(M)_n$) and the other ($(P)_n$; *iii*) a spontaneous resolution has occurred (conglomerate), and in the batch are found pure ($(M)_n$) and pure ($(P)_n$) crystals. Compound **1b** ($\theta = 18.43(1)^\circ$) belongs to the $P2_1/c$ space group with $a = 10.862(1)$, $b = 5.7620(5)$, $c = 12.927(2)$ Å and $\beta = 111.435(2)^\circ$. The helix of this racemic crystal corresponds to class *ii*; to describe the catemer, the connectivity of pyrazole centroids would be used. Compound **1b** forms a chain of order 2 with the properties, reported in Fig. 4, very similar to those found for another catemer, the 4-phenyl-5-azidopyrazole [50].

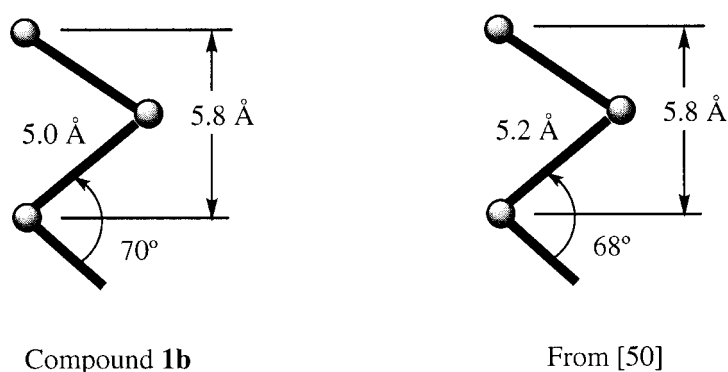


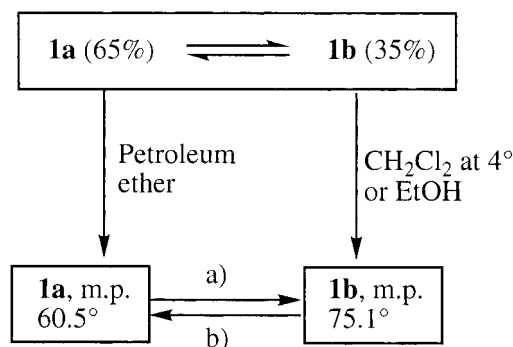
Fig. 4. Geometries of catemers of order 2 as defined by the centroids

DSC Experiments. When we recorded the differential scanning calorimetry (DSC) plots of compounds **1a** and **1b** at a rate of $10^\circ \text{ min}^{-1}$, tautomer **1b** melted at 75.1° and resolidified to yield tautomer **1a** with a melting point at 60.5° .

DFT Calculations (B3LYP/6-31G).** The optimized geometries correspond to the following values: **1a** ($E = -457.27423$ hartrees, $\mu = 2.42$ D, $\theta = 1^\circ$), **1b** ($E = -457.27389$ hartrees, $\mu = 2.55$ D, $\theta = 28^\circ$), **1a** being most stable by 0.91 kJ mol^{-1} . By applying the zero-point energy (ZPE) correction, the stability difference increases to 1.26 kJ mol^{-1} , that is, at 300 K, $K_T = 1.66$, 62% **1a**/38% **1b**. Since the dipole moments are very similar, no important solvent effects are expected in the composition mixture. We have now all the information to summarize in Scheme 1 the behavior of 3(5)-phenylpyrazole **1**.

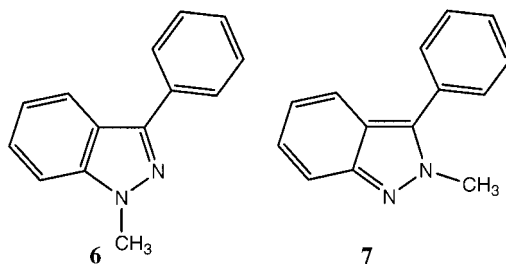
Note that, in the gas phase (DFT calculations) and in solution (NMR), tautomer **1a** is the more stable, while, in the solid state, **1a** corresponds to a metastable structure.

2.2. The Case of 3-Phenylindazole (2). This compound, as will be shown in the following discussion, is an example of polymorphism involving tautomer **2a**. It crystallized in two forms: the low-melting point (LMP, needles, 106.7° by DSC at a rate of $10^\circ \text{ min}^{-1}$) and the high-melting-point (HMP, cube-like shape, 115.3° by DSC at a rate of $10^\circ \text{ min}^{-1}$) form. The following experiments have been carried out: *i*) crystallization in petroleum ether (b.p. $35-60^\circ$) yielded both forms; *ii*) crystallization

Scheme 1. The Case of 3(5)-Phenylpyrazole **1a**) on Standing at Room Temperature or by Mechanical Grinding, b) by Melting

in benzene/cyclohexane yielded the high-melting-point form; *iii*) careful melting of the LMP form afforded the HMP polymorph.

NMR Spectroscopy in Solution. To exclude desmotropy, it is necessary to determine the tautomeric structures of both forms by solid-state NMR. To assign the signals of both possible tautomers of this compound, **2a** (1*H*) and **2b** (2*H*), we have prepared the corresponding *N*-Me derivatives **6** and **7**. The results are reported in Table 2.



A simple examination of the ^{13}C chemical shifts of Table 2 shows that only tautomer **2a** is present in solution (we have carried out other NMR experiments, both ^1H and ^{13}C , and never observed signals of the other tautomer, nor even broadening, for instance in $(\text{D}_{18})\text{HMPA}$ at 255 K). The differences in ^{15}N chemical shifts are due to the effect of the Me group and to modifications of the H-bonds involving the N-atoms.

^{13}C - and ^{15}N -CPMAS-NMR Spectroscopy in the Solid State. Both polymorphs, LMP and HMP, show very similar ^{13}C -CPMAS spectra, which are also very close to that of **2a** in solution. Therefore, we are in the presence of a case of polymorphism and not of desmotropy. Since, in the same crystallization dish, both are found, this is a new example of concomitant polymorphs.

X-Ray-Crystal and Molecular Structures of 3-Phenylindazole Polymorphs (2a (LMP) and 2a (HMP)). 3-Phenyl-1*H*-indazole crystallizes in two different habits: long needles for **2a** (LMP) and cube-shaped crystals for **2a** (HMP). The two crystal types belong to different crystal systems: monoclinic (**2a** (LMP): $a = 41.086(1)$, $b = 7.3860(2)$, $c = 23.391(1)$ Å, $\beta = 117.697(1)^\circ$, space group $C2/c$) and triclinic (**2a** (HMP): $a =$

Table 2. NMR Chemical Shifts of 1-Methyl-3-phenylindazole (**6**), 2-Methyl-3-phenylindazole (**7**) and 3-Phenylindazole (**2**) in (*D*₆)DMSO at 300 K, **2** in (*D*₈)THF at 205 K, and **2** in the Solid State

Nucleus	1	2	3	3a	4	5	6	7	7a	Ph Group
1-Methyl-3-phenyl-1 <i>H</i> -indazole (6) (<i>N</i> -Me at 35.42 ppm)										
¹³ C ^a)	–	–	133.36	120.61	120.75	121.13	126.12	110.07	141.17	141.96 (<i>ipso</i>), 128.86 (<i>ortho</i>), 126.67 (<i>meta</i>), 127.66 (<i>para</i>)
¹⁵ N ^a)	– 204.6	– 63.1	–	–	–	–	–	–	–	–
2-Methyl-3-phenyl-2 <i>H</i> -indazole (7) (<i>N</i> -Me at 38.62 ppm)										
¹³ C ^a)	–	–	134.99	120.51	119.87	121.57	125.74	116.78	147.14	143.17 (<i>ipso</i>), 129.35 (<i>ortho</i>), 129.13 (<i>meta</i>), 128.64 (<i>para</i>)
¹⁵ N ^a)	– 92.3	– 166.2	–	–	–	–	–	–	–	–
3-Phenylindazole (2)										
¹³ C ^a)	–	–	133.77	120.03	120.99	120.57	126.06	110.55	141.54	143.15 (<i>ipso</i>), 128.84 (<i>ortho</i>), 126.72 (<i>meta</i>), 127.61 (<i>para</i>)
¹⁵ N ^a)	– 197.0	– 86.8	–	–	–	–	–	–	–	–
¹³ C ^b)	–	–	135.31	121.24	121.66	121.61	126.69	111.14	142.81	144.34 (<i>ipso</i>), 129.51 (<i>ortho</i>), 127.65 (<i>meta</i>), 128.27 (<i>para</i>)
¹³ C ^c)	–	–	133.2	121.1	121.1	121.1	126.2	110.9	141.2	145.3 (<i>ipso</i>), 128.9 (<i>ortho</i>), 126.2 (<i>meta</i>), 128.9 (<i>para</i>)
¹⁵ N ^c)	– 197.0	– 86.8	–	–	–	–	–	–	–	–
¹³ C ^d)	–	–	134.0	119.8	119.8	119.8	127.2	109.2	141.4	145.0 (<i>ipso</i>), 127.2 (<i>ortho</i>), 127.2 (<i>meta</i>), 127.2 (<i>para</i>)
¹⁵ N ^d)	–	–	–	–	–	–	–	–	–	–

^a) DMSO. ^b) THF. ^c) CPMAS of LMP polymorph. ^d) CPMAS of HMP polymorph.

13.7818(4), $b = 13.7976(5)$, $c = 18.9445(3)$ Å, $\alpha = 94.300(3)$, $\beta = 95.131(3)$, $\gamma = 119.428(3)^\circ$, space group $P-1$). The asymmetric unit cell is composed of three 3-phenyl-1*H*-indazole molecules for **2a** (LMP) and of six molecules for **2a** (HMP). The structure of the asymmetric unit is shown in Figs. 5 (**2a** (LMP)) and 7 (**2a** (HMP)). In both structures, 3-phenyl-1*H*-indazole molecules are linked by H-bonds to form trimers, as can be observed in Figs. 5 and 6 for **2a** (LMP) and in Fig. 7 for **2a** (HMP).

DSC Experiments. When the DSC of the LMP form was recorded at $10^\circ \text{ min}^{-1}$, it melted at 106.7° . When heating is maintained above the melting point for 20 min and then the temperature first decreased (-50°) and then increased, the compound melted at 115.3° (HMP). When the temperature is increased to 170° , the compound reaches a glassy state needing several days to resolidify, and its DSC record shows both polymorphs. When the DSC were recorded at 1° min^{-1} an exothermic transition of LMP towards the HMP was observed.

DFT Calculations (B3LYP/6-31G).** Both tautomers of 3-phenylindazole have been fully optimized (no imaginary frequencies). They have the following intrinsic properties: **2a**: $E = -610.92081$ hartrees, $\mu = 1.73$ D, $\theta = 29.5^\circ$, and **2b**: $E = -610.91378$ hartrees, $\mu = 2.70$ D, $\theta = 33.7^\circ$. As expected, the 1*H*-tautomer **2a** is calculated to be by $18.44 \text{ kJ mol}^{-1}$ ($19.25 \text{ kJ mol}^{-1}$ with the ZPE correction) more stable than **2b**, and the increase in the dipole moment should not modify the equilibrium in solution. Since **1a** and **1b** are of similar stability, the observation that **2b** is significantly less stable than **2a** is not due to the Ph substituent but to 1*H*-indazoles being more aromatic than 2*H*-

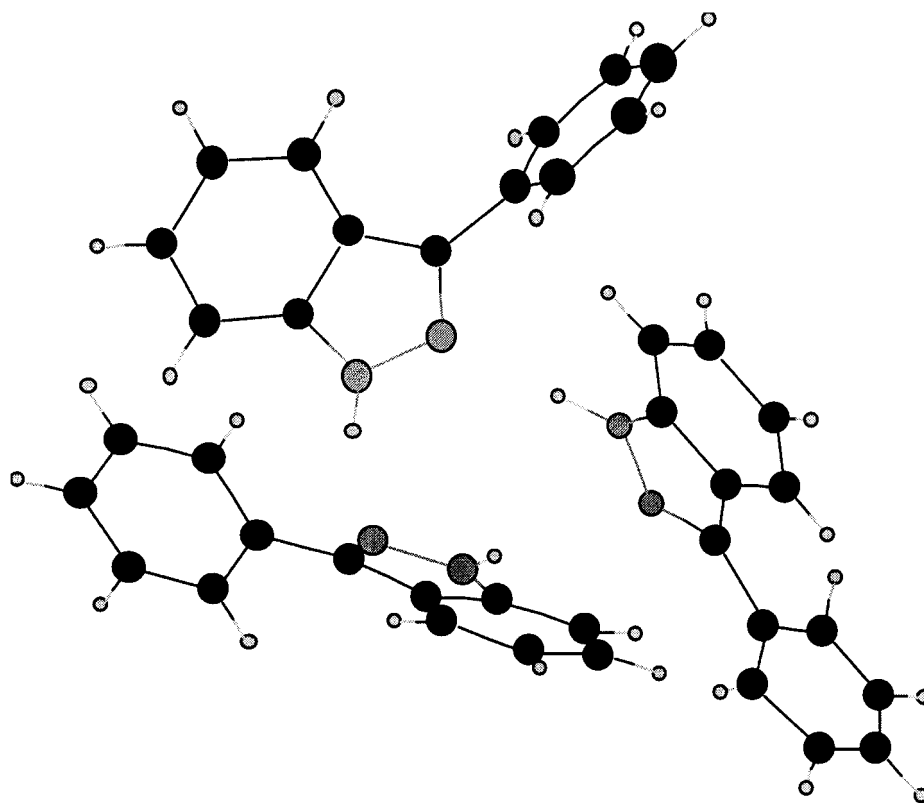


Fig. 5. Molecular structure of 3-phenyl-1H-indazole polymorph **2a** (LMP)

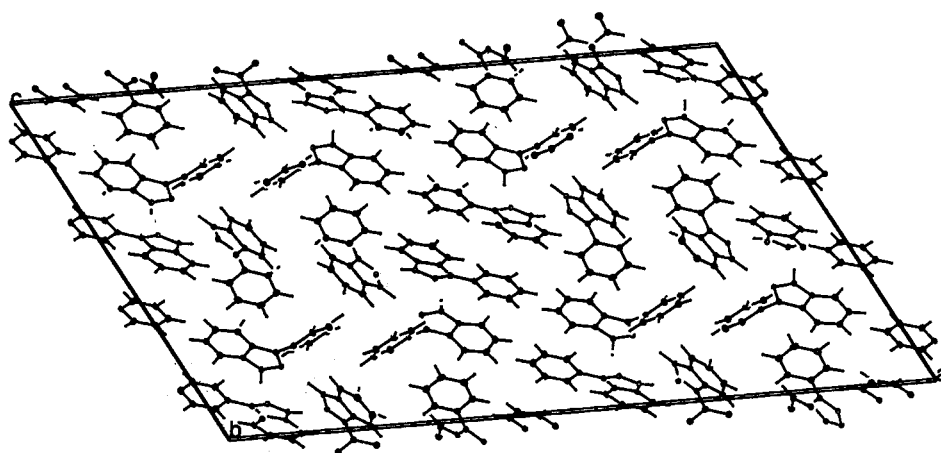


Fig. 6. Molecular packing for 3-phenyl-1H-indazole polymorph **2a** (LMP)

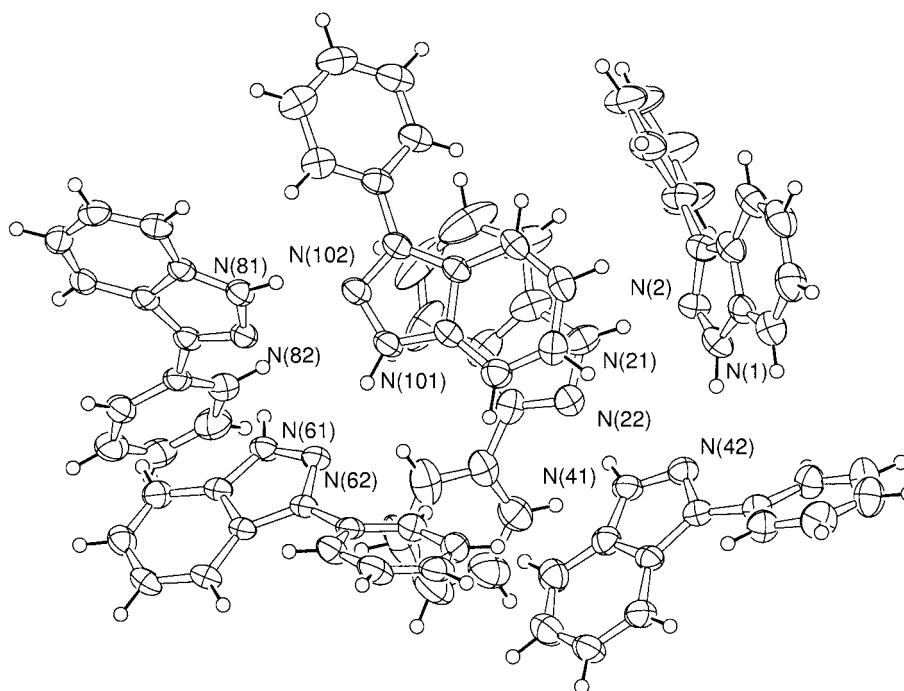
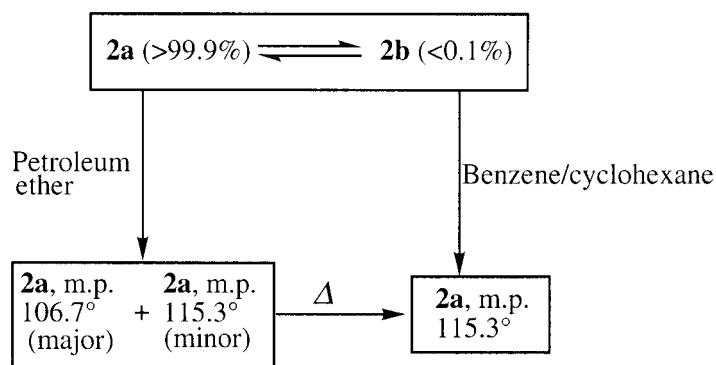


Fig. 7. Molecular structure of 3-phenyl-1H-indazole polymorph **2a** (HMP). Trimer 1: N(1)–N(2)/N(21)–N(22)/N(41)–N(42) and Trimer 2: N(61)–N(62)/N(101)–N(102)/N(81)–N(82)

indazoles. This is generally the case for all benzazoles: the benzenoid tautomer is more stable than the quinonoid one in the absence of other factors, such as lone pair/lone pair repulsions [44] [45]. At the B3LYP/6-31G** level, the three C(H)–C(H) bonds show less bond alternation in **2a** (1.387, 1.415, and 1.386 Å) than in **2b** (1.377, 1.428, and 1.376 Å). Scheme 2 summarizes the information we have gathered on compound **2**.

Scheme 2. The Case of 3-Phenylindazole (**2**)



Conclusions. – In two closely related compounds, we have found a case of desmotropy and a case of concomitant polymorphism, thus clarifying a long-standing problem. In the case of 3-phenylindazole, the difference in stability between the two tautomers is too great for the phenomenon of desmotropy to appear. On the other hand, 3(5)-phenyl-1*H*-pyrazole has precisely the thermodynamic properties to allow desmotropy, the two tautomers being of similar energy. This condition is not sufficient, however; for instance, a closely related compound, 3(5)-phenyl-5(3)-methylpyrazole crystallized, forming tetramers in which both tautomers are present [50]. Finally, we feel that the present research work is a posthumous homage to the memory of the great German chemist, *Karl von Auwers*, who was the most prominent figure in pyrazole and indazole chemistry in the last century.

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Experimental Part

Preparation of 3(5)-phenyl-1*H*-pyrazole **1** [51]. Acetophenone (2.00 g, 0.0166 mol) and HCOOEt (1.85 g, 0.0249 mol) were added, in one portion, with rapid stirring, to dry MeONa (0.93 g, 0.0166 mol in 15 ml of toluene) in a 50-ml round-bottomed flask provided with a magnetic stirrer and a reflux condenser topped with a drying tube. The mixture was stirred, after 1 h a solid appeared, the solid was filtered and washed with hot toluene and then with hexane. Finally, the product was air-dried and then made into a slurry with 10 ml of MeOH. To this MeOH slurry, hydrazine monohydrochloride (1.14 g, 0.0166 mol) and 10 ml of H₂O were added. After 30 min of stirring, MeOH was removed under reduced pressure. The remaining aq. soln. was extracted three times with CH₂Cl₂ (3 × 15 ml). The soln. was dried (Na₂SO₄), and CH₂Cl₂ was removed *in vacuo*. The product was crystallized from petroleum ether, and 1.11 g of solid was obtained (yield 50%, isolated product).

Preparation of 3-Phenyl-1*H*(2*H*)-indazole **2** [52]. In a 50-ml, double-necked, round-bottomed flask provided with a magnetic stirrer and a reflux condenser was placed *o*-aminobenzophenone (2.00 g, 0.0101 mol), and HCl (1.70 ml, 0.0203 mol) was added carefully. The soln. was cooled in ice, and the temp. was maintained at 0 to –5°, and a soln. of NaNO₂ (0.813 g, 0.0118 mol) in 7 ml of H₂O was added dropwise. The diazotized compound was neutralized with a soln. of Na₂SO₃. The mixture was extracted with AcOEt, dried, and evaporated to yield the 2-oxo-3-phenylindazole. This crude product was placed in a 250-ml round-bottomed flask provided with a reflux condenser and containing 50 ml of EtOH and was boiled gently until most compound had dissolved.

Meanwhile 10 g of a good grade of SnCl₂ in 30 ml of conc. HCl was dissolved. This soln. was added to the contents of the flask and boiled under reflux for a further 30 min; after cooling, EtOH was removed and then extracted with AcOEt (3 × 15 ml). The combined org. layers were washed with H₂O and dried (Na₂SO₄). Evaporation of the solvent gave an oily material, which was purified by column chromatography (silica gel; hexane/AcOEt) 7:3 (*R_f* 0.24): yellow solid (0.808 g, 41%).

Methylation of **2** [53]. In a 50-ml round-bottomed flask provided with a magnetic stirrer and a reflux condenser, 3-phenylindazole (0.179 g, 0.000923 mol), KOH (0.175 g, 0.00312 mol), MeI (0.525 g, 0.00370 mol), and MeOH (5 ml) were boiled for 4 h, cooled, and diluted with H₂O (20 ml). The mixture was extracted with CHCl₃ (3 × 10 ml) and dried (Na₂SO₄). A portion of the CHCl₃ soln. was evaporated and directly investigated by ¹H-NMR spectroscopy (a ratio of 70:30 1-methyl/2-methyl was found, which agrees with previous results, 74:26 [53]). Evaporation of the bulk of the CHCl₃ extract gave the crude mixture of *N*-methyl-3-phenylindazoles. This was separated by chromatography (silica gel; CHCl₃); the 1-Me isomer **6** (m.p. 79°; [53]: 80°) was eluted first, followed by the 2-Me isomer **7** (m.p. 48°; [53]: oil).

NMR Experiments. ¹³C- (100.62 MHz) and ¹⁵N-NMR (40.56 MHz) spectra in soln. were obtained with a *Bruker DRX-400* instrument (corresponding to 9.4 T). Variable-temp. ¹H-, ¹³C-, and ¹⁵N-NMR experiments were conducted on the same spectrometer with (D₈)THF and (D₁₈)HMPA as solvents. 2D-Inverse-proton-detected heteronuclear-shift-correlation spectra, gs-HMBC, gs-HMQC, were obtained with the standard pulse sequence [54]. Solid-state ¹³C- (50.32 MHz) and ¹⁵N- (20.28 MHz) CPMAS-NMR spectra have been obtained with a *Bruker AC-200* spectrometer at 298 K and a 7-mm *Bruker DAB-7* probehead, which achieves rotational

frequencies of *ca.* 3.5–4.5 kHz. Samples were carefully packed in ZrO₂ rotors, and the standard CPMAS pulse sequence was employed. To observe only the quaternary C-atoms, we run the NQS (Non-Quaternary Suppression) experiments by conventional cross-polarization (CP) at different contact times and with the dipolar dephased technique [55]. Chemical shifts (δ) in ppm are relative to Me₄Si and ¹⁵NH₄Cl (these were converted to MeNO₂ according to the relationship: δ (¹⁵N (MeNO₂)) = δ (¹⁵N(NH₄Cl)) – 338.1 ppm).

Crystallographic Data Collection and Structure Determination of 1b, 2a (LMP), and 2a (HMP). The results are reported in Table 3. Intensities were measured in the ϕ -scan mode on a Nonius CCD diffractometer (graphite monochromator, MoK α , λ = 0.71073 Å), and the Shelx 97 program for refinement of crystal structures was used [56].

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-184315, 184316, and 184317 for **1b**, **2a** (LMP), and **2a** (HMP), respectively. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 3. *Crystallographic Data Collection and Structure Determination of 1b, 2a (LMP) and 2a (HMP)*

	1b	2a (LMP)	2a (HMP)
Crystallized from	CH ₂ Cl ₂ at 4°	Petroleum ether	Petroleum ether
Empirical formula	C ₉ H ₈ N ₂	C ₁₃ H ₁₀ N ₂	C ₁₃ H ₁₀ N ₂
Formula weight	144.17	194.23	194.23
Crystal color, habit	Colorless, cube	Pale yellow, needles	yellow, prismatic
Crystal dimensions [mm]	0.35 × 0.30 × 0.30	0.5 × 0.3 × 0.1	0.35 × 0.30 × 0.20
Temp. [K]	293	293	178
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	<i>P</i> ₂ ₁ / <i>c</i>	<i>C</i> 2/ <i>c</i>	<i>P</i> -1
Reflections for cell determination	5627	21322	43711
2 θ Range [°]	4–52	4–52	4–52
<i>a</i> [Å]	10.862(1)	41.086(1)	13.7818(4)
<i>b</i> [Å]	5.7620(5)	7.3860(2)	13.7976(5)
<i>c</i> [Å]	12.927(2)	23.391(1)	18.9445(3)
α [°]	90.000	90.000	94.300(3)
β [°]	111.435(2)	117.697(1)	95.131(3)
γ [°]	90.000	90.000	119.428(3)
<i>V</i> [Å ³]	753.1(1)	6284.9(4)	3095.5(2)
<i>Z</i>	4	24	12
<i>D_x</i> [g cm ⁻³]	1.272	1.232	1.259
Absorption coefficient (MoK α) [cm ⁻¹]	0.078	0.074	0.076
2 θ _{max} [°]	52.6	52.7	50.8
Total reflections measured	5627	21322	43711
Unique reflections	1350	5994	11588
Absorption correction	none	none	none
<i>R</i> _{int}	0.036	0.047	0.051
Refined parameters	100	406	811
Reflections observed (<i>I</i> > 2 σ (<i>I</i>))	1266	4840	9735
H-Atoms	constrained	constrained	constrained
<i>R</i>	0.0622	0.0470	0.0801
<i>R_w</i>	0.1380	0.0998	0.1127
Weights ^a)	<i>k</i> ₁ = 0.0508; <i>k</i> ₂ = 0.2248	<i>k</i> ₁ = 0.0333; <i>k</i> ₂ = 3.2696	<i>k</i> ₁ = 0.1089; <i>k</i> ₂ = 3.3126
Final (shift/e.s.d.) _{max}	0.005	0.001	0.000
Goodness-of-fit	1.164	1.090	1.097
$\Delta\rho_{\text{fin}}$ (max/min) [e Å ⁻³]	0.121/–0.131	0.13/–0.15	0.700/–0.387

^a) $w = [\sigma^2 F_o^2 + k_1^2 P^2 + k_2 P]^{-1}$, with $P = (F_o^2 + 2 F_c^2)/3$

DSC Experiments. The melting temp. of the samples were determined with a *Seiko DSC 220C* instrument. The heating rates were normally $10^{\circ} \text{ min}^{-1}$, but other heating and cooling rates were used to study the transitions, with N_2 as the purge gas. As known, slight differences in the melting temp. appear depending on the heating rates. Melting points were also measured on a *Microscope Axiolab 'Zeiss'* with a *TMS 92 LINKAN* heating stage.

Computational Details. Calculations were carried out at the B3LYP/6-31G** level with basis sets of Gaussian-type functions with Windows Titan 1.0.5 from *Wavefunction Inc.*

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