

Synthesis, structure, electrostatic properties and spectroscopy of 3-methyl-4,5,6,7-tetrafluoro-1*H*-indazole. An experimental and *ab initio* computational study †



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The azine of pentafluorobenzaldehyde had been previously prepared from pentafluorobenzaldehyde and hydrazine. However, the analogous reaction of 2,3,4,5,6-pentafluoroacetophenone **1** with hydrazine did not result in the formation of azine **3** but resulted instead in the formation of 3-methyl-4,5,6,7-tetrafluoro-1*H*-indazole, **4**, via the hydrazone **2**. The resulting indazole was characterized by high resolution mass spectroscopy and ¹H-, ¹³C-, and ¹⁹F-NMR spectroscopy. The geometry and electrostatic properties of the parent indazole and its derivative, **4**, were studied with *ab initio* quantum theory and density functional methods. Our optimized structure of the parent indazole computed at the MP2(fc)/6-311G** level is presumably more accurate than the structure derived from microwave measurements. The preferred conformer of **4** was determined from RHF/6-31G* energies and full normal mode analyses were used to characterize both conformers. The minimum structure of **4** was refined at the MP2(fc)/6-311G** level of theory and compared to the unsubstituted structure. The electrostatic properties of the parent indazole and **4** are discussed and compared to those of benzene and hexafluorobenzene calculated at the same level. Natural bond order (NBO) calculations were performed to rationalize the difference in direction of the dipole moments of the parent indazole and **4**. The gauge-invariant atomic orbital (GIAO) method was employed to calculate atomic shielding tensors of the indazoles using density functional theory at the B3LYP/6-311+G(2d,p) level. The calculated chemical shifts were used to aid in assigning peaks in the NMR spectra.

Introduction

We have been interested in studying the linear and non-linear optical properties of crystals of *N*-perturbed donor–acceptor asymmetric conjugate systems of the azine type. We have systematically studied the crystal structures and the packing of symmetric^{1,2} and asymmetric^{3–5} acetophenone azines. These acetophenone azines have the general formula X–Ph–C(Me)=N–N=C(Me)–Ph–Y and they are called symmetric if X = Y and asymmetric if X ≠ Y. Our studies have resulted in the first realization of two prototypes of molecular organic materials with near-perfect dipole parallel-alignment in the pure crystal of 4-bromo- and 4-chloro-4'-methoxyacetophenone azines.^{3,4,6,7}

The *de novo* design of crystals is an undertaking of extraordinary difficulty since the lattice architecture results from the optimization of a large number of weak intermolecular interactions. The interactions are too complex to trace and the computation of lattice energies still presents a formidable challenge.⁸ Arene–arene interactions are central to the crystal lattice architectures of the acetophenone azines. The crystal structures of the prototypes of the piezoelectric azines show pairs of perfectly parallel aligned azine molecules with two T-contact arene–arene interactions. The Ph–CR=N–N=CR–Ph system thus constitutes a “double T-contact synthon” and we believe this motif to be the key to understanding the suprastructures of the prototypes. Double T-contacts occur when the arene rings of two compounds containing two arene groups each stack in

Table 1 Non-zero quadrupole components of benzene and hexafluorobenzene^a

Quadrupole tensor element ^b	Benzene		C ₆ F ₆	
	RHF	MP2(fc)	RHF	MP2(fc)
$Q_{xx} = Q_{yy}$	–31.3833	–31.6337	–68.7893	–70.9189
Q_{zz}	–39.7335	–40.7407	–59.3556	–60.3562

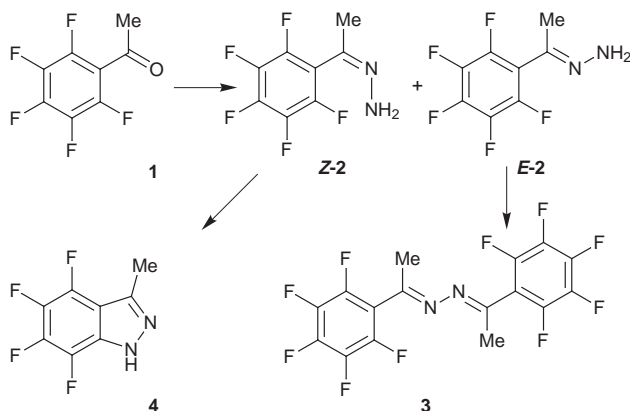
^a RHF and MP2(fc) refer to the RHF/6-31G* and MP2(fc)/6-311G** levels of theory, respectively. ^b Quadrupole moments in D Å.

such a way that two edge-to-face arene–arene contacts are realized.⁹

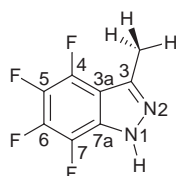
One strategy to increase the lattice energies of crystals of acetophenone azines aims at strengthening the arene–arene contacts. The components of the quadrupole moment tensor associated with an arene can be affected by placing substituents on the aromatic ring. The computed quadrupole moments of benzene and hexafluorobenzene are given in Table 1. These data demonstrate in a compelling fashion that polyfluorination is a particularly promising strategy to increase quadrupolarity; the components of the quadrupole moment of hexafluorobenzene are essentially twice as large as those of benzene.

In this context, we wanted to prepare the symmetrical azine **3** from 2,3,4,5,6-pentafluoroacetophenone **1** via the hydrazone **2** as shown in Scheme 1. However, no azine was formed when **1** was heated with hydrazine in toluene and we found that 3-methyl-4,5,6,7-tetrafluoro-1*H*-indazole **4** was formed instead. The molecular formula of **4** was verified via high resolution mass spectrometry. The confirmation of the structural formula of **4** via single crystal X-ray analysis was attempted but the fibrous nature of the material precluded the growing of suitable crystals. The structure of the indazole **4** (Scheme 2) was supported by comparing the measured ¹H-, ¹³C- and ¹⁹F-NMR spectra to the results of *ab initio* gauge-

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Scheme 1 Competition between formation of the azine **3** and the indazole **4** from the hydrazone **2** of 2,3,4,5,6-pentafluoroacetophenone **1**.



Scheme 2 Atom numbering of **4** according to the IUPAC nomenclature.

invariant atomic orbital (GIAO)¹⁰ computations of chemical shifts. We also report the *ab initio* optimized structure of the parent indazole and of **4** and a comparative analysis of their electronic structures in terms of molecular and atomic properties.

Experimental

Preparation of 3-methyl-4,5,6,7-tetrafluoro-1*H*-indazole, **4**

A 10.0 molar solution of 2.10 g (10.0 mmol) of 2,3,4,5,6-pentafluoroacetophenone **1** was prepared in 10.0 ml of toluene. To this solution, 0.5 ml (10 mmol) of hydrazine hydrate was added and was heated at reflux overnight. A solid precipitate was observed. This precipitate (0.41 g) was filtered and washed with toluene. The toluene filtrate was rotary evaporated to yield a yellowish solid, which was recrystallized from ethanol–water to yield a white fibrous solid (0.40 g). The NMR spectra were recorded with a Bruker DPX-300 NMR spectrometer, using a 5 mm broadband probe; δ_{H} (300.13 MHz, CDCl_3 , internal standard TMS) 11.60 (br s, 1H, NH), 2.57 (s, 3H, CH_3); δ_{C} (75.48 MHz, DMSO, internal standard TMS) 140.1 (m, C(3)), 138.6 (ddt, $J = 249$ Hz, $J' = 15$ Hz, $J'' = 4$ Hz, C(4) or C(6)), 137.9 (dtd, $J = 234$ Hz, $J' = 13$ Hz, $J'' = 3$ Hz, C(4) or C(6)), 133.3 (dt, $J = 241$ Hz, $J' = 15$ Hz, C(5)), 132.3 (ddm, $J = 249$ Hz, $J' = 16$ Hz, C(7)), 127.8 (m, $J = 8$ Hz, C(7a)), 108.6 (dd, $J = 19$ Hz, $J' = 4$ Hz, C(3a)), 12.6 (s, CH_3); δ_{F} (282.40 MHz, DMSO, internal standard CFCl_3) -150.5 (m), -158.6 (m), -160.3 (m), -169.6 (m). EIMS (m/z) 408.0 (7.3), 208.0 (7.4), 204.9 (9.0), 203.9 (M^+ , 100.0), 203.0 (70.6), 200.0 (10.5), 176.0 (18.6), 162.0 (7.5), 149.0 (8.7), 68.9 (5.6). HR EIMS (m/z) calculated for $\text{C}_8\text{H}_4\text{N}_2\text{F}_4$: 204.03105, found: 204.03171.

Computational details

Indazole is a planar molecule. Assuming C_s symmetry, two geometric conformers of the indazole **4** were recognized as possible energetic minima and these differed as to whether the methyl hydrogens are *eclipsed* (*ecl-4*) or *staggered* (*stag-4*) with respect to the C=N double bond of the five-membered ring. The geometries of both conformers of **4** were optimized at the RHF/6-31G* level. A normal mode analysis was then carried out at the same level to determine vibrational zero-point

energies and to characterize the structures as minima or saddle points.

The 6-31G* basis set^{11,12} was chosen due to the need to treat polar bonds in the molecule adequately, while a larger basis set was not deemed necessary for characterization of the conformers. Hartree–Fock theory was chosen to characterize the conformers for efficiency reasons and because RHF calculations generally give good results at stationary points. Furthermore, RHF/6-31G* calculated frequencies can be scaled to fit experiment and higher level calculations with high accuracy.¹³

A higher level geometry reoptimization was performed including electron correlation by way of Möller–Plesset perturbation theory¹⁴ truncated at second-order, designated MP2. Due to the size of the molecule, computational expense was a consideration and the frozen-core approximation was used in the MP2 calculation, designated as MP2(fc). The 6-311G** basis set¹⁵ was used for the reoptimization of *ecl-4*. The triply-split valence basis set allows greater flexibility in the valence region, reducing basis set truncation errors in the description of bonding. This improved valence description is viewed as being especially important in the study of molecules containing multiple and delocalized bonding systems. The 6-311G** basis set also improves the treatment of X–H polar bonds by explicitly adding p-type basis functions to hydrogen atoms. Furthermore, the use of this basis set for the MP2 calculations is deemed to be a good choice when we note that the 6-311G** Gaussian exponents and contraction coefficients were optimized at this same level of theory.

A natural bond orbital (NBO) population analysis,¹⁶ which localizes the many-electron wavefunction into Lewis-type electron-pairs was carried out at the MP2(fc)/6-311G** level of theory to determine natural atomic charges.

Finally, an NMR analysis was performed on the MP2(fc)/6-311G** optimized structure. This required the calculation of isotropic shielding tensors of the atoms in the indazole as well as in the reference molecules (TMS for ^1H - and ^{13}C -NMR, CFCl_3 for ^{19}F -NMR, and CH_3NO_2 for $^{14/15}\text{N}$ -NMR). The difference between the calculated shielding tensors gives the chemical shifts. The gauge-invariant atomic orbital (GIAO) method¹⁰ was used to calculate the shielding tensors at the B3LYP/6-311+G(2d,p) level of theory. Electron correlation was included in the NMR calculations by use of density functional theory (DFT) because of its reported accuracy and its availability for GIAO calculations in the Gaussian 94 suite of programs.¹⁷

The B3LYP functional was used, which combines Becke's three parameter exchange functional¹⁸ with the correlation functional of Lee, Yang and Parr.^{19,20} These are both non-local functionals whose combination is widely used and accepted. The 6-311+G(2d,p) basis set is similar to that used for reoptimization of the minimum structure, while improving the description of polar bonds and adding diffuse functions to heavy atoms, which improve the accuracy of NMR calculations.

All calculations were performed using the Gaussian 94 program¹⁷ on a Silicon Graphics Power Challenge-L computer.

Results and discussion

Preparation of 3-methyl-4,5,6,7-tetrafluoro-1*H*-indazole (**4**)

The azine of pentafluorobenzaldehyde had been previously prepared by stirring pentafluorobenzaldehyde with hydrazine in water at room temperature²¹ and we intended to prepare the symmetrical azine **3** from 2,3,4,5,6-pentafluoroacetophenone **1** via the hydrazone **2** in a similar fashion (Scheme 1). However, due to the insolubility of **1** in water, no azine was formed when this procedure was attempted with the acetophenone **1**. When **1** was heated with hydrazine in toluene, a reaction occurred and a

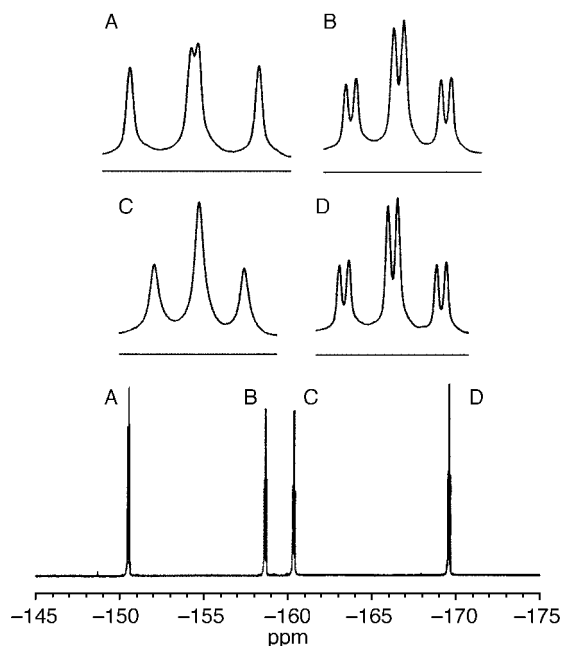


Fig. 1 The ^{19}F -NMR spectrum of indazole 4.

white precipitate formed. The product was crystallized from ethanol–water. Examination of the proton-decoupled ^{13}C -NMR spectrum of the product indicated that neither the hydrazone nor the azine had been produced. The ^{19}F -NMR spectrum showed only four sets of peaks. These data suggested that 3-methyl-4,5,6,7-tetrafluoro-1*H*-indazole, **4**, had been formed. The indazole was probably formed *via* the hydrazone **2** which cyclized *via* the displacement of an *ortho*-fluorine by the amino group to form **4**. Polyfluorinated aromatic compounds readily undergo nucleophilic aromatic substitution by a variety of nucleophiles.²² For example, when 2-(pentafluorophenyl)ethanamine is heated at reflux in DMF, 2,3-dihydro-4,5,6,7-tetrafluoroindole is formed by intramolecular displacement of a fluorine by the amine nitrogen.²³ Petrenko and Gerasimova^{24a} reported that the reaction of pentafluorobenzaldehyde and of pentafluoroacetophenone with phenylhydrazine leads to pentafluorohydrazone which can be cyclized to 3-phenylindazoles under mild conditions.^{24b} The pentafluorobenzaldehyde might form azine due to a preferential formation of the (*E*)-hydrazone. Furthermore, precedent for the formation of indazoles *via* the nucleophilic substitution of halogens by hydrazine amino groups in 2-halogeno-1-(1-hydrazonoalkyl)arenes has been presented in Stadlbauer's recent review of indazole chemistry.^{25a} The replacement of fluorine by hydrazine followed by pyrazole ring formation also presents a mechanistic possibility.^{25b}

The ^{19}F - and ^{13}C -NMR spectra of **4** are shown in Figs. 1 and 2. The assignments will be made below on the basis of *ab initio* computations of chemical shifts.

Ab initio study of 3-methyl-4,5,6,7-tetrafluoro-1*H*-indazole

There have been only relatively few quantum-mechanical studies of indazoles at the semi-empirical level^{26,27} or at the *ab initio* level.^{28–33} Most of the *ab initio* studies that were reported have been limited to Hartree–Fock level theory with small to modest basis sets. One of the earliest *ab initio* studies of indazole is the 1988 paper by Hodoscek *et al.*^{29b} In this study a minimal basis set was employed and the RHF/STO-3G calculations showed a preference for the 1*H*-tautomer. In 1992, Velino *et al.*³⁰ reported the microwave spectrum of the parent indazole together with RHF/4-21G calculations. Again, experiment and theory both clearly show a preference for the 1*H*-tautomer. The bond lengths of the RHF/4-21G computed structure were found to be somewhat underestimated (less than 0.02 Å). Interestingly, and most pertinent for the present study,

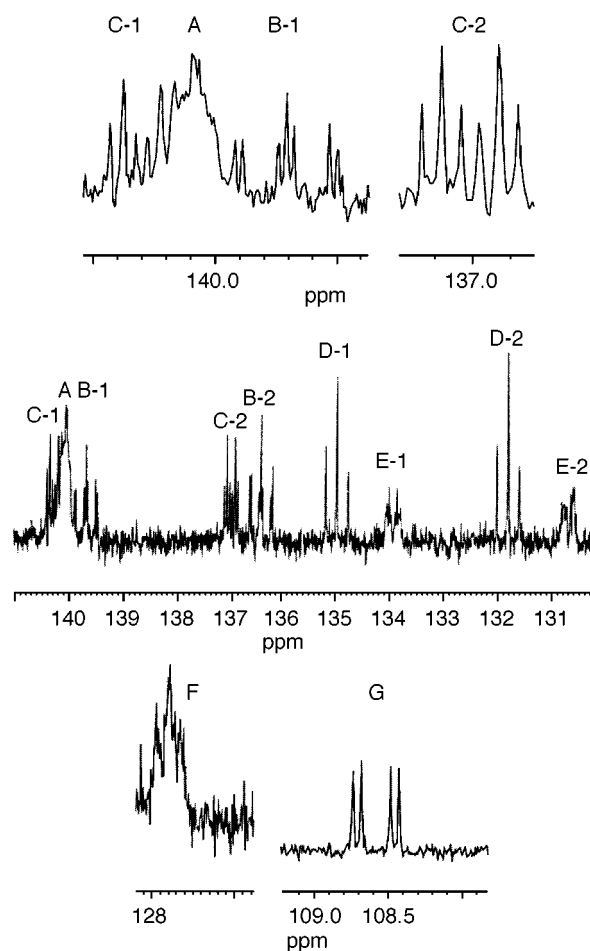


Fig. 2 The ^{13}C -NMR spectrum of indazole 4.

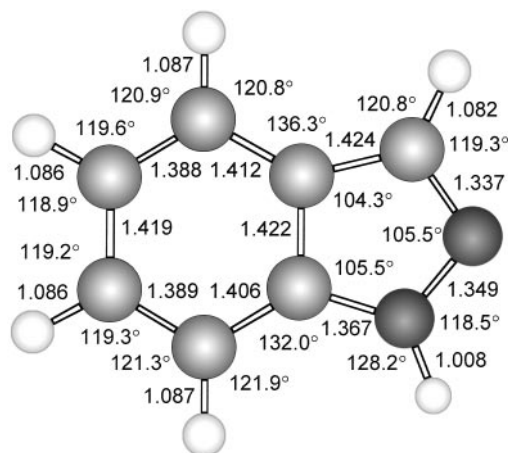


Fig. 3 Structure of the parent indazole as computed at the MP2(fc)/6-311G** level. Major structural parameters are displayed.

the authors succeeded in measuring the dipole moment of indazole and reported a value of 1.76(2) Debye. Williams and Whitehead³¹ presented an extensive comparison between heats of formation of aromatic nitrogen heterocycles computed with semi-empirical (MNDO, AM1, PM3) and *ab initio* (RHF/4-31G and RHF/6-31G**) methods. Recently, Catalan *et al.*³³ reported on the tautomerism of indazole and reported the MP2/6-31G** structure which was found to reproduce well the experimental moments of inertia of the 1*H*-tautomer.

Geometry and conformational preference

The RHF/6-31G* structures of parent indazole and two conformers of **4**, *ecl-4* and *stag-4* are shown in Figs. 3 and 4. The

parent indazole and the minimum structure *ecl-4* were also refined at the MP2(fc)/6-311G** level. Pertinent energy data and electrostatic properties are summarized in Tables 2 and 3, respectively. The refined structure of the parent indazole is shown in Fig. 3 and it is very close to the MP2/6-31G** structure by Catalan *et al.*³³ The agreement between the MP2(fc)/6-311G** and the experimental microwave structure reported by Velino *et al.*³⁰ is fairly good, but the experimental structure tends towards bond lengths which indicate more localized π -bonding in both the five- and six-membered rings than the MP2 structure. We believe that this is a result of the method used to interpret the microwave spectrum, which involved "correcting" an RHF/4-31G calculated structure. Hartree-Fock calculated structures, especially those using small basis sets, tend to underestimate bond delocalization, which could explain the discrepancies between our structure and the microwave geometry. Thus, we believe that our MP2(fc)/6-311G** optimized structure is more reliable than the reported experimental geometry.

The structure *stag-4* was found to exhibit one imaginary frequency (i 139 cm^{-1}) and the associated normal mode identifies this structure as the transition state for methyl rotation. The structure *ecl-4* is the minimum and all its vibrational frequencies are real. The activation barrier for this methyl rotation is only about 1.03 kcal mol^{-1} (Table 2). The structure of the minimum *ecl-4* was refined at the correlated level MP2(fc)/6-311G** and the resulting geometry is shown in Fig. 5. There are no significant differences in the bond lengths and bond angles of the fused-ring indazole skeleton when comparing **4** with the parent indazole. This is quite remarkable in that the strong electronic perturbation associated with fluorination hardly manifests itself in the structure.

NMR chemical shift assignments

We have computed the isotropic shielding tensors for all atoms in indazole and in *ecl-4* using density functional theory at the B3LYP/6-311+G(2d,p) level and based on the MP2(fc)/6-311G** optimized structures. These data were converted into chemical shifts and the resulting data are summarized in Table 4. Table 4 also includes measured data for indazole³⁴⁻³⁶ for comparison.

The computed data allow an assignment of the data meas-

Table 2 Electronic and vibrational zero-point energies of the parent and fluorinated indazoles

Molecule	Level ^a	E_{el}^b	VZPE ^c	$E_{\text{el}} + \text{VZPE}$
Indazole	RHF	-377.446718	0.116313	-377.330405
Indazole	MP2	-378.829263	—	-378.712953
<i>stag-4</i>	RHF	-811.859482	0.111612	-811.747870
<i>ecl-4</i>	RHF	-811.861256	0.111745	-811.749511
<i>ecl-4</i>	MP2	-814.292070	—	-814.180325

^a Theoretical level; RHF = RHF/6-31G*, MP2 = MP2(fc)/6-311G**.

^b Total energy E_{el} in atomic units (hartree/particle). ^c RHF/6-31G* vibrational zero-point energies, VZPE, are given in atomic units and they are scaled (factor = 0.9135).

Table 3 Electrostatic properties of the parent and fluorinated indazoles

Molecule	Level ^a	Dipole ^b	Quadrupole tensor elements ^b			
			Q_{xx}	Q_{yy}	Q_{zz}	Q_{xy}
Indazole	RHF	1.8200	-53.0281	-41.2500	-56.1135	+3.2311
Indazole	MP2	1.8445	-53.5479	-41.4180	-57.3164	+3.2776
<i>stag-4</i>	RHF	2.0832	-78.1329	-82.0096	-75.4210	-3.8685
<i>ecl-4</i>	RHF	2.0503	-78.0733	-82.2362	-75.4483	-3.8118
<i>ecl-4</i>	MP2	2.4117	-78.6908	-83.1602	-76.5024	-3.8728

^a Theoretical level; RHF = RHF/6-31G*, MP2 = MP2(fc)/6-311G**. ^b Dipole moments in Debye and quadrupole moments in D Å.

ured for *ecl-4*. The computed and experimental data do not match in absolute terms; the computed carbon chemical shifts are all overestimated (by 3.3–12.4 ppm) while all the fluorine chemical shifts are underestimated (by 12.9–20.4 ppm) and there is considerable variation between individual deviations. In most cases, the peak separations are of such a magnitude that the assignments based on relative chemical shifts appear reliable. Exceptions are C(4) and C(6), for which nearly identical chemical shifts are computed and neither carbon atom could be unambiguously assigned to either of the peaks at 137.9 ppm and 138.6 ppm. In this case, however, the splitting patterns due to CF-coupling allow one to differentiate between the two carbon atoms.

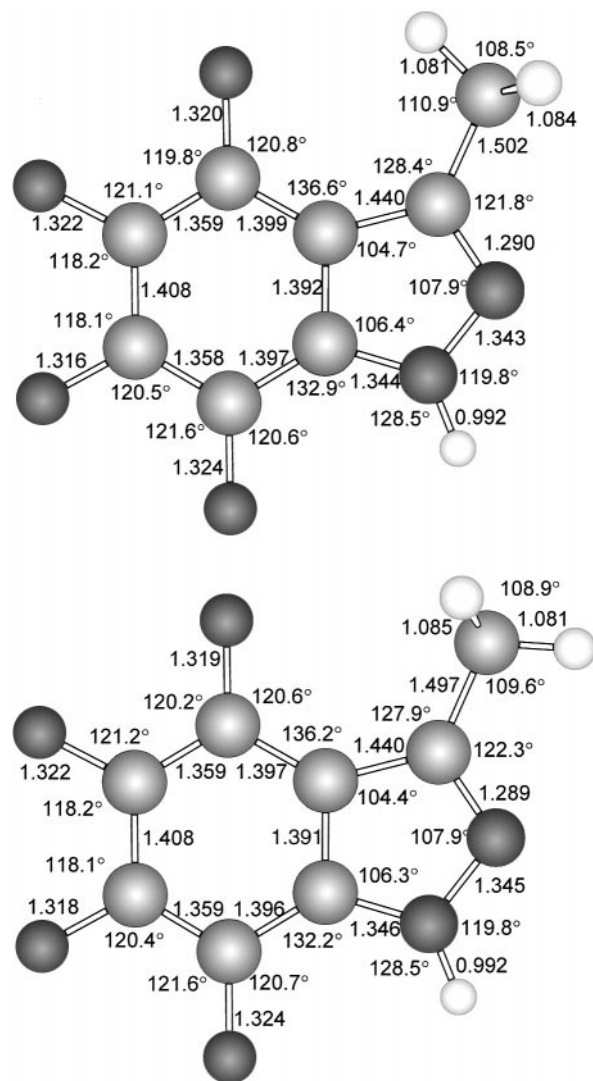


Fig. 4 Indazole conformations *stag-4* and *ecl-4*. The structure on the bottom is the minimum and the structure on top is the transition state structure for methyl rotation. Important parameters are given as computed at the RHF/6-31G* level.

Table 4 Computed^a and measured chemical shifts of indazole and 4

Atom	Indazole Chemical shift ^b			<i>ecl-4</i> Chemical shift ^c		
	Calc.	Expt.	Dev.	Calc.	Expt.	Dev.
C(3)	+141.44	+133.4	-8.0	+152.51	+140.1 (A)	-12.4
C(3a)	+130.79	+122.8	-8.0	+115.68	+108.6 (G)	-7.1
C(4)	+126.40	+120.4	-6.0	+149.77	+138.5 (C)	-11.3
C(5)	+126.92	+120.1	-6.8	+145.11	+133.3 (B)	-11.8
C(6)	+131.99	+125.8	-6.2	+149.79	+137.9 (D)	-11.9
C(7)	+113.45	+110.0	-3.4	+141.39	+132.3 (E)	-9.1
C(7a)	+146.37	+139.9	-6.5	+133.06	+127.8 (F)	-5.3
X-C(3) ^d	+8.28	+8.10	-0.18	+15.92	+12.6	-3.3
X-C(4) ^e	+8.05	+7.77	-0.28	-163.35	-150.5	+12.9
X-C(5) ^e	+7.49	+7.12	-0.37	-182.68	-169.6	+13.1
X-C(6) ^e	+7.69	+7.34	-0.35	-171.77	-158.6	+13.2
X-C(7) ^e	+7.68	+7.59	-0.09	-180.71	-160.3	+20.4
N(1)	-218.80	-194.40	+24.40	-229.68	^f	N/A
N(2)	-66.98	-65.61	+1.37	-69.67	^f	N/A
H _{oop} ^g	—	—	—	+2.70	+2.57	-0.13
H _{ip} ^g	—	—	—	+2.80	+2.57	-0.23
H-N(1)	+9.59	—	—	+9.33	+11.60 (br)	+2.27

^a Computed at the B3LYP/6-311+G(2d,p)//MP2(fc)/6-311G** level. Chemical shifts calculated as the difference in the computed isotropic GIAO magnetic shielding tensors of the atomic center and the relevant atom in the reference molecule. Standards; TMS: Isotropic carbon shielding tensor = 183.15 ppm and isotropic hydrogen shielding tensor = 31.91 ppm. Trichlorofluoromethane: Isotropic fluorine shielding tensor = 159.23 ppm. Nitromethane: Isotropic nitrogen shielding tensor = 159.45 ppm. ^b Measured spectra from Bouchet *et al.*³⁴ (¹³C), Palmer *et al.*³⁵ (¹H) and Fruchier *et al.*³⁶ (¹⁵N). ^c Assignments in parentheses refer to Figs. 1 and 2. ^d X = H, C. ^e X = H, F. ^f Not measured. ^g oop, out-of-plane; ip, in-plane.

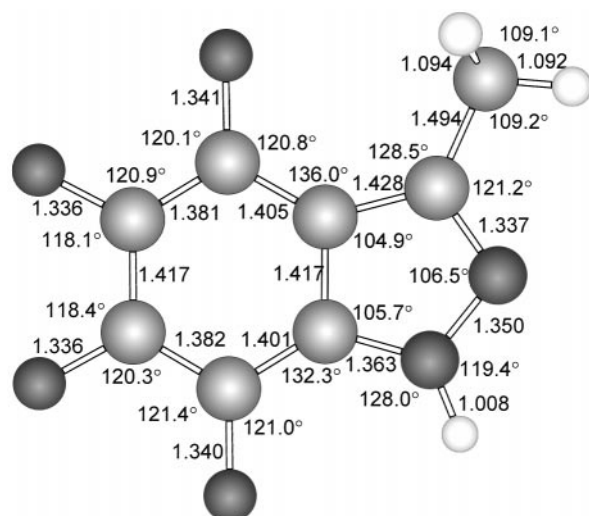


Fig. 5 Refined structure of the preferred indazole conformation *ecl-4* as computed at the MP2(fc)/6-311G** level. Major structural parameters are displayed.

Electronic structure: charges, dipoles and quadrupoles

There have been only two semi-empirical studies that concerned themselves with the charge distribution in the parent indazole. Catalan *et al.*²⁶ reported an INDO study and gave YSP charges and Escande *et al.*²⁷ reported Mulliken charges determined at the CNDO level. Computed charge distributions of the parent and fluorinated indazole were used to examine the effect of fluorination of the six-membered ring. The dipole and quadrupole moments are tabulated in Table 3, while Table 5 displays atomic charges for both molecules. The semi-empirical CNDO and INDO atomic charges were included in Table 5 for comparison and it can be seen that they do not agree in more than a rough qualitative fashion with our calculated natural charges at the MP2(fc)/6-311G** level of theory. Because of the greater reliability of *ab initio* calculated electrostatic properties, we will only discuss the atomic charges computed at the MP2 level of theory.

The effect of fluorination of the indazole can be seen most dramatically in the atomic charges of the fluorinated carbon atoms (*i.e.* C(4)–C(7)). These carbons bear a slight negative

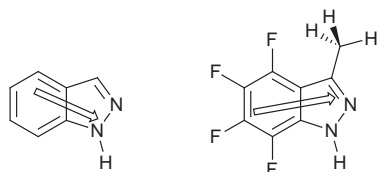
Table 5 Computed atomic charges

Atom	Indazole			<i>ecl-4</i> MP2(fc) natural charge ^a
	CNDO Mulliken charge	INDO YSP charge	MP2(fc) natural charge ^a	
C(3)	+0.0705	+0.184	+0.0368	+0.2328
C(3a)	-0.0432	+0.039	-0.1771	-0.2263
C(4)	+0.0301	+0.097	-0.1307	+0.4578
C(5)	-0.0297	+0.058	-0.2342	+0.3105
C(6)	+0.0269	+0.087	-0.1491	+0.3859
C(7)	-0.0441	+0.050	-0.2440	+0.3591
C(7a)	+0.1198	+0.228	+0.2045	+0.1581
X-C(3) ^b	-0.0101	-0.010	+0.1894	-0.5328
X-C(4) ^b	-0.0129	-0.021	+0.1944	-0.3727
X-C(5) ^b	-0.0077	-0.023	+0.1914	-0.3662
X-C(6) ^b	-0.0103	-0.025	+0.1907	-0.3625
X-C(7) ^b	-0.0023	-0.014	+0.1978	-0.3729
N(1)	-0.0878	-0.429	-0.4068	-0.4010
N(2)	-0.1001	-0.393	-0.2652	-0.2712
H _{oop} ^c	—	—	—	+0.1917
H _{ip} ^c	—	—	—	+0.2015
H-N(1)	+0.1009	+0.170	+0.4023	+0.4166

^a Computed charges from MP2(fc)/6-311G** natural bond order (NBO) calculations. ^b X = H, F. ^c Methyl hydrogens in *ecl-4* (oop, out-of-plane; ip, in-plane).

charge in the parent indazole, while having a strong positive character when the hydrogens are replaced by fluorine atoms. The reason for this can be easily explained by the strong inductive electron withdrawing ability of fluorine atoms. The only other large discrepancy in charges is the amount of positive character on C(3). To determine what proportion of the charge on C(3) is a result of fluorination of the six-membered ring, we must separate the effect of the electron donating methyl group, which is only present in the derivative **4**. The calculated charge on the C(3) hydrogen in the parent indazole is +0.1894, while the total charge of the methyl group bonded to C(3) in indazole **4** is +0.0521. This gives an estimate of the difference in inductive donation between H and Me to C(3), which helps us partition the charge difference on C(3) in the two compounds. Subtracting the X–C(3) charge difference from the C(3) charge difference in the two compounds shows that fluorination of the indazole contributes +0.0587 to the positive character of C(3).

Probably the most striking result is the unexpectedly small change in the magnitude of the dipole moment upon fluorination. At the RHF level of theory, the dipole moment is only 0.2632 Debye higher in the fluorinated species than in the parent indazole. Inclusion of electron correlation effects at the MP2(fc) level increases this difference to 0.5672 Debye, but the dipole increase remains rather small despite the high electronegativity of fluorine. However, the direction of the dipole is changed quite significantly (see Scheme 3). The dipole moment

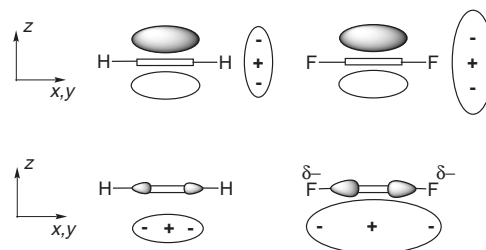


Scheme 3 Directions of the dipole moments in the parent indazole and in the fluorinated molecule *ecl-4*.

of the parent indazole lies on an axis approximately through C(3) and C(6) and our calculated dipole magnitudes of 1.8200 Debye (RHF/6-31G*) and 1.8445 Debye (MP2(fc)/6-311G**) agree to within less than 5% of the experimental value of 1.76(2).²⁸ Fluorination adds an almost equal component to the dipole moment along a perpendicular axis in the plane of the indazole. The relatively small increase in molecular dipole moment in comparison with the increased quadrupole components indicates that fluorination of asymmetric azines could be a promising route towards designing dipole-aligned molecular crystals. Molecular dipole alignment is an important aspect in designing molecular organic non-linear optically active crystals and quadrupole–quadrupole interactions are being investigated as a means for aligning dipolar molecules in the condensed phase.⁹

The change in the direction of the dipole associated with fluorination of the indazole can be explained in terms of electronegativities and bond polarizabilities. The fluorination of the six-membered ring leads to partial positive charges on the carbons to which the fluorine atoms are attached, atoms C(4), C(5), C(6) and C(7). The electron depletion on these atoms causes a polarization through the σ -framework and draws electron density from the five-membered ring. This electron density could be transferred through both the C(7a)–N(1) and the C(3a)–C(3) bonds. The higher electronegativity of nitrogen with respect to carbon should result in a more polarizable C(3a)–C(3) bond relative to the C(7a)–N(1) bond. In fact, this is what is observed in the NBO natural charges. The fluorination of the indazole polarizes the C(3a)–C(3) bond, resulting in a larger positive charge on C(3) and a build-up of negative charge on C(3a), while the charges on C(7a) and N(1) are virtually unaffected. This rearrangement of electron density explains the change in direction of the molecular dipole upon fluorination, shown in Scheme 3.

To understand the indazole quadrupole moments, we must first consider the calculated quadrupoles of benzene and hexafluorobenzene (Table 1). Both of these molecules have all negative components to their quadrupoles, that is the charge distributions are of the type (–)(+)(–). The negative Q_{zz} component is easily explained. The negative charge distributions above and below the ring are the result of the π -clouds of the aromatic rings, while there is a positive distribution associated with the carbon atoms in the z -plane (Scheme 4). Fluorination of the ring enhances this effect by withdrawing electron density from the carbons and increasing the positive charge on the ring, as shown in Scheme 4. The negative Q_{xx} and Q_{yy} tensor components are more difficult to explain. These components are equal because of the symmetry of benzene, but the hydrogens do not bear enough negative charge to explain the magni-



Scheme 4 The top row schematically illustrates the origin of the negative Q_{zz} quadrupole component of benzene and the effect of perfluorination. The negative Q_{xx} and Q_{yy} quadrupole components of benzene are associated with polarizations of the density in the regions of the C-atoms as indicated on the bottom. The effect of fluorination strengthens this effect through charge transfer associated with bond polarization.

tude of the quadrupole. However, one must realize that the bonds between the carbon and hydrogen atoms distort the electron density around the atoms. The carbon atoms' electron densities will be polarized towards the hydrogens by σ -bonding, resulting in a partial negative charge on the outside of the carbon skeleton and a partial positive charge inside the benzene ring (bottom of Scheme 4). The magnitude of these quadrupole components is increased upon fluorination because of the greater electronegativity of fluorine and, hence, a greater distortion of the electron density surrounding the carbon atoms. Furthermore, the F–C bonds are also fairly polar and will result in a significant negative charge on the fluorines, further increasing the magnitude of the Q_{xx} and Q_{yy} quadrupole components, as depicted in Scheme 4.³⁷

The quadrupole components given in Table 3 for the parent and fluorinated indazoles show the same trends as those in benzene and hexafluorobenzene. The Q_{xx} , Q_{yy} and Q_{zz} components are all negative and their magnitudes are increased dramatically when the six-membered ring is fluorinated. However, the asymmetry of the molecule results in slightly different Q_{xx} and Q_{yy} components as well as a non-zero Q_{xy} contribution to the quadrupole. One should note that, due to their non-zero dipoles, the indazole quadrupoles are dependent on the origin chosen for their calculation. The quadrupoles reported in Table 3 are calculated using standard orientation of the molecules, which places the origin at the center of nuclear charge.

Conclusions

The reaction of 2,3,4,5,6-pentafluoroacetophenone **1** with hydrazine results in the formation of 3-methyl-4,5,6,7-tetrafluoro-1*H*-indazole **4**. *Ab initio* energy and vibrational frequency calculations show that the conformer with a methyl hydrogen eclipsing the C=N bond of the five-membered ring is the minimum structure and that the barrier to the rotation of the methyl group is only 1.03 kcal mol⁻¹. Calculated GIAO atomic shielding tensors in most cases give very good agreement with the ¹H-, ¹³C- and ¹⁹F-NMR of **4** and the NMR spectra of parent indazole. With these computed chemical shifts a complete assignment was possible of the observed peaks in the spectra of **4**.

MP2(fc)/6-311G** optimized structures suggest that fluorination and replacement of H-C(3) by a methyl group have minimal effects on the bond angles and bond lengths of the fused-ring backbone of the indazole. Despite the geometrical similarities of indazoles, fluorination is shown to have dramatic effects on the electrostatic properties of the derivative **4**. As predicted from calculations on benzene and hexafluorobenzene, the inductive electron withdrawing effect of fluorine atoms on the six-membered ring results in a substantial increase in the non-zero components of the molecular quadrupole in **4** relative to the parent indazole. Fluorination also causes a slight increase and change of direction of the molecular dipole moment,

which is explained by intuitive bond polarizabilities and confirmed by NBO atomic charge calculations.

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References

- (a) G. S. Chen, M. Anthamatten, C. L. Barnes and R. Glaser, *J. Org. Chem.*, 1994, **59**, 4336; (b) G. S. Chen, M. Anthamatten, C. L. Barnes and R. Glaser, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1081; (c) R. Glaser, G. S. Chen and C. L. Barnes, *J. Org. Chem.*, 1993, **58**, 7446.
- R. Glaser, G. S. Chen, M. Anthamatten and C. L. Barnes, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1449.
- G. S. Chen, J. K. Wilbur, C. L. Barnes and R. Glaser, *J. Chem. Soc., Perkin Trans. 2*, 1995, 2311.
- R. Glaser and G. S. Chen, *Polym. Mater. Sci. Eng.*, 1996, **75**, 229.
- R. Glaser and G. S. Chen, *J. Comput. Chem.*, 1998, **19**, 1130.
- The piezoelectric material 4-bromo-4'-methoxyacetophenone azine has been featured as the Molecule of the Month for December 1997, see <http://www.bris.ac.uk/Depts/Chemistry/MOTM/motm.htm>.
- Crystal structure of the organic piezoelectric 4-chloro-4'-methoxyacetophenone azine. R. Glaser, M. Lewis and C. L. Barnes, manuscript in preparation.
- D. Steiger, C. Ahlbrandt and R. Glaser, *J. Phys. Chem. B*, 1998, **102**, 4257.
- M. Lewis, C. Barnes and R. Glaser, *Can. J. Chem.*, in the press.
- (a) K. Wolinski, J. F. Hilton and P. Pulay, *J. Am. Chem. Soc.*, 1990, **112**, 8251; (b) J. L. Dodds, R. McWeeny and A. J. Sadlej, *Mol. Phys.*, 1980, **41**, 1419; (c) R. Ditchfield, *Mol. Phys.*, 1974, **27**, 789; (d) R. McWeeny, *Phys. Rev.*, 1962, **126**, 1024; (e) F. London, *J. Phys. Radium*, Paris, 1937, **8**, 397.
- P. C. Hariharan and J. A. Pople, *Theor. Chim.*, 1973, **28**, 213.
- M. M. Francl, W. J. Pietro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. Defrees and J. A. Pople, *J. Chem. Phys.*, 1982, **77**, 3654.
- J. A. Pople, A. P. Scott, M. W. Wong and L. Radom, *Isr. J. Chem.*, 1993, **33**, 345.
- C. Möller and M. S. Plesset, *Phys. Rev.*, 1934, **46**, 618.
- R. Krishnan, J. S. Binkley, R. Seeger and J. A. Pople, *J. Chem. Phys.*, 1980, **72**, 650.
- NBO Version 3.1, E. D. Glendening, A. E. Reed, J. E. Carpenter and F. Weinhold.
- M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, Gaussian 94, Revision C.3; Gaussian Inc., Pittsburgh, PA, 1995.
- A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
- C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785.
- B. Miehlich, A. Savin, H. Stoll and H. Preuss, *Chem. Phys. Lett.*, 1989, **157**, 200.
- E. V. Aroskar, P. J. N. Brown, R. G. Plevey and R. Stephens, *J. Chem. Soc. (C)*, 1968, 1569.
- G. G. Yacobson and V. M. Vlasov, *Synthesis*, 1976, 652.
- I. L. Knunyants and G. G. Yacobson, eds., *Syntheses of Fluoroorganic Compounds*, Springer-Verlag, Berlin, 1985, p. 222.
- (a) N. I. Petrenko and T. N. Gerasimova, *J. Fluorine Chem.*, 1990, **49**, 359; (b) the work by Petrenko and Gerasimova suggested to us that indazole formation should occur at milder reaction conditions and this is indeed the case.
- W. Stadlbauer, *Indazole (Benzopyrazole)*, in Houben-Weyl, *Methoden der Organischen Chemie*, Heterenes III/2, pp. 764-864, Georg Thieme Verlag, Stuttgart, 1994, vol. E8b, (a) p. 786; (b) p. 796.
- J. Catalan, O. Mo, P. Perez and M. Yanez, *J. Mol. Struct.*, 1983, **94**, 143.
- A. Escande, J. Lapasset, R. Faure, E.-J. Vincent and J. Elguero, *Tetrahedron*, 1974, **30**, 2903.
- M. H. Palmer and S. M. F. Kennedy, *J. Mol. Struct.*, 1978, **43**, 203.
- (a) D. Kocjan, M. Hodosecek and D. Hadzi, *J. Mol. Struct. (THEOCHEM)*, 1987, **152**, 331; (b) M. Hodosecek, D. Kocjan and D. Hadzi, *J. Mol. Struct. (THEOCHEM)*, 1988, **165**, 115.
- B. Velino, W. Cane, A. Trombetti, G. Corbelli, F. Zerbetto and W. Caminati, *J. Mol. Spectrosc.*, 1992, **155**, 1.
- C. Williams and M. Whitehead, *J. Mol. Struct. (THEOCHEM)*, 1997, **393**, 9.
- R. Glaser, C. L. Mummert, C. H. Horan and C. L. Barnes, *J. Phys. Org. Chem.*, 1993, **6**, 201.
- (a) J. Catalan, J. L. G. de Paz and J. Elguero, *J. Chem. Soc., Perkin Trans. 2*, 1996, 57. (b) For an Addendum, see: J. Catalan, J. L. G. de Paz and J. Elguero, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1027.
- P. Bouchet, A. Fruchier, G. Joncheray and J. Elguero, *Org. Magn. Reson.*, 1977, **9**, 716.
- M. H. Palmer, R. H. Findlay, S. M. F. Kennedy and P. S. McIntyre, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1695.
- A. Fruchier, V. Pellegrin, R. Schimpf and J. Elguero, *Org. Magn. Reson.*, 1982, **18**, 10.
- For a similar discussion of the quadrupole moments of the 4-nitropyridine *N*-oxides NPO and POM, see: R. Glaser and G. S. Chen, *Chem. Mater.*, 1997, **9**, 28.

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