Study of the Addition Mechanism of 1H-Indazole and Its 4-, 5-, 6-, and 7-Nitro Derivatives to Formaldehyde in Aqueous Hydrochloric Acid Solutions

Ibon Alkorta,* Rosa M. Claramunt, José Elguero, Enrique Gutiérrez-Puebla, M. Ángeles Monge, Felipe Reviriego, and Christian Roussel

ABSTRACT: The reaction of NH-indazoles with formaldehyde in aqueous hydrochloric acid has been experimentally studied by solution and solid-state nuclear magnetic resonance (NMR) and crystallography. The mechanism of the formation of N$_1$-CH$_2$OH derivatives was determined. For the first time, 2-substituted derivatives have been characterized by multinuclear NMR. Theoretically, calculations with gauge-invariant atomic orbitals (GIAOs) at the Becke three-parameter (exchange) Lee-Yang-Parr B3LYP/6-311++G(d,p) level have provided a sound basis for the experimental observations. The first X-ray structures of four (1H-indazol-1-yl)methanol derivatives are reported.

INTRODUCTION

This work was aimed at a better understanding of a characteristic reaction of N-unsubstituted azoles and their reaction with formaldehyde to afford azolylmethanols. As a model of azole, indazole was selected because it was not clear what isomer would be obtained depending on the substituents in the ring. After solving this problem for 4-, 5-, 6-, and 7-nitro derivatives, the mechanism of the reaction should be established because it is common to all azoles and that the isolated compounds were characterized by multinuclear NMR. The present paper reports our study of the reaction of five NH-indazoles with formaldehyde in an aqueous acid solution, Scheme 1.

A search in different databases shows that the chemistry of indazoles is a very active field; the numbers of items are 11 723 (SciFinder), $^1$ 5142 (ScienceDirect), $^2$ and 4448 (Web of Science); $^3$ and most of the papers and patents deal with biological applications. $^4$–$^8$ Other applications (corrosion inhibitors) $^9$ and synthetic methods $^{10}$ are less reported, and the last place is occupied by indazole reactivity.

Five indazoles 1a−1e, existing in two tautomeric forms 1H and 2H, and their protonated indazolium cations 1aH$^+$−1eH$^+$, covering all of the substituted nitro compounds in the six-membered ring, will be discussed (Figure 1).

Some nitro-1H-indazoles, bearing or not other C-substituents, are powerful inhibitors of nitric oxide synthase isoforms, nNOS, iNOS, and eNOS. $^{11}$ Of the five possible C-nitro-1H-indazoles, 3-, 4-, 5-, 6-, and 7-, only 7-nitro-1H-indazoles (7-nitro, 3-bromo-7-nitro, and 3,7-dinitro) have inhibitory properties.

In 1969, $^{15}$ we reported that indazoles react with formaldehyde in aqueous HCl to afford (1H-indazol-1-yl)methanol derivatives. Indazole itself (1a) and 4-nitro (1b), 5-nitro (1c), and 6-nitro-1H-indazoles (1d) react, but 7-nitro-1H-indazole (1e) does not. The isolated compounds were characterized by $^1$H NMR in DMSO-$_d_6$ proving that they were 1-substituted indazoles. In 1986, the reaction was carried out in neutral conditions (ethanol). $^{16}$ In 2004, $^{17}$ the reaction of indazole 1a in acid conditions was re-examined; B3LYP/6-311++G(d,p) calculations indicated that the 1-substituted isomer (2a) was more stable than the 2-substituted isomer (3a) (Scheme 2), and the NMR data were extended to $^{13}$C and $^{15}$N nuclei together with GIAO calculations of absolute shieldings.

This reaction is common to all azoles (pyrazole in acid $^{15}$ and neutral conditions, $^{16,18,19}$ imidazole, $^{20,21}$ triazoles, $^{22,24}$ tetrazole, $^{25}$ benzimidazole, $^{16,26}$ and benzotriazole). $^{27−29}$ In the case of indazole, previous to our works, $^{15−17}$ Pozharskii et al. carried the reaction in 1964 in acid media. $^{30}$ Some azoles have...
two different tautomers; this is the case for 1,2,3-triazole, 1,2,4-triazole, tetrazole, indazole and benzotriazole; for these azoles, tautomer and isomer structures (position of the NH/NR) often differ according to the Curtin–Hammett principle and the Winstein–Holnes equation. In the case of indazole 1a, MP2/6-31G** calculations indicate that the 1H-tautomer is 15 kJ·mol⁻¹ more stable than the 2H tautomer. Similar values were obtained by other authors in the gas phase (14.5 kJ·mol⁻¹) and in water (15.9 kJ·mol⁻¹).

In summary, the theoretical results we have reported above concern exclusively thermodynamic aspects, differences in energy between tautomers and isomers, and NMR chemical shifts. Note that there were no theoretical studies on the reaction mechanism.

Although the reaction can occur in neutral conditions, we have carried out our calculations on indazolium cations because our experimental procedure always includes hydrochloric acid. There are two ways to prepare compounds 2a and 3a, from neutral indazoles 1a-1H and 1a-2H, reacting with neutral formaldehyde (Scheme 2a, a and d reactions) or with protonated formaldehyde (Scheme 2b, b and e reactions), or from protonated indazole 1aH⁺ (Scheme 2c reaction).

Obviously, the mechanism should involve protonated formaldehyde because it is a much weaker base (pKₐ = −4.2) than indazoles (1a, 1.04; 1b, 0.24; 1c, −0.96; 1d, −0.97; 1e, −0.99). Therefore, it is impossible to have a direct reaction between the indazolium cation and neutral or protonated formaldehyde (Scheme 2c reaction). We will see afterward how the reaction could involve indazolium cations with a relayed catalysis by a water molecule. In neutral conditions, zwiterions, zw, are intermediates to 3a and 2a.

The addition of azoles to carbonyl compounds is a reversible reaction that is more complete with aldehydes (for formaldehyde, see the Introduction section; for other aldehydes, see ref 36) than with ketones like acetone. The reverse reaction (elimination) is very fast in the ketone adduct and rather slow in the aldehyde adduct; the combination of these two reaction rates (addition and elimination) accounts for the position of the equilibrium to the point that has incorrectly been named irreversible for formaldehyde adducts. It depends also on the azole where electron-withdrawing groups like nitro substituents increase the sensitivity to hydrolysis, i.e., to an increase of the reverse reaction rate due to the increased leaving group character for nitro derivatives. The pure samples prepared in 1966 contain in 2021 about 50% of free NH-indazole, that is, t₁/₂ ~50 to 55 years in the solid state in a sealed tube (possibly formaldehyde polymerize into trioxymethylene or into paraformaldehyde). Starting from a pure adduct, crystallization in boiling water also leads to its partial decomposition.

Compounds 2aH⁺ and 3aH⁺ are in a formal way hemiaminals, where the usual loss of water would lead to 1-methylene-1H-indazol-1-iums, a class of unknown non-aromatic cations. In most cases, the synthetic procedure we have used afforded a pure compound (¹H NMR of the crude), but crystallization in boiling water reverts the reaction and mixtures of the adduct and free indazole are obtained in proportions close to 50:50.

## RESULTS AND DISCUSSION

After reporting the synthetic schemes, we will establish the structures of the different hydroxymethyl-indazoles we have identified in this work. Since some of them are formed in small quantities or are unstable, we have followed a logical chain (1) to determine by X-ray crystallography the structure of all possible compounds, i.e., obtain crystals of all abundant and stable compounds; (2) to carry out GIAO/DFT calculations to confirm the assignment of the NMR spectra; (3) to record the solid-state NMR spectra (CPMAS) of the compounds whose X-ray structures have been determined; and (4) to register solution NMR spectra of all of the compounds and compare the NMR chemical shifts determined in solution with GIAO/DFT-calculated values to identify the structures that cannot be isolated.

### Synthesis

The synthetic procedure reported in ref 15 (Scheme 3) was used with some differences. In the present work, we employ longer times and more water, particularly in the case of 7-nitro-1H-indazole (1e) that according to a previous report does not react with formaldehyde. In this last case, the effect of much longer times and microwave irradiation was also explored.

Crystallization in boiling water affords pure 2a; however, in the case of 2b, 2c, and 2d, it results in the partial hydrolysis of the N-substituent with formation of 1b, 1c, and 1d (between
Scheme 2. Formal Reactions between Both Tautomers of Indazole 1a and Indazolium Cation 1aH+ with Formaldehyde Corresponding to Neutral and to Acid Conditions

For compound 2c, the crystallization molecule of dioxane is not represented.

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Scheme 3. Reaction of Indazoles with Formaldehyde; Given Also the Relative Ratios and the Isomerization Case

Figure 2. 1-Methanol derivatives of the three parent benzazoles (top) and 1-methanol derivatives of three C-nitro indazoles (bottom). The structure of 2c contains a molecule of dioxane (not represented).
and $^{15}$N NMR chemical shifts. The spin–spin coupling constants, SSCCs, do not need any transformation. The calculated values are reported in Table 1; the remaining coupling constants are given in the Supporting Information.

Obviously, the $^1$H and $^{13}$C chemical shifts of the aromatic indazole ring in Table 1 depend on the presence and position of the nitro group. In $^1$H NMR, in what concerns the methanol group, the OH proton shows some interesting variations but, since this signal is strongly dependent on the solvent, they are of little interest. Note, however, that the difference between the 2 and 3 isomers is about 0.5 ppm except in the e series where it reaches 1.2 ppm. The CH$_2$ group appears between 5.5 and 5.6 ppm; only in compound 2e, it resonates at 6.2 ppm due to the proximity of the 7-nitro group.

The $^{13}$C chemical shifts are very different in isomers 2 and 3, a fact well known for other N-substituted indazoles. The signal of C3, a singlet or a doublet with a small coupling constant, is also a useful probe to determine the position of the CH$_2$OH group: 135 ppm (2) and 123 ppm (3) in average. The $^{15}$N chemical shifts of N1 and N2 atoms are also very different for isomers 2 and 3.

The SSCCs of the methanol group are slightly larger in the 2 series (−10.7 Hz) than in the 3 series (−9.4 Hz). The ortho SSCCs are normal and the W coupling $^5J_{HH}$ between protons H3 and H7 is calculated to be 0.7−0.8 Hz. The $^7J_{HH}$ coupling constants are small (between 0.2 and 0.5 Hz) except when there is a nitro group in the central carbon [H−C−C(NO$_2$)−C−H] where it attains 1.4−1.5 Hz; this effect of the nitro group has been reported for benzene derivatives.

Solid-State Nuclear Magnetic Resonance (SSNMR) Results (CPMAS Experiments). The chemical shifts of the four compounds, 2a−2d, whose X-ray structures have been determined in this work, are given in Table 2. As often happens in CPMAS, some signals are split, for instance, those of compound 2c. For this compound, when comparing its chemical shifts $\delta_{\text{Exp}}$ (Table 2) with the calculated values $\delta_{\text{GIAO}}$ (Table 1), mean values have been used.

Comparing the values in Tables 1 and 2 results in the following regression equations

$$\delta_{\text{Exp}} = -0.4 + 0.995\delta_{\text{GIAO}}, \quad n = 44, \quad R^2 = 0.997$$  \hspace{1cm} (1)

$$\delta_{\text{Exp}} = 1.3 + 0.982\delta_{\text{GIAO}} + 8.7 \text{NO}_2 - 16.0 \text{N}_2, \quad n = 44, \quad R^2 = 0.9994$$  \hspace{1cm} (2)

The largest residuals for $^{15}$N signals in the simple regression equation, eq 1, correspond to NO$_2$ and N2. Including these effects as dummy variables, eq 2 was obtained with +9.7 and −16.0 ppm corrections for NO$_2$ and N2, respectively. In any case, the $^{15}$N chemical shifts only can correspond to (indazol-1-yl)methanol isomers 2.

NMR in Solution. The experimental chemical shifts and SSCC in DMSO-$d_6$ solution are reported in Table 3.

In the $^1$H NMR spectrum of the reaction crude between protonated 7-nitroindazole ($^{1e}$H) and formaldehyde, we observed three triplets of the same intensity, 1:1:1, and approximately the same coupling constant, 8.0, 7.9, and 7.9 Hz for the 7.48, 7.38, and 7.28 ppm signals, respectively.
Table 1. GIAO/B3LYP/6-311++G(d,p)-Calculated $^1$H, $^{13}$C, and $^{15}$N NMR Chemical Shifts (δ in ppm) and Coupling Constants (J in Hz)

| nuclei | 2a | 3a | 2b | 3b | 2c | 3c | 2d | 3d | 2e | 3e |
|--------|----|----|----|----|----|----|----|----|----|----|
|        | $^1$H (ppm) | $^{13}$C (ppm) | $^{15}$N (ppm) |
| H3     | 7.83 | 134.0 | -181.1 |
| H4     | 7.65 | 126.6 | -60.7 |
| H5     | 7.16 | 120.6 | -5.64 |
| H6     | 7.37 | 120.8 | 5.64 |
| H7     | 7.48 | 120.7 | 5.64 |
| CH$_3$ | 5.64 | 72.4 | 72.4 |
| OH     | 1.59 | 76.7 | 76.7 |
| CH$_2$ | 1.59 | 77.0 | 77.0 |

Table 2. $^{13}$C and $^{15}$N NMR Data of (1H-Indazol-1-yl)Methanol Derivatives in the Solid State (CPMAS)

| nuclei | 2a | 2b | 2c | 2d |
|--------|----|----|----|----|
|        | 4-NO$_2$ | 5-NO$_2$ | 6-NO$_2$ | 7-NO$_2$ |
| H3     | 7.87 | 8.00 | 7.94 | 7.88 |
| H4     | 8.70 | 8.78 | 7.64 | 7.61 |
| H5     | 8.25 | 8.40 | 8.23 | 8.17 |
| H6     | 8.36 | 8.55 | 8.82 | 8.49 |
| H7     | 8.07 | 7.64 | 8.13 | 8.05 |
| C3     | 121.2 | 141.7 | 141.7 | 137.3 |
| C4     | 123.0 | 141.7 | 141.7 | 137.3 |
| C5     | 121.3 | 141.7 | 141.7 | 137.3 |
| C6     | 123.0 | 141.7 | 141.7 | 137.3 |
| C7     | 109.0 | 115.3 | 115.3 | 115.3 |
| CH$_3$ | 69.3 | 70.7 | 70.7 | 69.8 |
| N1     | -173.4 | -172.9 | -172.9 | -172.9 |
| N2     | -68.2 | -63.3 | -63.3 | -63.3 |
| NO$_2$ | -6.4 | -5.9 | -5.9 | -5.9 |

5). By analogy to other compounds, these multiplets should correspond to three H5 protons coupled with H4 and H6.

When the spectrum of 1e was recorded at 500 MHz in DMSO-d$_6$, its $^1$H NMR spectrum shows some very unusual $^1$H-$^1$H coupling constants (Figures 6 and 7).

Those measured in Figure 6 are reported on the left side in Figure 7. Because prototropy couplings with the NH are very rare and have been observed only on 3-azido-1H-indazole, we assigned this to the azido group blocking the tautomeration of indazole.53 Indazole tautomer 1H resembles 1H-indole where H1 is coupled, besides to H2, to H3 and H4.54 The calculated SSCCs of 1e−1H are given on the right side in Figure 7. The strong HB between H1 and one oxygen atom of the nitro group prevents the prototropy and allows the SSCCs with H1 to be observed. Note that the $^1$H NMR spectrum of 1e−1H has been described several times but these small couplings were never reported.47,55,56

The spectrum of 1e−1H in the region of the NH proton (DMSO-d$_6$ at 500 MHz) shows two signals, a large one (13.95 ppm, 94%) and a small one (14.83, 6%), as shown in Figure 8. We assign the small signal to tautomer 1e−1H by analogy with the GIAO calculations, 10.14 and 10.81 ppm. The differences are 0.88 ppm, experimental, and 0.67 ppm, calculated, and the shift produced by the solvent is about 3.9 ppm. The other signals of the minor tautomer are not observed except that of H6 that appears at 8.58 ppm ($J_{6e} = 7.9$, $J_{6f} = 0.9$ Hz) due to the spinning side bands and the big signals of the 1e−2H tautomer. An equation relies on experimental and calculated values if the effect of DMSO on NH signal is taken into account: $\text{Exp.} = (0.95 \pm 0.16) + (3.8 \pm 0.4) \text{NH}$, $n = 7$, $R^2 = 0.998$.

Actually, the triplets of Figure 5 correspond to a 1:1 mixture of 1e−1H (H5 at 7.38 ppm) and 3e (H5 at 7.28 and OH at 7.48 ppm). The A$_S$X system of the methanol part appears well resolved in some $^1$H NMR spectra in DMSO-d$_6$ ($J_{13} \sim 7.5$ Hz) (Figure 9), which is not always the case for common alcohols.
indazoles. COSY experiments correlate OH signals when signals are under the larger signals of 2.0 Hz.

H4 in 1H NMR chemical shifts, the OH phase), we have used simple regressions between both values, except in two cases. First, in 1H NMR chemical shifts, the OH 

Table 3. 1H, 13C(1H), and 15N NMR Data of (1H-Indazol-1-yl)Methanol Derivatives in DMSO-d6 Solution

| nuclei       | 2a b | 2b | 3b | 2c | 2d | 1e→2H | 2e | 3e |
|--------------|------|----|----|----|----|-------|----|----|
| H3           | 8.09 | 8.54| 8.91| 8.42| 8.34| 8.43  | 8.30| 8.85|
| H4           | 7.72 | NO2 | NO2 | 8.83| 8.03| 8.33  | 8.19| 8.37|
| H5           | 7.17 | 8.20| 8.21| NO2 | 7.99| 7.37  | 7.38| 7.28|
| H6           | 7.41 | 7.68| 7.40| 8.27| NO2 | 8.36  | 8.28| 8.48|
| H7           | 7.77 | 8.27| 8.30| 7.92| 8.78| NO2   | NO2 | NO1 |
| CH2          | 5.73 | 5.79| 5.79| 5.78| 5.86| 5.83  | 5.83| 5.80|
| OH           | 6.68 | 6.95| 7.50| 6.94| 6.93| 6.59  | 7.48| 7.48|
| C5           | 134.2| 132.1| 124.8| 136.4| 134.0| 136.2 | 135.5| 120.4|
| C5a          | 126.0| 116.6| 113.9| 123.3| 127.4| 127.6 | 130.6| 125.7|
| C4           | 121.6| 140.6| 143.0| 118.9| 122.2| 130.4 | 128.8| 126.7|
| C5           | 121.7| 118.7| 120.7| 141.4| 115.3| 120.7 | 121.3| 120.4|
| C6           | 127.0| 126.0| 123.8| 121.0| 145.9| 124.0 | 124.8| 125.7|
| C7           | 111.0| 118.3| 126.6| 112.0| 107.2| 132.6 | 138.2| 137.4|
| C7a          | 139.8| 139.7| 149.2| 140.8| 137.6| 132.4 | 130.8| 140.1|
| CH2          | 71.6 | 71.5| 75.8| 71.4 | 71.4 | 71.4  | 75.3 | 76.2|
| N1           | −180.8 b| −173.7| −90.2| −174.3| −173.0| −170.1| −86.5| −134.5|
| N2           | −60.5 b| −50.6| −134.2| −50.3| −45.2| −47.7 | −13.9| −17.4|
| NO2          | −15.6| −15.9| −17.1| −16.6| −13.9| −17.4 | 7.5 | 7.9 |
| 1H (ppm)     |      |      |      |      |      |      |      |      |
| 13C (ppm)    |      |      |      |      |      |      |      |      |
| 15N (ppm)    |      |      |      |      |      |      |      |      |
| SSCC (Hz)    |      |      |      |      |      |      |      |      |
| 1H CH2OH     | −7.3 c| −7.5 c| −8.0 c| −7.5 c| −7.4 c| −7.7 c| −7.9 c|      |
| 1H NH3       | 8.5  | NO2 | NO2 | NO2 | NO2 | NO2  | 7.9 | 7.9 |
| 1H NH2       | 7.5  | 7.3 | 7.7 | NO2 | NO2 | NO2  | 7.9 | 7.9 |
| 1H NH2       | 8.0  | 7.6 | 8.4 | 9.2 | NO2 | NO2  | 7.9 | NO2 |
| 1H NH2       | 1.0  | NO2 | NO2 | NO2 | 2.2 | NO2  | 0.9 | 1.0 |
| 1H NH2       | 0.9  | 0.9 | 0   | 1.0 | 0  | 0    | 0   | 0   |
| 1H NH2       | 0.8 d| 0.9 | 0   | 1.0 | 0  | 0    | 0   | 0   |

*Italic type: predicted values. bFrom ref 17: 13C NH3 = 7.9, 13C NH2 = 13.0, 13C CH2OH = 2.7 Hz,17 calculated, this work. cFrom ref 47. dNot measured. eAssignment based on coupling constants (Figure 5). fNot observed.

Figure 5. 7.2–7.5 ppm region of the 1H NMR in DMSO-d6 at 400 MHz of the reaction product between 1H1H and formaldehyde.

Note that the 3JHHNH and 3JHHN are identical for 2e and different for 3e: this is characteristic of 1- and 2-substituted indazoles.47 COSY experiments correlate OH → CH2 → H3 → H4 → H5 → H6 in the case of 2e and 3e with some exceptions when signals are under the larger signals of 1e.

To compare the experimental values of Table 3 (DMSO-d6 solution) with the calculated chemical shifts in Table 1 (gas phase), we have used simple regressions between both values, except in two cases. First, in 1H NMR chemical shifts, the OH signal is systematically underestimated because our equations relating absolute shieldings in the gas phase to chemical shifts in solution correct general solvent effects and not the hydrogen bond between the OH and DMSO.57,58 Second, in the JCH2OH SSCC, the same happens for the same reason. To correct these deviations, an additional variable (1 if OH was present and 0 if it was absent) was added.59 In any case, the intercept was not significant and the regressions were repeated imposing intercept = 0, but the squared correlation coefficient, R2, was that of the regression with the intercept because imposing the intercept to be 0 increased considerably the deviations, an additional variable (1 if OH was present and 0 if it was absent) was added.59 In any case, the intercept was not significant and the regressions were repeated imposing intercept = 0, but the squared correlation coefficient, R2, was that of the regression with the intercept because imposing the intercept to be 0 increased considerably the R2 value (Table 4). The slopes are close to 1.0; the experimental 1H chemical shifts of the OH are 5.1 ppm higher on average than the calculated ones, while the SSCCs involving the OH group, JCH2OH, are 3.5 Hz lower.

The most interesting 1H NMR spectra are those of the crude of 2b (Figure 10, neutral solid in DMSO-d6 solution) and those of the crude of 3e freshly prepared (Figure 11, filtered solid in DMSO-d6 solution) and after a week in the NMR tube. After crystallization (see the Supporting Information), the 3% amount of 3b has been eliminated.

Figure 11 (top) corresponds to a mixture of starting 7-nitro-1H-indazole 1e and its 2-methanol derivative, 3e. After a week, Figure 11 (bottom), 3e (neutral) has decomposed into 1e and...
a small quantity of another compound that we have identified as isomer 2e.

This behavior (Scheme 4) will be explained by the theoretical calculations in the following section.

**Reaction Mechanism: DFT Calculations.** According to the conclusions of the NMR analyses, the five indazoles regroup in three cases: obtaining in HCl (aq) 1-methanol derivatives (unsubstituted a, 5-nitro c, and 6-nitro d), obtaining a mixture of 1- and 2-methanol derivatives (95/5 4-nitro b), and obtaining a 2-methanol derivative 3e that in DMSO-d6 decomposes and partly isomerizes into 1-methanol derivative 2e (7-nitro e).

In Table 5 are the energies corresponding to the equilibria between 2 and 3 isomers; in all cases, the 1-CH2OH isomer is...
more stable than the 2-CH$_2$OH one, similarly to what happens for the NH tautomers; note that the values are similar except in the case of the e series where the difference is much larger, about 3.5 times. This is due to a strong hydrogen bond between the N–H and O=N–O$^-$ bonds (Figure 12) that disappears in the N-1-substituted derivative, confirming the NMR discussion about the HB (Figures 6 and 7). An analogous HB is present in 3,7-dinitro-1H-indazole,\textsuperscript{62} Protonation on N2 must reinforce the strength of the HB, being now N1(1$^+$)···H···O. The X-ray distances of the atoms involved in the hydrogen bond are the mean of two very similar structures,\textsuperscript{63,64} the only difference between the experimental and the calculated geometry lies in the N–H distance, which is underestimated by X-ray crystallography,\textsuperscript{65} this in turn affects the O···H distance.

The differences decrease in the order a > d > c > e > b. The formation of 2e from 3e is not related to the \( \Delta \Delta E \) value (13.7 kJ mol$^{-1}$) but simply that it is only in the e series that 2-isomer 3 is formed since in all cases the 2 isomers are more stable than the 3 isomers.

The mechanism for the unsubstituted indazole, a series, is represented in a simplified way in Scheme 6 and in a more realistic way, including TSs and IRCs (see the Supporting Information), in Figure 13.

The differences in stability of the five pairs of indazolium salts are reported in Scheme 6 and Table 6. In this table, N1 and N2 indicate the position of the CH$_2$OH group and complex, TS, and adduct corresponds to the complex, transitions state, and adduct in Scheme 5.

Although there are some differences in Table 6, the behavior of the a, b, c, and d series is similar (see mean a–d): in 1-series, a barrier of about 72 kJ mol$^{-1}$, the adduct being more stable than the complex by about 52 kJ mol$^{-1}$; in 2-series, a barrier of about 63 kJ mol$^{-1}$, the adduct being more stable than the complex by about 2 kJ mol$^{-1}$. The differences between both series, bottom of Table 6, are very small, ±1.6 kJ mol$^{-1}$. The e series is very different; when reacting by N2–H, far from the nitro group, the behavior is near identical, 52.3/50.5 and 61.8/63.4 kJ mol$^{-1}$, but when reacting N1–H, hydrogen-bonded to the nitro group, the complex spontaneously isomerizes to the complex formed by N2–H, which leads to 3eH$^+$OH$_3$ (Scheme 6). This explains why this isomer reacts differently from all of the other indazoles.

\section{CONCLUSIONS}

We have demonstrated that the reaction of NH-indazoles with formaldehyde, previously reported to yield exclusively 1-CH$_2$OH derivatives, gives rise in some cases to 2-CH$_2$OH indazoles, as found for 4-nitro-1H-indazole (1b) and 7-nitro-1H-indazole (1e). This result is important when hydroxymethyl-indazoles are used as intermediates without isolating them.

The structure, tautomerism, and reactivity of 1e are of interest because of its unique ability to inhibit both MAO-B and nNOS, two biologically important enzyme systems. Furthermore, its general use as an investigative drug to study the inhibition of nNOS makes the structural study of this molecule very relevant.\textsuperscript{12,13} This compound is the first reported indazole where both tautomers have been observed and the second in which spin–spin coupling constants with H1 have been observed observed and determined.

The X-ray structures of four 1-CH$_2$OH indazoles, (1H-indazol-1-yl)methanol (2a), (4-nitro-1H-indazol-1-yl)-methanol (2b), (5-nitro-1H-indazol-1-yl)methanol (2c), and (6-nitro-1H-indazol-1-yl)methanol (2d), were solved, offering a solid ground for NMR spectra in the solid state, and, in turn, these spectra were used for assigning the NMR spectra in DMSO-$d_6$ solution.

Theoretical calculations at the B3LYP/6-311+G(d,p) level have been used to understand the reaction mechanism and, in particular, the different behavior of 1e. Besides, GIAO calculations based on the optimized geometries proved an excellent tool to identify indazole isomers.

\section{EXPERIMENTAL SECTION}

\textbf{General Methods.} Acetonitrile, nitromethane, dioxane, heptane, hydrochloric acid, and indazoles were purchased from Merck without further purification. Melting points were determined by a capillary method in a Metler Toledo scientific melting point apparatus (MP760) at a heating rate of 1 °C/min. A PerkinElmer Spectrum Two, fitted with a diamond single-bounce ATR, was used to collect the IR spectra at 4 cm$^{-1}$ spectral resolution with four co-adds (i.e., the number of averaged replicate spectra). The compound was pressed on the diamond crystal and measured directly without any further sample. For $^1$H and $^{13}$C NMR spectra, see below. Reactions heated

\begin{table}[h]
\centering
\caption{Results of the Slopes of the Five Regression Equations: Experimental Values = a Calculated Values + b OH Protons}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{eq} & \textbf{no. of points} & \textbf{a calc.} & \textbf{b OH} & \textbf{$R^2$} & \textbf{RMS error} \\
\hline
1 & $^1$H chemical shifts & 44 & (1.02 ± 0.01) & (5.1 ± 0.1) & 0.947 & 0.23 ppm \\
2 & $^{13}$C chemical shifts & 53 & (0.996 ± 0.002) & & 0.994 & 1.7 ppm \\
3 & $^{15}$N chemical shifts & 6 & (0.986 ± 0.005) & & 1.000 & 1.7 ppm \\
4 & $^1$H, $^{13}$C, and $^{15}$N & 103 & (0.994 ± 0.001) & (5.1 ± 0.5) & 1.000 & 1.2 ppm \\
5 & $^1$H–$^1$H SSCC & 25 & (1.08 ± 0.02) & −(3.5 ± 0.3) & 0.962 & 0.6 Hz \\
\hline
\end{tabular}
\end{table}

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under microwave irradiation were carried out for 60 min at 80 °C in sealed reaction vessels of a Biotage Initiator microwave oven reactor (frequency: 2045 GHz). Analytical HPLC was performed with a SunFire C18, 3.5 μm column (4.6 mm × 50 mm). Mobile phase A

Figure 10. 1H NMR spectrum of crude of 2b in DMSO-d₆ solution containing 95% of 2b and 5% of 3b.

Figure 11. Top: 1H NMR spectrum of the crude of 3e in DMSO-d₆ solution freshly prepared; bottom: 1H NMR spectrum of the crude of 3e in DMSO-d₆ solution after a week in the NMR tube (both at 400 MHz). The signals in the 4.5−5.0 ppm region and a doublet in the 5.5−6.0 region are not indazole derivatives but most probably formaldehyde short polymers.
was CH₃CN + 0.08% formic acid, and mobile phase B was H₂O + 0.05% formic acid. The gradient was from 10 to 95% of acetonitrile.

UV diode array detection was carried out from 190 to 440 nm. All of the indazolyl-N-methanol derivatives were synthesized using the method reported in the literature with some differences: the reactions were stirred overnight at room temperature to ensure that all final products were obtained and no crystallization from water was used (because the starting products were obtained in this solvent). Indazoles (42 mmol) are suspended in 30 mL of 30% hydrochloric acid and then 3.85 mL of a 30% aqueous solution of formaldehyde (42 mmol) was added. After 1 h, 30 mL of water was added and the acid and then 3.85 mL of a 30% aqueous solution of formaldehyde was added. After 1 h, 30 mL of water was added and the mixture was kept overnight at room temperature. The precipitate was collected by filtration to give a solid. To obtain crystals, the solid was suspended in the solvent specified for each compound and heated and the solution was filtered to remove undesirable products. By slow cooling, crystals were precipitated and removed from the solvent to give the desired compound. Crystallization solvents were specified for each compound. Compound 2b (4-NO₂) was obtained as a minor product and could not be isolated and was only observed by NMR.

Compound 2e and 3e (7-NO₂) could not be isolated due to decomposition but could be detected by NMR.

**Table 5. Energies (kJ·mol⁻¹) Corresponding to Scheme 3 Calculated at the DLPNO-CCSD(T)/def2-TZVP//B3LYP/6-311++G(d,p) Level**

| parent | 4-NO₂ | 5-NO₂ | 6-NO₂ | 7-NO₂ |
|--------|-------|-------|-------|-------|
| a      | 0     | 0     | 0     | 0     |
| b      | 10.5  | 16.5  | 16.9  | 13.3  |
| c      | 0.0   | 0.0   | 0.0   | 0.0   |
| d      | 18.3  | 10.5  | 16.3  | 42.9  |

The values are given relative to reference compounds.

**Figure 12.** Experimental (adapted) and calculated structures of 1e–1H.
Scheme 5. Proposed Mechanism Illustrated for a Series

\[
\text{Complex} \quad \xrightarrow{\text{Adduct}} \quad \text{Adduct}
\]

N1: 1aH⁺·CH₂O·H₂O

The indazolium rings are rotated in the right part of the figure to keep formaldehyde, water molecules, and the hydroxymethyl group at the same position.

Figure 13. Mechanisms corresponding to Scheme 4.

Scheme 6. Relative Stability of Water-Solvated 1- and 2-Methanol Indazolium Salts

N2: 1aH⁺·CH₂O·H₂O

TS_{N1}

N1: 2aH⁺·OH₂

N2: 1aH⁺·CH₂O·H₂O

TS_{N2}

N2: 3aH⁺·OH₂

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microscope. Data were collected at 250 K on a Bruker X8 four circle kappa-diffractometer equipped with a Cu Incoatec microsource operating at 50 W power (50 kV, 1.0 mA) to generated Cu Kα radiation (\( \lambda = 1.54178 \) Å) and a Bruker VANTEC 500 area detector (microgap technology). Diffraction data were collected exploring over a hemisphere of the reciprocal space in a combination of \( \varphi \) and \( \omega \)
Table 6. Energies (kJ mol⁻¹) Corresponding to Scheme 6; x = a, b, c, d, e

| water | parent a | 4-NO₂ b | 5-NO₂ c | 6-NO₂ d | 7-NO₂ e | mean a–d |
|-------|----------|---------|---------|---------|---------|----------|
| N1–complex 1xH⁺CH₃O·H₂O        | 0.0  | 0.0     | 0.0     | 0.0     | 0.0     | 0.0      |
| N1–TS  | 82.2   | 67.9    | 69.7    | 70.1    | 70.1    | 72.5     |
| N1–adduct 2xH⁺OH₂        | −54.6 | −49.3   | −48.9   | −46.8   | −29.7   | −49.9    |
| N2–complex 1xH⁺CH₂O·H₂O    | −2.3  | −2.7    | −1.4    | 0.1     | 0.0     | −1.6     |
| N2–TS  | 74.6   | 57.8    | 60.2    | 61.0    | 61.8    | 65.4     |
| N2–adduct 2xH⁺OH₂        | −38.1 | −55.9   | −54.9   | −53.1   | −52.3   | −50.5    |
| N2–adduct − N1–adduct     | 16.5  | −6.6    | −6.0    | −6.2    | −22.6   | −0.6     |

**The differences between the N-complexes and between the N-adducts are also reported. The energies correspond to DLPNO/CCSD(T) single-point calculations including the contribution of PCM=water. The gas phase values are reported in the Supporting Information.** See the comment below.

scans to reach a resolution of around 0.85 Å, using the Bruker APEX2 software suite (each exposure, depending on ω₀, was of 10, 30, or 60 s covering 1° in ω or φ). Unit cell dimensions were determined by a least-squares fit of reflections with I > 2 σ(I). Data were integrated and scaled using the SAINTplus program.66 A semiempirical absorption and scale correction based on equivalent reflection was carried out using SADABS.71 Space group determination was carried out using XPREP.69 The structure was solved by direct methods using SHELXT,68 showing all no-hydrogen atoms. Additional cycles of re-examined and tested using PLATON.71 A summary of the main scans is shown in Figure S19a–d.

**NMR Spectroscopy.** Solution spectra were recorded either on three spectrometers, a Bruker DRX-400 (9.4 Tesla, 400.13 MHz for ¹H, 100.62 MHz for ¹³C and 40.54 MHz for ¹⁵N), a Bruker Avance III HD-400 (¹H 399.86 MHz, ¹³C 100.55 MHz), and a Varian SYSTEM 500 NMR (¹H 499.81 MHz, ¹³C 125.69 MHz) equipped with a 5 mm HCN cold probe. Chemical shifts (δ in ppm) are given from the internal solvent: DMSO-d₆, at 2.50 ppm for ¹H NMR and at 39.5 ppm for ¹³C NMR, and nitromethane was used as an external reference for ¹⁵N NMR. For ¹³C, WALTZ-16 was used to broaden proton decoupling and ¹⁵N NMR spectra were acquired using 2D (¹H–¹³C) gradient-selected heteronuclear multiple bond correlation by means of standard pulse sequences and in absolute mode.

Typical parameters: for ¹H spectra, spectral width of 5200 Hz, acquisition time of 6.3 s, digital resolution of 0.41 Hz per point, and pulse width of 7.6 μs at an attenuation level of -1 dB; for ¹³C spectra, spectral width of 20.2 kHz, acquisition time of 1.6 s, digital resolution of 1.12 Hz per point, pulse width of 14.5 μs at an attenuation level of -4 dB, and relaxation delay of 2 s; the FIDS were multiplied by an exponential weighting (λb = 1 Hz) before Fourier transformation.

Solid-state ¹³C (100.73 MHz) and ¹⁵N (40.60 MHz) CPMAS NMR spectra were obtained on a Bruker WB 400 spectrometer at 300 K using a 4 mm DVT probehead. Samples were carefully packed in a 4 mm diameter cylindrical zirconia rotor with Kel-F end caps. ¹³C spectra were originally referenced to a glycerine sample, and then the chemical shifts were recalculated to the Me₃Si [for carbonyl atom (glycine) δ = 176.1 ppm] and ¹⁵N spectra to ¹⁵NH₃Cl and then converted to the nitromethane scale using the following relationship: δ¹⁵N (nitromethane) = δ¹⁵N (ammonium chloride) −338.1 ppm. Typical acquisition parameters for ¹³C CPMAS are as follows: 3.2 μs 90° ¹H pulses and decoupling SPINAL 64 sequence spectral width, 40 kHz; recycle delay, 5–120 s; acquisition time, 30 ms; contact time, 2–4 ms; and spin rate, 12 kHz.

Typical acquisition parameters for ¹⁵N CPMAS are as follows: 3.2 μs ¹H 90° pulses (SPINAL 64) spectral width, 40 kHz; recycle delay, 5–120 s; acquisition time, 35 ms; contact time, 7–9 ms; and spin rate, 6 kHz.

Abbreviations for multiplicity are as follows: d indicates doublet, t indicates triplet, m indicates multiplet, bs indicates broad singlet, dd indicates broad doublet, dd indicates double doublet, dt indicates double triplet. Chemical shifts are reported in ppm referenced to DMSO-d₆ at 2.50 ppm for ¹H NMR and at 39.5 ppm for ¹³C NMR, and coupling constants in hertz (Hz).

The assignment of the signals in solution is based on conventional 2D techniques, ¹H–¹H COSY, HMBC, and HSOQC, and by comparisons with calculated values.

**Computational Details.** All of the calculations were carried out using the Gaussian-16 package.73 In all cases, we used the B3LYP/6-311++G(d,p) method.74 Frequency calculations were carried out to verify that the structures obtained correspond to energetic minima (I = 0) or to transition states (TS, I = 1). These geometries were used for the calculation of the absolute chemical shieldings with the GIAO method56 and the SSCC.

Equations 3–5 were used to transform absolute shieldings into chemical shifts.46

\[
\delta^1H = 31.0 - 0.97 \times \sigma^1H, \text{ (reference TMS, 0.00 ppm)} (3)
\]

\[
\delta^{13}C = 175.7 - 0.963 \times \sigma^{13}C, \text{ (reference TMS, 0.00 ppm)} (4)
\]

\[
\delta^{15}N = -152.0 - 0.946 \times \sigma^{15}N, \text{ (reference MeNO}_2, 0.00 \text{ ppm)} (5)
\]

To locate the intermediates at either sites of the TS point, we followed the vibrational mode of the imaginary frequency, forward and backward, along the intrinsic reaction coordinate (IRC)78 and relaxed the geometry for searching an energy (local) minimum. Although all of the stationary points were calculated at the B3LYP/6-311+G(d,p) level, they were recalculated at the 6-31G* level to calculate the IRCs.

To have a better description of the energy, domain-based local pair natural orbital coupled cluster method with single, double, and perturbative triple excitations, DLPNO-CCSD(T)80,81 with the def2-TZVP basis set82 has been carried out on the B3LYP/6-311+G(d,p) geometries with the Orca program (Version 5.0.1).83 The effect of the solvent has been taken into account by optimizing the structures using the polarizable continuum model (PCM)44 with the water parameters at the B3LYP/6-311+G(d,p) level.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00154.

Reproduction of the ¹H and ¹³C NMR spectra of all novel compounds; details of computational methods and details of the crystal structure determinations of 2a
Accession Codes
CCDC 2113708–2113711 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION
Corresponding Author
Ibón Alkorta — Instituto de Química Médica, CSIC, E-28006 Madrid, Spain; orcid.org/0000-0001-6876-6211; Email: ibon@iqm.csic.es

Authors
Rosa M. Claramunt — Departamento de Química Orgánica y Bio-Órgánica, Facultad de Ciencias, UNED, E-28040 Madrid, Spain; orcid.org/0000-0001-6634-2677
José Elguero — Instituto de Química Médica, CSIC, E-28006 Madrid, Spain; orcid.org/0000-0002-9213-6858
Enrique Gutiérrez-Puebla — Departamento de Nuevas Arquitecturas en Química de Materiales, Instituto de Ciencia de Materiales de Madrid (ICMM-CSIC), E-28049 Madrid, Spain
M. Ángeles Monge — Departamento de Nuevas Arquitecturas en Química de Materiales, Instituto de Ciencia de Materiales de Madrid (ICMM-CSIC), E-28049 Madrid, Spain; orcid.org/0000-0003-2242-7593
Felipe Reviriego — Instituto de Ciencia y Tecnología de Polímeros, CSIC, E-28006 Madrid, Spain
Christian Roussel — Aix-Marseille Université, CNRS, 13397 Marseille, France

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.2c00154

Notes
The authors declare no competing financial interest.

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