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Conformational Analysis of 1- and 3-Isopropylindoles. A ^{1}H NMR and Molecular Mechanics Study

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The conformations of the isopropyl groups in a series of 1- and 3-isopropylindoles have been studied by ^{1}H NMR and molecular mechanics technique. The isopropyl group is shown to assume both a *syn* and an *anti* conformation, and the equilibrium between these is shown to depend on the steric size of the substituent in position 2. The *syn* form is relatively more favoured in the 3- than in the 1-isopropylindoles, which can be explained by differences in the lengths of the ring bonds to N-1 and C-3.

The energy barriers to *syn-anti* exchange are 45–46 kJ mol^{-1} in the 1-iPr compounds when R_2=Me or CO_2Me. This barrier is lower in the 3-iPr analogues and could only be measured when R_1=iPr, R_2=Me (35 kJ mol^{-1}).

In the 1-iPr compounds a 3-Me group exerts no observable buttressing effect on a 2-Me group, unlike the situation in 1-iso-propylnaphthalenes, where introduction of a 3-Me group leads to an apparent diminution of the steric effect of the 2-Me group ("negative buttressing"). In 1-isopropyl-2-methylindole a 3-Br also exerts a negative buttressing effect.

The conformations of the sugar residue in nucleosides are similar to those of simple secondary alkyl groups attached to planar frameworks, *i.e.* with the secondary hydrogen atom in or nearly in the sp^2 plane and with the larger groups on either side of the plane. In this way the well-known *syn* and *anti* forms of nucleosides arise.[1]

We intend to study the circular dichroism (CD) spectra of nucleoside models as a function of the *syn–anti* equilibrium. In these, we will replace the base by the indole ring system, chosen because the directions of the electronic transition moments of its first $\pi\rightarrow\pi^*$ transitions are known from experiment.[2] The sugar moiety is replaced by a "rotor" R of the type CH_3-CH-X, where X is a chromophore with a well defined $\pi\rightarrow\pi^*$ transition of known energy. In such a system, it is possible to calculate the signs and magnitudes of the rotational strengths of the first $\pi\rightarrow\pi^*$ transitions in the indole ring by the exciton model, once the geometric relations of the two transition moments are known.[3]

It has been shown that rotors R with X=CO_2H or CO_2CH_3 behave very much like isopropyl groups when attached to planar frameworks.[4] Therefore, in order to learn how substituents in positions 2 and 3 of the indole ring affect the *syn–anti* equilibrium of an isopropyl group in position 1, we have performed a dynamic ^{1}H NMR and molecular mechanics study of a series of 1-isopropylindoles (*1a–1f*). In order to elucidate the effect of a change in geometry of the environment of the isopropyl group, we have also studied a smaller number of 3-isopropyl analogues (*2a–2c*). In these, the isopropyl group is more distant from the aromatic ring but closer to the 2-substituent (see Fig. 1), and the C-3–iPr bond is longer than the N-1–iPr bond.

In the 1-isopropylindoles it is possible to study the buttressing effect of bromine atoms and methyl groups in position 3. Since the effects of these groups were quite different, we found it of interest to study the buttressing effect of a methyl group in a similar system with a six-membered ring, and for this purpose we have prepared 1-isopropyl-2,3-dimethylnaphthalene (*3a*). The data for this compound are compared with those of the 3-unsubstituted analogue *3b*.[5]

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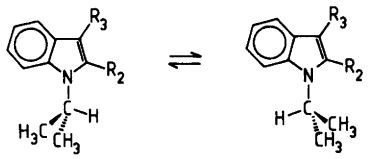
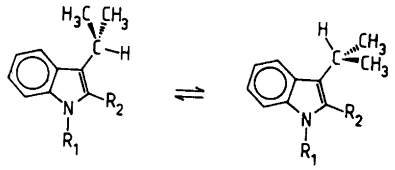


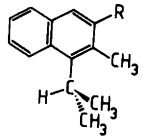
syn *anti*

1a, $R_2=R_3=H$
1b, $R_2=Me$, $R_3=H$
1c, $R_2=R_3=Me$
1d, $R_2=Me$, $R_3=Br$
1e, $R_2=CO_2Me$, $R_3=H$
1f, $R_2=Me_2COH$, $R_3=H$



syn *anti*

2a, $R_1=Me$, $R_2=H$
2b, $R_1=R_2=Me$
2c, $R_1=iPr$, $R_2=Me$



3a, $R=CH_3$
3b, $R=H$

EXPERIMENTAL

Preparative part. Most *N*-alkylindoles are rather unstable liquids, and they are conveniently stored as crystalline picrates.

1-Isopropylindole (*1a*) was prepared according to Michaelis.[6] The decarboxylation of the intermediate 2-carboxylic acid was performed in a Claisen flask under reduced pressure (0.1 kPa), and the product distilled (b.p. 76 °C) as a pale yellow liquid (yield 25 %), which was further purified by GLC (OV-101, 170 °C). No crystalline picrate could be obtained. Anal. $C_{11}H_{13}N$: C, H, N, MS [IP 70 eV; *m/e* (% rel. int.)]: 159 (50, M), 144 (100, $M-CH_3$), 117 (42, $M-C(CH_3)_2$). ^1H NMR (100 MHz, $CDCl_3$, 35 °C): δ 1.47 (6H, d, J 6.7 Hz, $CH(CH_3)_2$), 4.62 (1H, sept., J 6.7 Hz, $CH(CH_3)_2$), 6.49 (1H, d, J 3.2 Hz, H-3), 6.98–7.66 (5H, m).

1-Isopropyl-2-methylindole (*1b*) was prepared from acetone 1-isopropylphenylhydrazone[7,8] by a modified Fischer indole synthesis procedure.[9] The crude product was purified by column chromatography in dichloromethane on silica gel (Merck 60, 230–400 mesh) and transferred into a picrate, m.p. 129–130 °C, 40 % yield after recrystallization from 95 % aqueous ethanol. Anal. $C_{18}H_{18}N_4O_7$: C, H, N, MS: 173 (73, M), 158 (100, $M-CH_3$), 143 (10, $M-2CH_3$), 130 (98, $M-CH(CH_3)_2$. ^1H NMR (100 MHz, $CDCl_3$, 35 °C): δ 1.50 (6H, d, J 7.2 Hz, $CH(CH_3)_2$), 2.34 (3H, d, J 1.0 Hz, CH_3-2), 4.53 (1H, sept., J 7.2 Hz, $CH(CH_3)_2$), 6.15 (1 H, quart., J 1.0 Hz, H-3), 6.89–7.59 (4H, m).

1-Isopropyl-2,3-dimethylindole (*1c*) was prepared essentially according to Cardillo *et al.*,[10] with the modification that the sodium salt of 2,3-dimethylindole was prepared directly with sodium hydride in dry DMF and the isopropyl bromide was added at such a rate that the temperature in the cooled solution did not exceed 2 °C. After 1 h the temperature was raised to room temperature and kept there until after 22 h the product composition was constant, as checked by GLC (3 % Dexil 300 at 150–250 °C). If the synthesis was carried out at higher temperature, elimination was the only reaction observed. After purification by column chromatography on silica gel (Merck 60, 70–230 mesh), mobile phase toluene–light petroleum (b.p. 40–60 °C; 80:20) the product was transferred into a picrate, m.p. 145–146 °C, 10 % yield after recrystallization from 95 % aqueous ethanol. Anal. Found: C 53.9, H 4.81, N 13.3. Calc. for $C_{19}H_{20}N_4O_7$: C 54.8, H 4.84, N 13.5. MS: 187 (98, M), 172 (100, $M-CH_3$), 144 (89, $M-CH(CH_3)_2$), 130 (48, $M-CH(CH_3)_2-CH_3$). ^1H NMR (100 MHz, $CDCl_3$, 35 °C): δ 1.53 (6H, d, J 7.0 Hz, $CH(CH_3)_2$), 2.21 (3H, CH_3-3), 2.30 (3H, CH_3-2), 4.57 (1H, sept., J 7.0 Hz, $CH(CH_3)_2$), 6.98–7.51 (4H, m). The 2- and 3-methyl protons form an A_3B_3-system, but only the 3-methyl resonance shows fine structure ($J\approx1$ Hz), since the 2-methyl resonance is somewhat broadened by exchange at this temperature.

3-Bromo-1-isopropyl-2-methylindole (*1d*). Pyridinium tribromide seems to be the reagent of choice for 3-bromination of indoles.[11] Pyridinium perbromide (2.2 g, 6.9 mmol) in pyridine (30 ml) was added to a solution of *1b* (1.2 g, 6.9 mmol) in pyridine (50 ml) at −10 °C. After 1.5 h at −10 °C and 1 h at +5 °C, evaporation gave *1d* (1.64 g, 94 % yield) as a pale yellow oil, nearly pure according to ^1H NMR, picrate, m.p.

118.5–119 °C after recrystallization from 95 % aqueous ethanol. Anal. $C_{18}H_{17}BrN_4O_7$: C, H, N, O. MS; 253 (42, M, ^{81}Br), 251 (46, M, ^{79}Br), 238/236 (21/24, M–CH_3), 211/209 (42/45, M–$C(CH_3)_2$), 130 (100, M–$C(CH_3)_2$–Br). ^1H NMR (100 MHz, $CDCl_3$, 35 °C): δ 1.49 (6H, d, J 7.1 Hz, $CH(CH_3)_2$), 2.38 (3H, s, CH_3-2), 4.57 (1H, sept., J 7.1 Hz, $CH(CH_3)_2$), 7.00–7.54 (4H, m).

1-Isopropyl-2-methoxycarbonylindole (*1e*) was prepared by methylation of 1-isopropylindole-2-carboxylic acid[6] with dimethyl sulfate in DMSO–NaOH at 70 °C. Work-up followed by column chromatography on silica gel (Merck 60, 230–400 mesh) in methylene chloride gave a nearly pure liquid product (82 % yield), which crystallized (m.p. 54–57 °C) after final purification by GLC (OV-101, 200 °C). Anal. $C_{13}H_{15}NO_2$: C, H, N, MS: 217 (35, M), 202 (15, M–CH_3), 186 (6, M–OCH_3), 175 (17, M–$C(CH_3)_2$), 170 (18, M–OCH_3–CH_3–H), 143 (100, M–CH_3O–$CH(CH_3)_2$). ^1H NMR (360 MHz, $(CD_3)_2O$, 25 °C): δ 1.62 (6H, d, J 7.1 Hz, $CH(CH_3)_2$), 3.82 (3H, s, OCH_3), 5.84 (1H, sept., J 7.1 Hz, $CH(CH_3)_2$), 7.01–7.63 (5H, m).

1-Isopropyl-2(1-methyl-1-hydroxyethyl)indole (*1f*) was prepared by addition of a solution of *1e* (3.2 g, 14.8 mmol) in dry ether (15 ml) to a solution of methylmagnesium iodide (30 mmol) in dry ether (30 ml) at room temperature. After refluxing for 2 h work-up gave a pale yellow oil, which crystallized on refrigeration. Three recrystallizations from light petroleum (b.p. 40–60 °C) gave colourless crystals (1.8 g, 56 % yield), m.p. 87.5–88 °C. Anal. $C_{14}H_{19}NO$: C, H, N. MS: 217 (48, M), 202 (10, M–CH_3), 184 (8, M–CH_3–H_2O), 160 (100, M–$C(CH_3)_2$–CH_3). ^1H NMR (360 MHz, $(CD_3)_2O$, 25 °C): δ 1.62 (6H, d, J 7.3 Hz, $CH(CH_3)_2$), 1.65 (6H, s, $(CH_3)_2COH$), 2.05 (1H, s, $(CH_3)_2COH$), 5.72 (1H, sept., J 7.3 Hz, $CH(CH_3)_2$), 6.23 (1H, d, H-3), 6.87–7.53 (4H, m).

3-Alkylindoles are conveniently prepared by reacting 1-indolylmagnesium halides with alkyl halides in anisole.[12,13]

3-Isopropyl-1-methylindole (*2a*). The ether was distilled from a solution of methylmagnesium iodide (0.13 mol) in ether (50 ml) and at the same rate replaced by sodium-dried anisole (totally 50 ml) under nitrogen atmosphere. The solution was cooled to +10 °C, and indole (11.7 g, 0.1 mol) in dry anisole (50 ml) was added at such a rate that the temperature did not exceed +12 °C. After 0.5 h at +10 °C and 2 h at +20 °C, the solution was cooled to −6 °C, and isopropyl bromide (17.2 g, 0.14 mol) was slowly added to the solution. After 20 h at −6 °C, GLC analysis (OV–101) showed about 20 % conversion. After 40 h at +22 °C, no more change was observed. Water (400 ml) and 0.5 M HCl (30 ml) were added, and the mixture was extracted with ether (4×75 ml). The combined ether phases were washed with saturated aqueous $NaHCO_3$ solution (75 ml) and water (2×50 ml), dried with $MgSO_4$ and evaporated. The anisole was distilled off, and the remaining oil (*ca.* 50 % yield) was used without further purification in the next step. GLC showed only small quantities (<2 %) of 1-isopropylindole (*1a*) and 1,3-diisopropylindole.

The crude 3-isopropylindole from the first step (0.1 mol) was added at +5 °C to a suspension of sodium hydride (3.6 g, 0.15 mol) in dry DMF (50 ml). After 1.5 h at +10 °C, dimethyl sulfate (15.1 g, 0.12 mol) in dry DMF (30 ml) was added. After 5 h at room temperature, a mixture of ethanol and conc. NH_3 (1:1, v:v, 50 ml) was added, followed by water (300 ml). The solution was extracted with ether (4×75 ml), and the combined ether phases were extracted with water (5×50 ml), dried with $MgSO_4$, and evaporated. GLC of the residue showed only *2a, i.e.* the methylation had been quantitative. After final purification by "flash chromatography"[14] on silica gel (Merck 60, 230–400 mesh) with light petroleum (b.p. 40–60 °C), toluene (9:1), the product was transferred into a picrate, m.p. 88.5–90 °C after recrystallization from 90 % aqueous ethanol. Anal. (picrate) $C_{18}H_{18}N_4O_7$: C, H, N. MS (indole): 173 (35, M), 158 (100, M–CH_3), 143 (19, M–$2CH_3$), 130 (5, M–$CH(CH_3)_2$), 115 (13, M–CH_3–$CH(CH_3)_2$). ^1H NMR (360 MHz, $(CD_3)_2O$, 27 °C): δ 1.35 (6H, d, J 6.9 Hz, $CH(CH_3)_2$), 3.18 (1H, doublet of septets, J 6.9 and 0.8 Hz, $CH(CH_3)_2$), 3.66 (3H, s, N–CH_3), 6.80 (1H, d, J 0.8 Hz, 2-*H*), 6.95–7.12 (2H, m, 5-*H*, 6-*H*), 7.22 (1H, m, 7–*H*), 7.54 (1H, m, 4-*H*).

3-Isopropyl-1,2-dimethylindole (*2b*) was prepared in 70 % yield by the same procedure as *2a*, starting from 2-methylindole. GLC showed only small quantities of *1b* and *2c* as by-products, and flash chromatography with light petroleum (b.p. 40–60 °C), toluene (85:15) as for *2a* gave a crystalline product, m.p. 62–63 °C after recrystallization from methanol. Anal. $C_{13}H_{17}N$: C, H, N. MS: 187 (31, M), 172 (100, M–CH_3), 157 (23, M–$2CH_3$), 144 (6, M–$CH(CH_3)_2$). ^1H NMR (360 MHz, $(CD_3)_2O$, 27 °C): δ 1.40 (6H, d, J 7.2 Hz, $CH(CH_3)_2$), 2.32 (3 H, s, 2-CH_3), 3.20 (1 H, septet, J 7.2 Hz, $CH(CH_3)_2$), 3.55 (3H, s, N–CH_3), 6.87–7.02 (2H, m. 5-H, 6-H), 7.17 (1H, m, 7-H), 7.58 (1H, m, 4-H).

1,3-Diisopropyl-2-methylindole (*2c*). A mixture of 2-methyl-3-isopropylindole and 2-methylindole (*ca* 7:3, totally 0.06 mol, taken from the synthesis of *2b*) in dry DMF (20 ml) was added

under nitrogen to a cooled (+5 °C) and agitated suspension of sodium hydride (2.16 g, 0.09 mol) in dry DMF (20 ml). After 1.5 h at room temperature, the solution was cooled to +10 °C, and isopropyl bromide (11.1 g, 0.09 mol) in DMF (20 ml) was added slowly with agitation. After 3 d, the same quantities of sodium hydride and isopropyl bromide were added under the same conditions, and this was repeated a further three times at intervals of 3 d. The progress of the reaction was followed by GLC. Work-up, followed by flash chromatography as for *2a* gave a liquid product, which was nearly pure according to GLC. Final purification by preparative GLC on OV-101 at 200 °C gave a colourless product, which crystallized on standing, m.p. 54.5–56 °C. No crystalline picrate could be obtained from this product. Anal. $C_{15}H_{21}N$: C, H, N. MS: 215 (34, M), 200 (92, M–CH_3), 172 (5, M–$CH(CH_3)_2$), 158 (100, M–CH_3–$CH(CH_3)_2$), 143 (22). ^{1}H NMR (360 MHz, $(CD_3)_2O$, 27 °C): δ 1.39 (6H, d, J 7.1 Hz, 3-$CH(CH_3)_2$), 1.56 (6H, d, J 6.9 Hz, N–$CH(CH_3)_2$), 2.35 (3H, s, 2-CH_3), 3.20 (1H, septet, J 7.1 Hz, 3-$CH(CH_3)_2$), 4.65 (1H, septet, J 6.9 Hz, N-$CH(CH_3)_2$), 6.84–6.98 (2H, m, 5-H, 6-H), 7.39 (1H, m, 7-H), 7.59 (1H, m, 4-H).

1-Isopropyl-2,3-dimethylnaphthalene (3a). Aluminium chloride (95.8 g) was added with rapid agitation to a solution of 2,3-dimethylsuccinic anhydride [15] (39.5 g, 0.3 mol) in dry benzene (180 ml). All catalyst had dissolved after 0.5 h at reflux, and water (150 ml) and conc. HCl (50 ml) were added to the cooled solution. Excess benzene was removed by steam distillation, and on cooling crude *3-benzoyl-2-methylbutanoic acid* precipitated. It was purified by dissolution in boiling 15 % aqueous sodium carbonate solution (200 ml), treatment with charcoal, and acidification at +50 °C. On cooling, the pure acid separated as colourless crystals (47 g, 76 % yield), m.p. 130 °C.

Water (75 ml), conc. HCl (175 ml), toluene (100 ml) and 3-benzoyl-2-methylbutanoic acid (47 g, 0.23 mol) were added in this order to amalgamated zinc (100 g). The mixture was refluxed with vigorous agitation for 28 h, and conc. HCl (50 ml) was added every 6 h. After cooling, the organic layer was separated, and the aqueous phase was diluted with water (200 ml) and extracted with ether (3×75 ml). After washing with water and drying, evaporation of the organic phases gave 2,3-dimethyl-4-phenylbutanoic acid as a colourless oil (32 g, 75 % yield) after vacuum distillation, b.p. 137–138 °C (5.3 kPa).

This acid (32 g, 0.17 mol) was converted to acid chloride by reaction with phosphorus pentachloride (38.2 g, 0.18 mol). The phosphorus oxychloride formed was removed by evaporation with five portions of dry benzene (25 ml), after which the 2,3-dimethyl-4-phenylbutanoyl chloride was dissolved in dry benzene (60 ml). The solution was filtered and added slowly with cooling (–5 °C) and stirring to a suspension of aluminium chloride (30 g) in dry benzene (100 ml). After 1 h at +5 °C and 3 h at room temperature, ether (60 ml) and 5.5 M HCl (150 ml) were added. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with 5.5 M HCl (3×100 ml), saturated aqueous $NaHCO_3$ solution (2×100 ml), 5 % aqueous NaOH solution (2×100 ml), water (2×100 ml), and finally saturated aqueous NaCl solution (2×100 ml). In every step, the aqueous phase was extracted with ether (100 ml), which was added to the organic phase. After drying and evaporation, the residue from the organic phase was vacuum distilled to give pure 2,3-dimethyl-1-keto-1,2,3,4-tetrahydronaphthalene (13.1 g, 46 % yield), b.p. 103–104 °C (12 kPa), as a mixture of diastereomers.

This ketone (13.1 g, 0.075 mol) was added under nitrogen with cooling and stirring to a solution of isopropylmagnesium bromide prepared from isopropyl bromide (14.8 g, 0.12 mol) and magnesium turnings (2.88 g, 0.12 mol) in dry ether (60 ml), at such a rate that the temperature did not rise above +1 °C. After 16 h at –2 °C and work-up, the product contained according to GLC–MS (OV-101, 100–280 °C; 10 °C/min) as the two major products the desired 1-isopropyl-2,3-dimethyl-1,2,3,4-tetrahydro-1-naphthol (60 %) together with 2,3-dimethyl-1,2,3,4-tetrahydro-1-naphthol (35 %), both as mixtures of diastereomers.

In the final dehydration-dehydrogenation step, the above product was intimately mixed with Pd/C (2 g, 5 %) and kept at 250 °C for 2 h. After cooling, addition of ether, filtration and evaporation, GLC–MS analysis as above showed a >90 % conversion into 2,3-dimethylnaphthalene and 1-isopropyl-2,3-dimethylnaphthalene. The latter compound was isolated from the mixture as a colourless liquid by preparative GLC (OV-101, 200 °C), and it was characterized as a crystalline picrate, m.p. 132 °C after recrystallization from 95 % aqueous ethanol. Anal. (picrate) $C_{21}H_{21}N_3O_7$: C, H, N. MS (hydrocarbon): 198 (52, M), 183 (100, M–CH_3), 168 (40, M–2CH_3), 153 (23, M–3CH_3). ^{1}H NMR (100 MHz, $CDCl_3$, 35 °C) δ 1.52 (6H, d, J 7.5 Hz, $CH(CH_3)_2$), 2.39 (6H, s, 2-CH_3 and 3-CH_3), 3.94 (1H, sept., J 7.5 Hz, $CH(CH_3)_2$), 7.03–7.24 (5H, m). The identity of all intermediates in this reaction sequence was ascertained by ^{1}H NMR and/or mass spectra.

^{1}H NMR spectra of *1a, 1b, 1d,* and *3a* were recorded on a JEOL Model MH-100 spectrometer with standard variable temperature attachment (VT 3-C). The samples were 0.5–0.6 M in dichlorofluoromethane with TMS added to provide an internal lock signal, and they were degassed by the high vacuum freeze-thaw technique before being sealed off.[16] The temperature was measured as previously described.[17]

The ^{1}H NMR spectra of *1c, 1d, 1e, 1f,* and *2a–2c* were recorded on a Nicolet Model 360 WB spectrometer with standard variable temperature controller and with an internal deuterium lock. The samples were 0.05 M in dimethylether-d_6 with TMS, degassed and sealed as above. The temperature scale of the instrument was calibrated by the use of a sample of methanol in acetone-d_6, which in turn had been calibrated by the technique described in Ref. 17, using the Jeol MH-100 instrument.

The fractional populations (p) and the rate constants were evaluated by visual fitting of spectra calculated by the McConnell formalism for uncoupled two-site exchange systems to the experimental spectra.[18,19] The evaluation of T_2 values for bandshape calculations was based on the bandwidths of reference signals unperturbed by the exchange as described previously.[20] In some cases a final adjustment could be made in the band-fitting procedure.

No splitting of ^{1}H resonances due to slow *syn-anti* exchange of the 3-isopropyl group could be observed in the low-temperature spectra of *2a–2c.* In the spectrum of *2c,* however, the doublet due to 4-H broadened below −100 °C, and at −113 °C it had diminished in intensity to 51 % of the original value (measured with the 7-H resonance as standard). At still lower temperatures the 4-H doublet became sharper, and at −130 °C its intensity was nearly the same as that of the 7-H doublet. A smaller selective broadening was also observed on the 3-isopropyl methyl resonance. To simulate these spectra, it is necessary to know the population or the shift difference, $\delta\nu$. *A priori,* none of these quantities is known, but by giving $\delta\nu$ values in the range 50–100 Hz ($\delta\nu$=77 Hz for 7-H in the rotation of the 1-isopropyl group at higher temperature) and assuming the lowest intensity of the 4-H resonance to occur in the range −113±5 °C, we obtain p_{syn}=0.97±0.01 and $\Delta G^{\neq}_{syn\rightarrow anti}$=35±1 kJ mol^{-1}. A slight selective broadening of the 4-H resonance was observed also in the spectrum of *2b* at −130 °C, but at lower temperature general broadening occurred, and no meaningful simulations could be performed.

The free energies of activation and the differences in free energy were calculated using eqns. 1

Table 1. ^{1}H Chemical shifts (δ), fractional populations, $\Delta G^{\neq}$ (*syn–anti*) and $\Delta G°$ (*syn–anti*) for compounds *1–3*.

Compd	Solvent	*syn* form $(CH_3)_2CH$	*syn* form $(CH_3)_2CH$	*syn* form R_2	R_3/R_1	p_{syn}	$(CH_3)_2CH$	*anti* form $(CH_3)_2CH$	*anti* form R_2	R_3/R_1	$\Delta G^{\neq}$/kJ mol^{-1} (*syn→anti*)	$\Delta G°$/kJ mol^{-1} (*syn→anti*)
1a	$CHCl_2F$/ $CHClF_2$(7:3)	–	–	–	0.00	1.39	4.53	–	6.51	–	–	
1b	$CHCl_2F$	1.57	4.55	2.36	6.18	0.86	1.48	4.80	2.52	6.25	46.2	3.33
1c[a]	$(CD_3)_2O$	1.55	4.59	2.30	2.19	0.86	1.46	4.89	2.46	2.19	46.0	3.29
1d	$CHCl_2F$	1.58	4.55	2.41	–	0.83	1.50	4.79	2.56	–	46.6	3.01
1d[a]	$(CD_3)_2O$	1.59	4.68	2.42	–	0.83	1.50	5.00	2.57	–	46.0	3.03
1e[a]	$(CD_3)_2O$	1.61	6.08	3.82	–	0.86	1.63	5.10	3.83	–	44.7	3.33
1f[a]	$(CD_3)_2O$	1.61	5.74	1.62	6.26	1.00	–	–	–	–	–	–
2a[a,b]	$(CD_3)_2O$	–	–	–	–	0.00	1.30	3.14	–	3.69	–	–
2b[a,b]	$(CD_3)_2O$	1.38	3.15	2.32	3.68	–	–	–	–	–	–	–
2c[a,c]	$(CD_3)_2O$	1.56	4.61	2.31	–	0.86	1.47	4.90	2.46	–	48.7	3.31
2c[a,b]	$(CD_3)_2O$	1.38	3.14	–	–	0.93	–	–	–	–	35	4.7
3a	CS_2	1.49	3.70	(2.34,2.30)		0.72	1.41	4.00	–	–	56.3	1.76
3b[d]	CS_2	1.50	3.66	2.43	–	0.77	1.39	4.14	2.52	–	56.6	2.24

[a] 360 MHz. [b] 3-iPr group. [c] 1-iPr group. [d] From Ref. 5.

(based on the Eyring equation[21]) and 2, where p_{syn} is the fractional population of the *syn* form.

$$\Delta G^{\ddagger}\ (syn \rightarrow anti) = RT\ ln\ \frac{k_B\ T}{h\ k_{syn \rightarrow anti}} \qquad (1)$$

$$\Delta G^{\circ}\ (syn\text{–}anti) = -RT \ln\ (p_{syn}/p_{anti}) \qquad (2)$$

The errors in $\Delta G^{\ddagger}$ and ΔG° are mainly due to errors in the temperature measurement. We estimate the absolute temperatures measured on the JEOL instrument to be correct to ±1 °C or better, and the relative temperatures to ±0.3 °C. This corresponds to errors in $\Delta G^{\ddagger}$ of *ca.* ±0.3 kJ mol^{-1} and in ΔG° of *ca.* ±0.02 kJ mol^{-1}.

The ^{1}H chemical shifts, the *p* values, the free activation energies and the free energy differences for compounds *1–3* are found in Table 1. The *p* values are all recalculated to T=223 K to make them comparable, assuming a negligible entropy difference.

The calculations were performed on a PDP 11/34 computer with a GT 42 graphic terminal and a Printronic lineprinter/plotter of the Computer Graphics Laboratory for Organic Chemistry of the University of Lund.

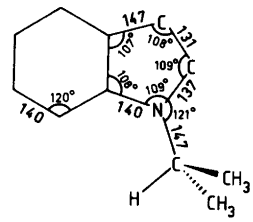


Fig. 1.

Molecular mechanics calculations. The minimum energy conformations and barriers to rotation of the isopropyl group in *1a* and *1b* were calculated, using the Allinger 1973 force-field (MM1),[22] excluding π-electron calculations and with a rigid indole skeleton. The benzene ring was taken as a regular hexagon with 140 pm side, and the bond lengths and angles in the five-membered ring are shown in Fig. 1. The non-

Table 2. Force-field parameters (energies in kJ mol^{-1}).[a]

Bond stretching
E_s=301.0 k_s $(l-l_0)^2[1+C_s\ (l-l_0)]$
C_s=−2.00

Bond type	l_0/Å	k_s/mdyn Å^{-1}
C(sp^3)–N(sp^2)	1.449	3.40

Bond bending
E_b=0.091688$k_b(\theta-\theta_0)^2[1+C_f(\theta-G_0)]$
C_f=−0.006

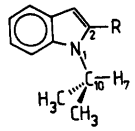
Angle	θ_0/deg	k_b/mdyn Å rad^{-2}
C(sp^2)–N(sp^2)–C(sp^2)	121.0	0.70
C(sp^3)–C(sp^2)–N(sp^2)	112.7	0.40
C(sp^3)–C(sp^3)–N(sp^2)	109.47	0.42
H–C(sp^3)–N(sp^2)	109.47	0.42
H–C(sp^2)–N(sp^2)	110.0	0.40

Torsion
E_t=0.5V_1(1+cos ω)+0.5V_2(1−cos 2 ω)+0.5V_3(1+cos 3 ω)

Dihedral angle	V_2/kJ mol^{-1}	V_3/kJ mol^{-1}
C(sp^3)–C(sp^3)–N(sp^2)–C(sp^2)	5.00	
C(sp^3)–C(sp^3)–N(sp^2)–C(sp^2)		1.00
C(sp^3)–C(sp^2)–N(sp^2)–C(sp^3)	5.00	
H–C(sp^3)–N(sp^2)–C(sp^2)		1.00
H–C(sp^2)–N(sp^2)–C(sp^3)	6.00	
H–C(sp^2)–N(sp^2)–C(sp^2)	6.00	

[a] The symbols are defined in Ref. 22.

Table 3. Calculated strain energies for *1a* and *1b* as a function of the $H_7C_{10}N_1C_2$ dihedral angle (θ).

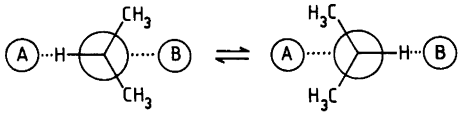


R	Maximum energy conformation		Minimum energy conformation		Energy barrier *syn*→*anti*/kJ mol^{-1} (kcal mol^{-1})
	θ°	Energy/kJ mol^{-1}	θ°	Energy/kJ mol^{-1}	
H (*1a*)	85	234.4	1.1	211.2 (*syn* form)	23.2 (5.5)
			150	204.5 (*anti* form)	
			177.3	206.9 (local minimum)	
CH_3 (*1b*)	90	245.7	0	207.6 (*syn* form)	38.1 (9.1)
			160	209.6 (*anti* form)	

standard force-field parameters are shown in Table 2. The reaction coordinate for the rotation of the isopropyl group was followed by constraining the $H_7C_{10}N_1C_2$ dihedral angle (see Table 3) while allowing the energy to minimize with respect to all other degrees of freedom. The forced rotation was performed in steps of 5° in the regions 0–30, 60–120 and 150–180°, and in longer steps in between. The calculated energies and the corresponding angles are found in Table 3.

RESULTS AND DISCUSSION

The ^{1}H NMR spectra at low temperature of most of compounds *1* indicate the presence of two rotamers, assigned to the *syn* and *anti* forms. It has been shown for several systems[5,17,23,24] that the equilibrium between the two states of an isopropyl group attached to a planar system (*4a*



4a *4b*

and *4b*) is governed by the relative sizes of the flanking groups *A* and *B*, *i.e.* the form *4a* is favoured when *A*>*B* and *vice versa*. In the molecules *1* the flanking entities are the 7-(*peri*)hydrogen and the substituent in position 2, with a possible buttressing effect of the substituent in position 3.

1-Isopropylindole (*1a*) shows no selective broadening in the ^{1}H NMR spectrum down to −130 °C at 100 MHz. This may be due to a low barrier to rotation, to preponderance of one rotamer, or to both. According to the molecular mechanics calculations (Table 3), the molecule has three energy minima from θ=0° to θ=180°. The highest of these (θ=1.1°) represents the *syn* form. The next one, at θ=177.3°, is 4.3 kJ mol^{-1} lower, but it is a shallow local minimum and may be disregarded. The lowest minimum (θ=150°) represents the *anti* form and is 6.7 kJ mol^{-1} below the *syn* form. The barrier to rotation of the isopropyl group from the *syn* to the *anti* form is calculated to be 23.2 kJ mol^{-1}.

The calculated *syn*–*anti* energy difference corresponds to only 0.35 % of the *syn* form at −130 °C under the reasonable assumption of equal entropy for the two forms. Given the modest chemical shift differences between the *syn* and *anti* forms of *1b* to *1d* and *1f* (Table 1), one can calculate[25] that with this population ratio and a free energy barrier lower than 30 kJ mol^{-1}, no selective broadening should be observed above −130 °C. Support for the reliability of the calculated energies in *1a* can be taken from the good agreement between experimental and calculated energies in *1b*. Furthermore, the isopropyl methyl protons in *1a* are more strongly shielded than in any of the other compounds *1*, indicating that they are mainly in an unencumbered environment. Therefore, we regard *1a* as a good representative of the *anti* form. This means that the *peri* hydrogen atom acts as a larger flanking entity than the 1-hydrogen atom. This is

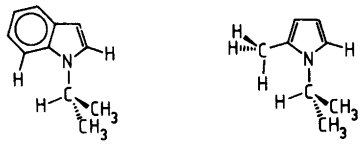


Fig. 2.

reasonable, since the effect of the *peri* hydrogen simulates that of a methyl group in an eclipsed position (Fig. 2).

In the spectrum of *1b*, the resonances of two forms are observed in the ratio 86:14 at low temperature, and here the assignment of the minor rotamer to the *anti* form is based on the deshielding of the 2-methyl protons in this form compared to those in the *syn* form. Such differences are quite general in equivalent systems[5,17,23] and are ascribed to the van der Waals effect.

In *1c* and *2c* the 3-methyl and 3-isopropyl groups exert no buttressing effect, leading to the same population of the *anti* form as in *1b*. The 3-bromine atom in *1d*, on the other hand, exerts a *negative* buttressing effect. Berg and Russel[26,27] have recently observed negative buttressing when methyl or bromine in the 3-position acts on a methyl group in the 2-position in a series of 1-isopropylbenzenes and -pyridines. When the same substituents act on a 2-bromine atom, substantial positive buttressings are observed. The negative buttressings are ascribed to the favoured conformations of two methyl groups or of one bromine atom and one methyl group in neighbouring positions (Fig. 3).

These conformations lead to increased energy of the *syn* conformation of the isopropyl group. In the indole case, the smaller ring size evidently leads to a diminution of the interaction between the methyl groups to such a degree that no buttressing is observed. In *1d*, the interaction between the bromine atom and the 2-methyl group is still sufficient to give a negative buttressing.

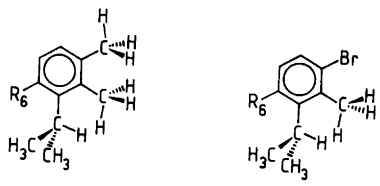


Fig. 3.

In order to verify the effect of the ring size, the naphthalene *3a*, which can be seen as a ring-expanded analogue of *1c*, was prepared, and its conformational ratio was compared with that of *3b*, which has been studied by Mannschreck and Ernst.[5] Here, the expected negative buttressing effect of the 3-methyl group was observed (Table 1). The barriers to the isopropyl group rotation are *ca.* 10 kJ mol^{-1} lower in the indoles than in the naphthalenes, and this is probably an effect of the larger angles between the substituents in the five-membered ring.

A similar unfavourable interaction as the one depicted in Fig. 3, *i.e.* the peri-interaction in the *anti* form (Fig. 2), is probably responsible for the considerable prevalence of the *syn* form in the 2-substituted indoles.

In *1e* the methoxycarbonyl group shows the same steric effect as the methyl group in *1b*. Due to its flat shape, the steric effect of the CO_2Me group depends on its orientation with respect to neighbouring groups. In cyclohexane, it is "smaller" than a methyl group, the $-\Delta G_x^\circ$ values being 5.3 and 7.1 kJ mol^{-1} for the CO_2Me and the Me groups respectively.[28] In *1e*, the larger steric effect can be ascribed to its conjugation with the electron-rich indole ring with the concomitant requirement for coplanarity. No rotational barriers are known for indole-2-carboxylic acid derivatives, but the substantial barrier (46.9 kJ mol^{-1}) in 1-methylpyrrole-2-aldehyde[29] indicates that the barrier to rotation of the CO_2Me group in *1e* is not negligible.

2(1-Methyl-1-hydroxyethyl)indole (*1f*) showed ^{1}H resonances of only the *syn* rotamer also at 360 MHz and −140 °C. This is as expected, since the *anti* form must be very strained.

In the ^{1}H NMR spectra of *2a*, no effects of slow rotation were observed, and, as for *1a*, the reason is probably a low barrier and a strong preference for the *anti* form. For *2b*, a slight selective broadening of the 4-H resonance at −130° may indicate a low barrier (<31 kJ mol^{-1}) to *syn*→*anti* exchange and a low population of the *anti* form. For *2c*, finally, a *ca.* 3 % population of the *anti* form and a *syn-anti* barrier of *ca.* 35 kJ mol^{-1} could be measured unambiguously.

The low barrier to rotation of the 3-iPr group in *2b* and *2c* can be ascribed to the greater length of the C-3−iPr compared to the N-1−iPr bond.

The lower population of the *anti* form of the 3-iPr than of the 1-iPr group in compounds with the same 2-substituent can be explained by the greater length of the C-3–C-8 compared to the N-1–C-9 bond and by the smaller length of the C-2–C-3 compared to the N-1–C-2 bond.

Summing up, we find that the 1-isopropylindoles in general behave according to our expectations, *i.e.* that the isopropyl group assumes the *syn* and *anti* conformations, and that the equilibrium between these is governed by the steric size of the substituent in position 2 and to some extent also of that in position 3. The barriers separating the *syn* and *anti* forms are in general high enough to permit the observation of the individual rotamers by NMR.

3-Isopropylindoles seem to behave in the same way, but due to low barriers and unfavourable rotamer distributions they are less amenable to NMR studies. In general, however, our results indicate that a study of the conformational effects on CD spectra of indoles substituted by chiral rotors is warranted.

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