

Synthesis of novel 1-methylindole trimer and tetramer under Friedel–Crafts reaction conditions and determination of their structures by X-ray crystallography

Shashi B. Mahato,^{*a} Subhadra Garai,^a Manuela Weber^b and Peter Luger^b

^a Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Jadavpur, Calcutta-700032, India

^b Institut für Kristallographie, Freie Universität Berlin, Takustr. 6, D-14195 Berlin, Germany

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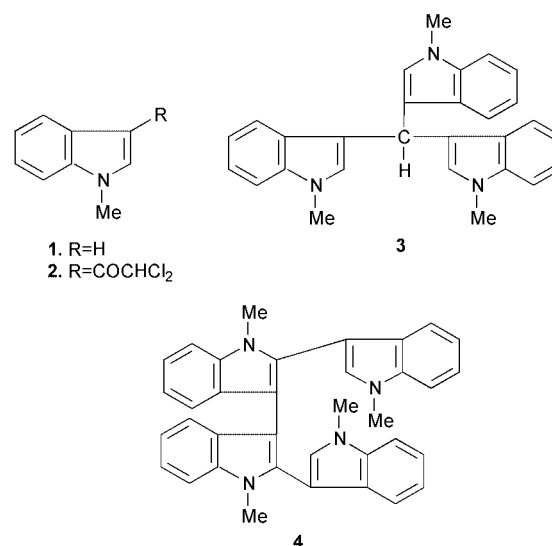
One-step synthesis of novel 1-methylindole trimer and tetramer under Friedel–Crafts reaction conditions is reported. The use of excess of the substrate and the catalyst and application of elevated temperature were necessary for success of the synthesis. The complete structures of the products were unambiguously elucidated by single-crystal X-ray analysis, and rationalization of their formation is attempted.

The indole nucleus occurs in a wide variety of biologically active compounds. Considerable attention had been given to the study of acid-catalysed polymerization of indoles, and different structures for their dimers were proposed on the basis of theoretical considerations and systematic degradative studies.¹ After our successful synthesis of polyaryl compounds using arenes of varying nucleophilicity under Friedel–Crafts conditions^{2–5} we focused our attention on using indoles as substrates and synthesized novel indolylquinolines⁶ of biological interest^{7,8} as well as 2-methylindole analogues and skatole dimers.⁹ This paper reports a one-pot synthesis of novel 1-methylindole trimer and tetramer using 1-methylindole **1** as substrate under Friedel–Crafts reaction conditions.

Results and discussion

When reaction was carried out at ambient temperature in nitrobenzene with stoichiometric amounts of 1-methylindole as substrate, dichloroacetyl chloride as acylating agent and anhydrous AlCl₃ as the catalyst, the 3-acylated derivative **2** was obtained as the only isolable product. The formation of **2** is in accord with the results reported in the literature.^{10,11} However, when the substrate, the catalyst and the acylating agent were used in the proportions 1:1:0.4 at 102–105 °C in nitrobenzene, two other products, **3** and **4**, besides **2** were isolated. The elemental and mass spectral analyses of products **3** and **4** revealed the involvement of three and four moles of 1-methylindole in the formation of products **3** and **4**, respectively. The MS, ¹H and ¹³C NMR data of **3** and **4** appeared to be inadequate for complete analysis of their structures, which were elucidated unambiguously by single-crystal X-ray analysis.

The molecular structures of compounds **3** and **4** shown in the ORTEP¹² drawings in Figs. 1 and 2 are interesting. The molecule **3** consists of three indole fragments linked to the central carbon atom C-1. Bond lengths and angles in the indole groups compare well and are within the expected ranges. The indole groups are planar with deviations of contributing atoms from the least-squares plane of $\sigma = 0.021$ for indole group I (C-2–C-10, C-41), $\sigma = 0.037$ for indole group II (C-11–C-19, C-131), and $\sigma = 0.011$ for indole group III (C-20–C-28, C-221). The interplanar angles are all close to 120° [I/II = 108.8(2)°, I/III = 116.2(2)°, II/III = 112.0(2)°], so that in good approximation the molecule has a (non-crystallographic) three-fold



symmetry with a pseudo-three-fold axis passing through C-1–H-1.

The molecule of **4** consists of four indole fragments which are linked *via* the covalent bonds C-9–C-10, C-11–C-19, and C-1–C-28. Bond lengths and angles in the four indole groups compare well and are within the expected ranges. Each indole fragment is planar with deviations of contributing atoms from a least-squares plane through non-H-atoms of $\sigma = 0.053$ for indole group I (C-1–C-9), $\sigma = 0.045$ for indole group II (C-10–C-18), $\sigma = 0.005$ for indole group III (C-19–C-27), and $\sigma = 0.0027$ for indole group IV (C-28–C-36); groups III and IV are almost parallel with an interplanar angle of 10.4(2)° while the angles between the other indole planes are more or less ($\pm 10^\circ$) around 120°.

There are no close contacts in the lattices of **3** and **4** so that no indication of noticeable intermolecular interaction exists.

The formation of product **3** is rationalized as shown in Scheme 1. Usual Friedel–Crafts acylation of **1** produces the normal 3-acylated product **2**, which presumably on decarbonylation liberates **5**. Decarbonylation of aldehydes and ketones can take place^{13–15} and a mechanism for decarbonylation of aldehydes has been reported.¹⁶ Although 3-acylated product **2**

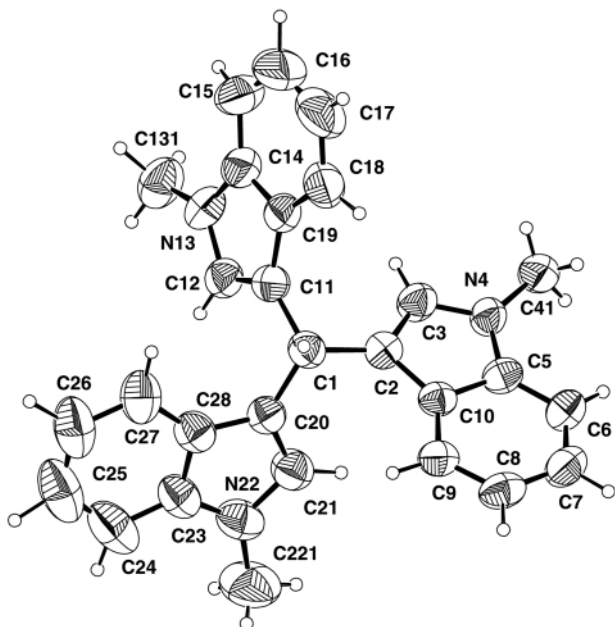


Fig. 1 ORTEP drawing of the molecular structure of compound 3, with crystallographic numbering scheme.

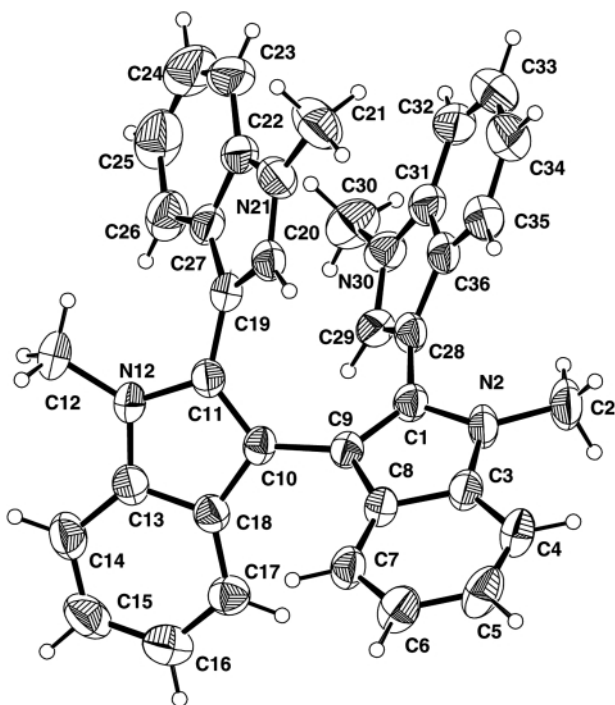
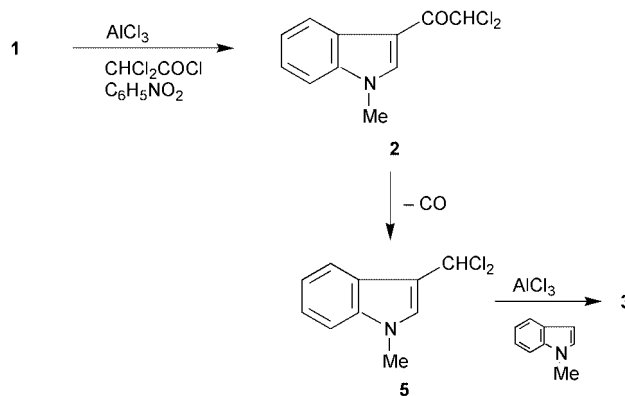


Fig. 2 ORTEP drawing of the molecular structure of compound 4, with crystallographic numbering scheme.

was isolated, the intermediate **5** could not be obtained probably because of its faster rate of alkylation of two mols of **1** producing the new 1-methylindole trimer **3**. Moreover, the intermediate formation of 3-dichloroacetyl-1-methylindole **2** was ascertained when it produced the same trimer **3** (yield 12%) on being used as the substrate under identical reaction conditions.

Apparently there is no role of dichloroacetyl chloride in the generation of the tetramer **4**. In fact its formation (yield 7%) could be confirmed in the absence of the acylating agent under similar conditions. 2,3-Dimerization has been reported¹ to occur in a study of acid-catalysed polymerization of indole. We propose that 2,3-dimerization of indole followed by 3,3-dimerization of the intermediate dimer, leads to the formation of the tetramer **4**. However, further work is needed to clarify the mechanism involved.



Scheme 1

In conclusion we have developed a single-step process for the preparation of the interesting 1-methylindole trimer and tetramer under Friedel–Crafts conditions with the prospect of expanding it to other 1-substituted indoles as substrates.

Experimental

MPs were determined in open capillaries and are uncorrected. ¹H and ¹³C NMR spectra were recorded on a 300 MHz spectrometer using TMS as internal standard. Mass spectra were obtained under electron impact at 70 eV. Anhydrous aluminium chloride was purchased from Merck. Reagents and solvents were of analytical grade or were purified by standard procedures prior to use. Silica gel for column chromatography and TLC was from Sisco Research Laboratories, Mumbai. Petroleum spirit refers to the fraction of distillation range 60–80 °C.

General procedure

The products were synthesized using the substrate, the acylating agent and the catalyst in the molar proportions 1 : 1 : 0.4. The substrate (3 g) was dissolved in nitrobenzene (10 ml), and the solution was cooled to 15–20 °C, followed by the gradual addition of the catalyst (3.06 g). The acylating agent (0.9 ml) was slowly added with constant stirring. The reaction mixture was kept at ambient temperature (25 °C) and then at 102–105 °C for 4 h, then overnight at ambient temperature, decomposed with ice–HCl, extracted with diethyl ether, and the solvent was removed from the extract under reduced pressure and the products purified by column chromatography over silica gel (mobile phase, 10% EtOAc in petroleum spirit) followed by crystallization. The compounds were numbered according to their decreasing order of polarity.

Compound 2. Colourless solid (35% yield), mp 210 °C; ν_{\max} (KBr)/cm⁻¹ 3100, 1662, 1580, 1528, 1460, 1370, 1235, 1125, 1085, 925, 870; δ_{H} (300 MHz; CDCl₃; Me₄Si) 3.96 (3H, s), 6.42 (1H, s), 7.28–7.82 (3H, m), 8.09 (1H, s), 8.16–8.48 (1H, m); m/z (EI) 243 (M⁺ + 2), 241 (M⁺) (Found: C, 54.63; H, 3.79; N, 5.70. C₁₁H₉Cl₂NO requires C, 54.57; H, 3.75; N, 5.79%).

Compound 3. Colourless solid (15% yield), mp 215 °C; ν_{\max} (KBr)/cm⁻¹ 2905, 1595, 1478, 1395, 1310, 1250, 1128, 1091, 940; δ_{H} (300 MHz; CDCl₃; Me₄Si) 3.50 (3H, s), 3.95 (3H, s), 4.54 (3H, s), 7.06–7.53 (13H, m), 8.01 (1H, d, *J* 7.6 Hz), 8.06 (1H, s), 8.65 (1H, d, *J* 7.8 Hz); δ_{C} (75 MHz; CDCl₃; Me₄Si) 32.2, 32.9, 35.3, 77.5, 109.1, 109.3, 118.9, 119.1, 119.5, 119.8, 120.4, 122.1, 122.6, 123.0, 124.0, 124.3, 127.9, 137.4; m/z (EI) 403 (M⁺) (Found: C, 83.30; H, 6.18; N, 10.35. C₂₈H₂₅N₃ requires C, 83.34; H, 6.25; N, 10.41%).

Compound 4. Colourless solid (10% yield), mp 270 °C; ν_{\max} (KBr)/cm⁻¹ 3090, 1660, 1585, 1530, 1130, 925, 870; δ_{H} (400

MHz; CDCl₃; Me₄Si) 3.66 (12H, s), 6.63 (2H, s), 6.99 (4H, t), 7.19 (4H, t), 7.28 (4H, d, *J* 7 Hz), 7.49 (4H, d, *J* 7 Hz); δ_C (100 MHz; CDCl₃; Me₄Si) 32.7, 109.0, 118.2, 118.4, 120.2, 121.2, 127.6, 128.0, 137.4; *m/z* (EI) 518 (M⁺) (Found: C, 83.42; H, 5.80; N, 10.74. C₃₆H₃₀N₄ requires C, 83.37; H, 5.83; N, 10.80%).

X-Ray experiments, structure determination and refinements †

X-Ray work was performed in almost the same way for both the compounds. In the first step crystal quality, preliminary cell constants and space groups were estimated from rotation Weissenberg photographs.

Phase determination was carried out successfully with direct methods using SIR92,¹⁷ yielding unambiguously all non-hydrogen atoms for both structures.

Least-square refinements done with the corresponding programs of the SHELXL¹⁸ system proceeded straightforwardly. First, isotropic, later, anisotropic, thermal parameters were assigned to all non-hydrogen atoms. The hydrogens, which could all be located from difference syntheses, were included with isotropic temperature factors. After convergence of all parameters no significant peaks or holes were seen in final difference syntheses.

Crystal data of 3. C₂₈H₂₅N₃, *M_r* = 403.51, space group orthorhombic, *P*2₁*ab*. Crystals were obtained from hexane. The specimen used for X-ray experiments had dimensions of 0.75 × 0.13 × 0.10 mm. Lattice constants (Å, degrees) *a* = 9.527(2), *b* = 12.367(5), *c* = 18.594(7), cell volume *V* = 2190.8 Å³, formula units/cell *Z* = 4, X-ray density ρ_x = 1.223 g cm⁻³, number of independent reflections 2058, unobserved [*F*_o < 4σ(*F*_o)] 659, linear absorption coefficient μ(Cu-K_α) = 5.57 cm⁻¹, *R*₁ = 0.046, *wR*₂ = 0.108.

Crystal data of 4. C₃₆H₃₀N₄, *M_r* = 518.64, space group triclinic, *P*1̄. Crystals were obtained from CHCl₃. The specimen used for X-ray experiments had dimensions of 0.62 × 0.08 × 0.06 mm. Lattice constants (Å, degrees) *a* = 10.595(5), *b* = 11.125(4), *c* = 13.020(1), α = 78.57(6), β = 68.32(6), γ = 86.25(3), cell volume *V* = 1397.8 Å³, formula units/cell *Z* = 2, X-ray density ρ_x = 1.232 g cm⁻³, number of independent reflections 5024, unobserved [*F*_o < 4σ(*F*_o)] 2248, linear absorption coefficient μ(Cu-K_α) = 5.65 cm⁻¹, *R*₁ = 0.059, *wR*₂ = 0.130.

† CCDC reference number 207/443. See <http://www.rsc.org/suppdata/p1/b0/b002074p/> for crystallographic files in .cif format.

Atomic co-ordinates, bond lengths and angles, anisotropic displacement parameters and hydrogen coordinates of compounds **3** and **4** (14 pages) are deposited in the Cambridge Crystallographic Data Centre.

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References

- 1 G. F. Smith, *Advances in Heterocyclic Chemistry*, Academic Press, New York, 1963, vol. 2, p. 300.
- 2 S. B. Mahato, N. B. Mandal, A. K. Pal and S. K. Maitra, *J. Org. Chem.*, 1984, **49**, 718.
- 3 S. B. Mahato, N. B. Mandal, A. K. Pal and S. K. Maitra, *Tetrahedron*, 1987, **43**, 4439.
- 4 S. B. Mahato, N. B. Mandal, A. K. Pal, S. K. Maitra, C. Lehmann and P. Luger, *J. Org. Chem.*, 1988, **53**, 5554.
- 5 S. B. Mahato, P. Luger and M. Weber, *J. Chem. Res. (S)*, 1992, 294.
- 6 S. B. Mahato, N. B. Mandal, S. Chattopadhyay, G. Nandy, P. Luger and M. Weber, *Tetrahedron*, 1994, **50**, 10803.
- 7 S. Ray, P. K. Sadhukhan, N. B. Mandal, S. B. Mahato and H. K. Majumdar, *Biochem. Biophys. Res. Commun.*, 1997, **230**, 171.
- 8 G. Chakrabarti, A. Basu, P. P. Manna, S. B. Mahato, N. B. Mandal and S. Bandyopadhyay, *J. Antimicrob. Chemother.*, 1999, **43**, 359.
- 9 S. B. Mahato, N. B. Mandal, S. Chattopadhyay, P. Luger and M. Weber, *Tetrahedron*, 1995, **51**, 12667.
- 10 Y. Murakami, M. Tani, K. Tanaka and Y. Yokoyama, *Heterocycles*, 1984, **22**, 241.
- 11 M. Tani, T. Aoki, S. Ito, S. Matsumoto, M. Hideshima, K. Fukushima, R. Nozawa, T. Maeda, M. Toshiro, Y. Yokoyama and Y. Murakami, *Chem. Pharm. Bull.*, 1990, **38**, 3261.
- 12 C. K. Johnson, ORTEP II Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA, 1976.
- 13 P. Sykes, *Mechanism in Organic Chemistry*, Orient Longman, New Delhi, 6th edn., 1992, p. 145.
- 14 B. Capon, *Org. React. Mech.*, 1980, 24.
- 15 G. Domazetis, B. Tarpey, D. Dolphin and B. R. James, *J. Chem. Soc., Chem. Commun.*, 1980, 939.
- 16 J. A. Kampmeier, S. H. Harris and D. K. Wedegaertner, *J. Org. Chem.*, 1980, **45**, 315.
- 17 A. Altomare, G. Cascarono, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polidori and M. Camalli, SIR92 Program for Automatic Solution of Crystal Structure, *J. Appl. Crystallogr.*, 1994, **27**, 435.
- 18 G. M. Sheldrick, SHELXL-97, An Integrated System for Solving and Refining Crystal Structures from Diffraction Data, 1997, Universitat Gottingen.