Tetrahedron Letters, Vol.22, No.23, pp 2225 - 2228, 1981
Printed in Great Britain

0040-4039/81/232225-04$02.00/0

CONFORMATIONAL BEHAVIOUR AND INCLUSION COMPOUND FORMING PROPERTIES OF 5, 18-DISUBSTITUTED DERIVATIVES OF 5, 11, 12, 18-TETRAHYDROTRIBENZO[b, f, j][1, 4]DIAZACYCLODODECINE-6, 17-DIONE

W. David Ollis,* Julia Stephanidou Stephanatou, and J. Fraser Stoddart

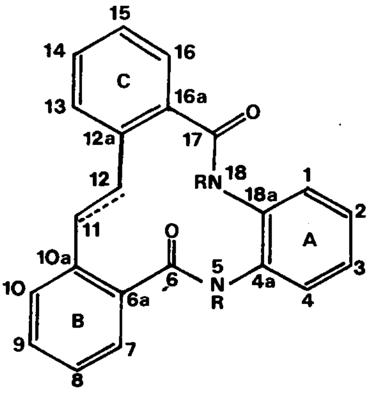
Department of Chemistry, The University, Sheffield S3 7HF

Gulten G. Unal[1] and David J. Williams*

Chemical Crystallography Laboratory, Imperial College, London SW7 2AY

Summary. An X-ray structure analysis shows that the 5, 18-dimethyl derivative (5) of the title compound (4) crystallises from xylene as a 1:1 inclusion compound in which the host molecules adopt propeller-like conformations (7 and 7*) with almost perfect C_2 symmetry. Dynamic ^{1}H n.m.r. spectroscopy shows that the 5, 18-dibenzyl derivative (6) of (4) forms a 1:1 inclusion compound with ethanol in the solid state and undergoes ring inversion (7 $\rightleftharpoons$ 7*) between enantiomeric propeller-like conformations in solution against a barrier of 21.1 kcal mol^{-1}.

Trianthranilides have been shown[2-4] to share with trisalicylides (e.g. tri-o-thymotide[5-8]) and trithiosalicylides[9, 10] a propensity for forming inclusion compounds and undergoing spontaneous resolution on crystallisation. In our quest for topologically related molecules exhibiting one or both of these properties, we have prepared[11] the 5, 18-dimethyl (2) and 5, 18-dibenzyl (3) derivatives of the olefinic bislactam (1). X-Ray crystal structure analysis revealed[11] that (2) adopts a severely distorted propeller-like conformation in the solid state on account of the conjugational demands for planarity imposed upon the trans-stilbenoid portion of the molecule. Despite the fact that dynamic ^{1}H n.m.r. spectroscopy on (3) demonstrated[11] that the barrier to ring inversion between enantiomeric propeller-like conformations is sufficiently high (namely 20.4 kcal mol^{-1}) in solution not to exclude the possibility of spontaneous resolution, this phenomenon was not found to characterise crystals of compound (2). Nor did compounds (1) - (3) exhibit a willingness to form inclusion compounds with solvent molecules on crystallisation. However,



	-------	R
1	CH=CH	H
2	CH=CH	Me
3	CH=CH	CH_2Ph
4	CH_2-CH_2	H
5	CH_2-CH_2	Me
6	CH_2-CH_2	CH_2Ph

we were not discouraged by these preliminary findings and speculated that replacing the olefinic double bonds between rings B and C in compounds (1) – (3) with bismethylene units would relieve conjugational constraints and might lead to more 'symmetrical' molecular geometries and hence to the desired lattice properties. Consequently, compounds (4) – (6) were prepared.[12] In this communication, we report on (i) the solid state structure of (5) as disclosed by X-ray crystallography, (ii) the conformational behaviour of (5) in solution as indicated by n.m.r. spectroscopy, and (iii) the ability of both (5) and (6) to form inclusion compounds on crystallisation.

An X-ray crystal structure analysis of the 5,18-dimethyl derivative (5) shows (see Figure 1) that in the solid state the molecules adopt an almost perfect C_2–P conformation (7) with the non-crystallographic two-fold axis of symmetry bisecting the mid-points of the C(2)–C(3), C(4a)–C(18a), and C(11)–C(12) bonds. An interesting additional conformational feature emerges from the crystallographic analysis. In trisalicylide derivatives (e.g. tri-o-thymotide[6] and tri-o-carvacrotide[10]) where propeller conformations are adopted in the solid state, the torsional angles associated with the ArC–CO and O–CAr bonds have average values of ca. 60° and ca. 90°, respectively. In the case of compound (5), however, we witness a propeller-like conformation where the equivalent torsional angles are all very nearly equal (see Figure 1) and are distributed within the 12-membered ring such that the molecules have almost perfect C_2 symmetry (see Figure 2). The single crystal which was employed in the X-ray diffraction experiment was obtained after recrystallisation from xylene (a mixture of constitutional isomers) during several months. In addition to the information on the solid state conformation, the structure analysis shows that (5) forms a 1:1 inclusion compound with o-xylene.[13] The guest molecules are disordered and assume two distinct orientations in the inclusion regions of the host lattice such as to simulate the entrapment of a naphthalene molecule.

The ^{1}H n.m.r. and ^{1}H-decoupled ^{13}C n.m.r. spectra of the 5,18-dimethyl derivative (5) recorded in CDCl$_3$ at ambient temperature support the view that this compound also adopts a conformation

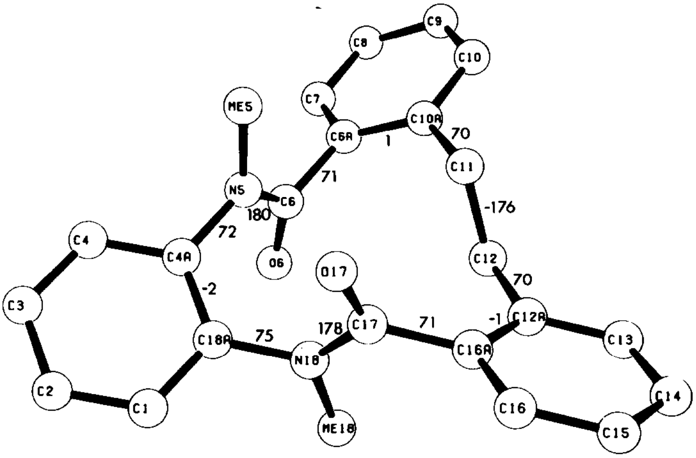
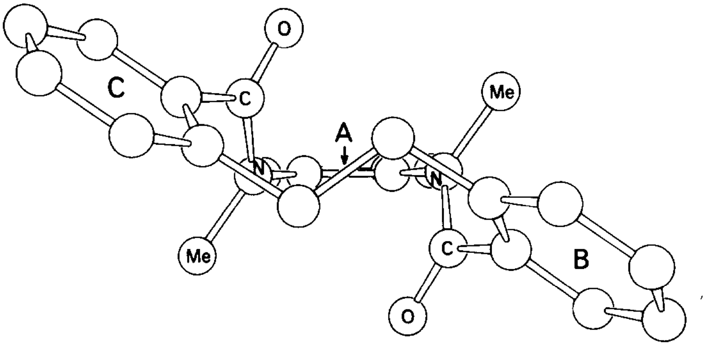


Figure 1. The solid state conformation of the 5,18-dimethyl derivative (5) showing the torsional angles

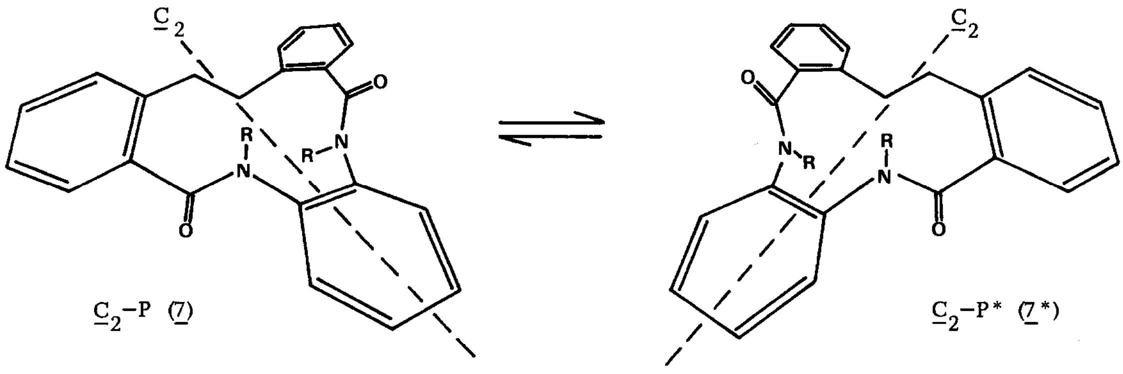
Figure 2. The solid state conformation of the 5, 18-dimethyl derivative (5) showing its $\underline{C}_2$ symmetry.



with $\underline{C}_2$ symmetry in solution. The presence of an AA'BB' system for the bismethylene protons indicates that ring inversion is slow on the ^{1}H n.m.r. time scale.[14] This conclusion was confirmed by examining the ^{1}H n.m.r. spectrum[12] of the 5, 18-dibenzyl derivative (6) at high temperatures in CD_3SOCD_3. The AB system observed for the prochiral benzylic methylene protons at room temperature coalesced to a singlet at +146°C. The rate constant of 88 s^{-1} calculated at the coalescence temperature corresponds to a $\Delta G^{\ddagger}$ value of 21.1 kcal mol^{-1} for ring inversion which is presumably a $\underline{C}_2$–P $\rightleftharpoons$ $\underline{C}_2$–P* (7 $\rightleftharpoons$ 7*) process.[15]

An interesting additional property of the 5, 18-dibenzyl derivative (6) is its striking ability to form a 1:1 inclusion compound with ethanol.[17] This was first noted when (6) was dissolved in chloroform containing 2% of ethanol (present as a stabiliser), the solvent removed under vacuum at room temperature, and the residue recrystallised from ether-light petroleum (b.p. 60-80°C) giving a crystalline sample which was shown by ^{1}H n.m.r. spectroscopy ($CDCl_3$) to contain a molar proportion of ethanol. This ethanol can be removed from the crystals under vacuum (< 1.0 mm Hg) at +90°C within four hours.

Crystallographic Data: Crystals of (5) [$C_{24}H_{22}N_2O_2$, C_8H_{10}] are monoclinic, $\underline{a}$ = 43.431 (2), $\underline{b}$ = 7.707 (1), $\underline{c}$ = 13.586 (1) Å, β = 96.35 (1)°, $\underline{U}$ = 4520 Å^3; space group $\underline{C}2/\underline{c}$, $\underline{Z}$ = 8, $\underline{D}_c$ = 1.40 g cm^{-3}. Of the 3374 independent reflections ($\theta \leqslant 60°$) measured on a diffractometer using Cu–$\underline{K}_\alpha$ radiation, 576 were classified as unobserved. The structure was solved by direct methods and refined to give an $\underline{R}$ value of 0.061.



$\underline{C}_2$–P (7)

$\underline{C}_2$–P* (7*)

References and Footnotes

1. Present address: A. U. Eczacilik Fakultesi, Tandogan, Meydani, Ankara, Turkey.
2. W. D. Ollis, J. A. Price, J. S. Stephanatou, and J. F. Stoddart, Angew.Chem.Internat.Edn., 1975, 14, 169; W. D. Ollis, J. S. Stephanatou, J. F. Stoddart, and A. G. Ferrige, Angew.Chem.Internat.Edn., 1976, 15, 223.
3. D. J. Williams, J.Chem.Soc. Chem.Comm., 1977, 170.
4. S. J. Edge, W. D. Ollis, J. S. Stephanatou, J. F. Stoddart, D. J. Williams, and K. A. Woode, Tet.Letters, following communication.
5. H. M. Powell, Nature, 1952, 170, 155; D. Lawton and H. M. Powell, J.Chem.Soc., 1958, 2339.
6. D. J. Williams and D. Lawton, Tet.Letters, 1975, 111.
7. R. Arad-Yellin, S. Brunie, B. S. Green, M. Knossow, and G. Tsoucaris, J.Amer.Chem.Soc., 1979, 101, 7529; R. Arad-Yellin, B. S. Green, M. Knossow, and G. Tsoucaris, Tet.Letters, 1980, 387.
8. R. Gerdil and J. Allemand, Tet.Letters, 1979, 3499; Helv.Chim.Acta, 1980, 63, 1750.
9. G. B. Guise, W. D. Ollis, J. A. Peacock, J. S. Stephanatou, and J. F. Stoddart, Tet.Letters, 1980, 4203.
10. E. Gil, A. Quick, and D. J. Williams, Tet.Letters, 1980, 4207.
11. W. D. Ollis, J. S. Stephanatou, J. F. Stoddart, A. Quick, D. Rogers, and D. J. Williams, Angew.Chem.Internat.Edn., 1976, 15, 757.
12. Reaction of o-phenylenediamine with the bisacyl chloride (m.p. 164–167°) of dibenzyl-2, 2'-dicarboxylic acid (R. C. Fuson, J.Amer.Chem.Soc., 1926, 48, 830) in benzene solution at room temperature gave the bislactam (4) (62%; m.p. > 300°). N-Methylation (MeI, NaH, Me_2SO) of (1) afforded the 5, 18-dimethyl derivative (5) (90%; m.p. 273°); τ ($CDCl_3$) 2.62–2.73 (12H, m, aromatic protons), 6.78 (6H, s, 2 x NMe), and 6.95–7.22 (4H, AA'BB' system, CH_2CH_2); δ^{TMS} ($CDCl_3$) 171.2 (CO), 139.7, 137.4, 136.6, 130.0, 129.4, 128.8, and 126.6 (aromatic carbons), 38.6 (NMe), and 36.5 (CH_2). N-Benzylation ($PhCH_2Br$, NaH, Me_2SO) of (4) afforded the 5, 18-dibenzyl derivative (6) (66%; m.p. 149–150°); τ ($CDCl_3$) 2.22–3.44 (22H, m, aromatic protons), 5.07 and 5.23 (4H, AB system, J_{AB} = 14.7 Hz, 2 x $PhCH_2$), and 6.48–7.24 (4H, AA'BB' system, CH_2CH_2).
13. It would appear that regioselection of the ortho isomer occurs during crystallisation from 'mixed' isomers of xylene.
14. The temperature dependence of the ^1H n.m.r. spectrum of (5) was examined (i) below ambient temperature in $CDCl_3$–CS_2 (1 : 2) and (ii) above ambient temperature in $PhNO_2$. At -80°C, the singlet[12] for the N-methyl protons and the AA'BB' system[12] for the bismethylene protons were broadened slightly in keeping with the presence of one ground state conformational type (i.e. 7 and 7*) in solution where ring inversion between enantiomers is slow on the ^1H n.m.r. time scale. At +140°C, the AA'BB' system coalesces to a singlet indicating that ring inversion ($7 \rightleftharpoons 7^*$) is becoming rapid on the ^1H n.m.r. time scale at this temperature.
15. The rate constant, k_c, calculated at the coalescence temperature was obtained using the expression $k_c = \pi[(\nu_A - \nu_B)^2 + 6J_{AB}^2]^{\frac{1}{2}}/2^{\frac{1}{2}}$, where $\nu_A - \nu_B$ = 13.0 Hz and J_{AB} = 15.2 Hz.
16. The complete conformational itinerary for this ring inversion process is analogous to that discussed previously (see ref. 11) for derivatives of the olefinic bislactam (1). It involves C_2 symmetrical and asymmetrical helical conformations as intermediates.
17. A very recent publication by E. Weber and F. Vögtle (Angew.Chem.Internat.Edn., 1980, 19, 1030) describes their important discovery that certain pyridino crown compounds selectively form inclusion compounds (ligand:guest, 2:1) with methanol, ethanol, and the homologous series of unbranched alcohols from propan-1-ol to hexan-1-ol. Other compounds which have recently been reported (J. A. Hyatt, E. N. Duesler, D. Y. Curtin, and I. C. Paul, J.Org.Chem., 1980, 45, 5074 and H. J. Bestmann, E. Wilhelm, and G. Schmid, Angew.Chem.Internat.Edn., 1980, 19, 1012) to form inclusion compounds (ligand:guest, 1:2) with alcohols include cyclotriveratrylene (propan-2-ol) and tetraphenylsquaramidine (methanol). Trianthranilide derivatives also have a remarkable propensity for forming 1:1 inclusion compounds with ethanol (see ref. 2).

(Received in UK 20 March 1981)