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SYNTHESIS AND CONFORMATIONAL BEHAVIOUR OF TETRA-ANTHRANILIDES

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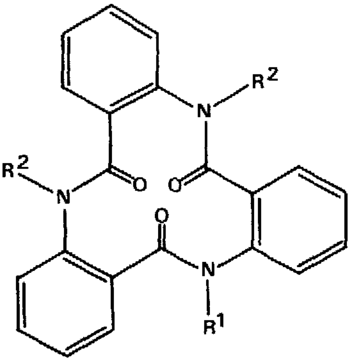
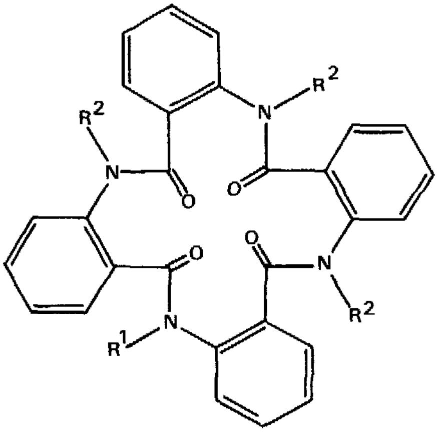
Summary. The tetra-anthranilide derivatives (5)–(7) have been synthesised. X-Ray crystallography shows that N,N',N''-trimethyltetra-anthranilide (5) adopts a conformation with three trans- and one cis-amide linkages in the solid state. Dynamic ^{1}H n.m.r. spectroscopy indicates that N-benzyl-N',N'',N'''-trimethyl-tetra-anthranilide (7) exists as an interconverting ternary mixture of chiral non-planar conformational diastereoisomers in solution.

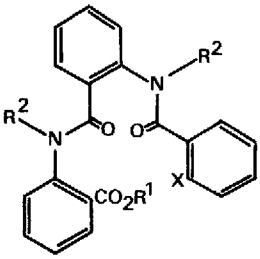
In view of the stereochemical complexities exhibited by the 12-membered rings in some suitably substituted trianthranilides (e.g. 1 – 4) from both the dynamic[1,2] and static[3] vantage points, it became of considerable interest to explore the conformational behaviour of the 16-membered rings in the homologously related tetra-anthranilides. In this communication, we describe the synthesis of N,N',N''-trimethyl- (5), N,N',N'',N'''-tetramethyl- (6), and N-benzyl-N',N'',N'''-trimethyl- (7) tetra-anthranilides, discuss the conformation adopted by compound (5) in the solid state, and explore tentatively the conformational behaviour of compounds (6) and (7) in solution

The key acyclic amino acid intermediate (14) was obtained[4] from N-[2-(o-nitrobenzamido)-benzoyl]anthranilic acid[5] (8) in six steps (i) treatment of (8) with p-MeC$_6$H$_4$N=NNHMe[6] in

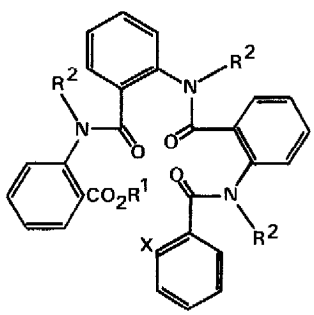


	R1	R2	
1	H	Me	5
2	Me	Me	6
3	H	CH$_2$Ph	
	CH$_2$Ph	Me	7
4	CH$_2$Ph	CH$_2$Ph	





	R^1	R^2	X	
8	H	H	NO_2	
9	Me	H	NO_2	11
10	Me	H	NH_2	
	Me	Me	NO_2	12
	Me	Me	NH_2	13
	H	Me	NH_2	14



tetrahydrofuran affording the methyl ester (9), (ii) reduction ($TiCl_3$, EtOH, H_2O)[7] of the aromatic nitro group in (9) giving methyl dianthranolyl anthranilic acid (10), (iii) o-nitrobenzoylation (o-$NO_2C_6H_4COCl$, LiOH, C_6H_6, H_2O) of (10) leading to the methyl ester (11), (iv) methylation (MeI, NaH, DMSO) of (11) affording the N,N',N''-trimethyl derivative (12), (v) reduction ($TiCl_3$, EtOH, H_2O)[7] of the aromatic nitro groups in (12) giving the N,N',N''-trimethyl derivative (13) of methyl trianthranolyl anthranilic acid, and finally (vi) de-esterification (LiOH, MeOH) of (13) yielding (14), m p 173–177° Cyclisation of (14) was achieved by treatment with N,N'-dicyclohexylcarbodiimide in dichloromethane to give N,N',N''-trimethyl-tetra-anthranilide (5), m p. 295° (ex. MeOH–p-dioxan during four months), in low yield (ca. 2%). Methylation (MeI, NaH, DMSO) of (5) gave N,N',N'',N'''-tetramethyltetra-anthranilide (6), m.p >300° (ex MeOH), ^{1}H n m.r. data at 30°C τ (CD_2Cl_2) 2.33–2.65 (16H, m, aromatic protons) and 6.74 (12H, s, 4 x NMe) On cooling the CD_2Cl_2 solution down to -100°C, the spectral line shapes remained essentially unchanged. This observation is consistent with either one of the two following interpretations (i) ring inversion and interconversion processes are still occurring rapidly on the ^{1}H n m r. time scale even at -100°C, or (ii) the ground state conformation "frozen out" at -100°C has averaged C_4 symmetry,[8] characteristic of certain conformations with all-cis and all-trans amide linkages. At this stage, it became obvious to us that a prochiral probe had to be introduced into a tetra-anthranilide derivative in order to achieve a better understanding of its conformational behaviour in solution The benzyl group was selected as a suitable probe Benzylation of (5) gave N-benzyl-N',N'',N'''-trimethyltetra-anthranilide (7), m.p >300° (ex toluene), ^{1}H n.m r data at 40°C τ ($CDCl_3$) 2 15–3.15 (21H, m, aromatic protons), 4 93 (2H, broad signal, benzylic methylene protons), and 6.50, 6.57, 6.61, and 6.66 (9H, signals of different intensities and variable line shapes, 3 x NMe) On cooling down to -30°C, significant alterations in line shapes characterised spectra In particular, the broad signal for the benzylic methylene protons at 40°C eventually gave rise (see Figure 1) to three AB systems (τ_{A1} 4 06, τ_{B1} 5.39, J_{A1B1} = 15.0 Hz, τ_{A2} 4 37, τ_{B2} 5.54, J_{A2B2} = 15.5 Hz, τ_{A3} 4 84, τ_{B3} 5.04, J_{A3B3} = 15.1 Hz)[9] with relative intensities of 0.27, 0.23, and 0 50 for A1B1, A2B2, and A3B3 respectively at -30°C. Thus, three conformational diastereoisomers of (7) coexist in $CDCl_3$ solution

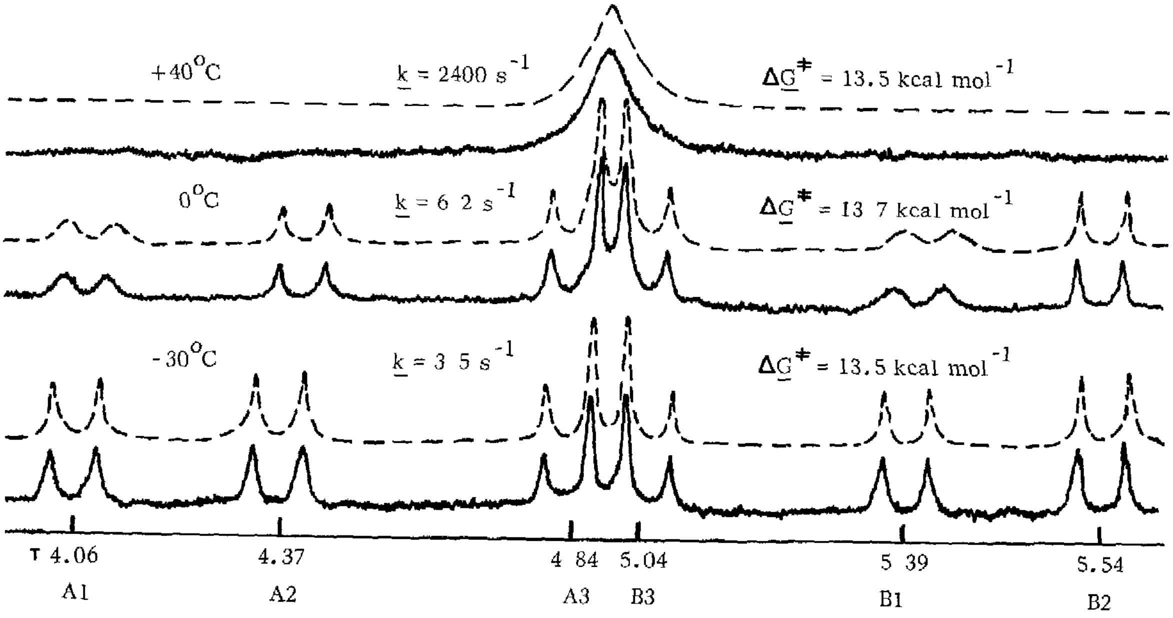


Figure 1. Observed (full line) and computed (broken line) spectra of the benzylic methylene protons of N-benzyl-N', N'', N''' -trimethyltetra-anthranilide (7)

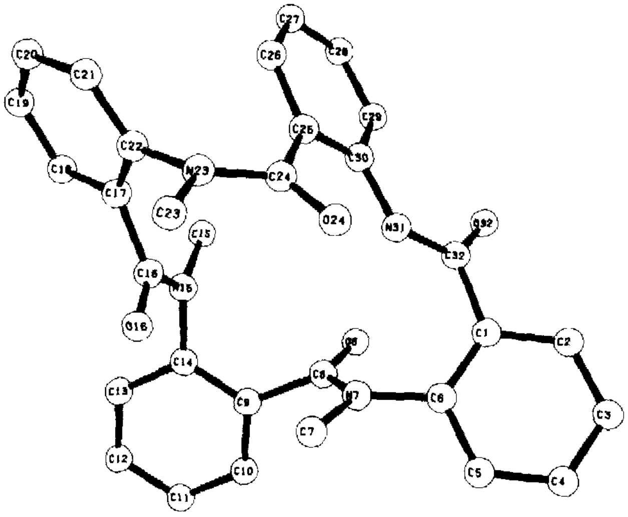


Figure 2. The solid state conformation of N, N', N''-trimethyltetra-anthranilide (5)

in these proportions at this temperature. Computer analysis of the partial spectra shown in Figure 1 was carried out using a program written[10] for exchange of nuclei between all six sites of three AB systems. An average free energy of activation ($\Delta G^{\ddagger}$) of 13.6 kcal mol[11] for the conformational changes associated with interconversions between the three conformational diastereoisomers was obtained Although it is not possible to assign conformations to these three diastereoisomers of (7), an X-ray crystal structure analysis (see Figure 2) of *N*,*N*',*N*"-trimethyltetra-anthranilide (5) has established that this derivative adopts a conformation with three *trans*- and one *cis*-amide linkages. Whilst this conformation might correspond with one of the three observable ground state conformations of *N*-benzyl-*N*',*N*",*N*"'-trimethyltetra-anthranilide (7) in solution, it must also be recognised that (*i*) a strong intramolecular $>C=O\cdots H-N<$ hydrogen bond [2 712 (2) Å] between N(31) and O(24) in addition to (*ii*) lattice forces characteristic of the particular crystalline state[11] could be responsible for the relative stabilisation of this solid state conformation for *N*,*N*',*N*"-trimethyltetra-anthranilide (5)

Crystallographic Data Crystals of (5) are monoclinic, a = 22.227 (1), b = 13 752 (1), c = 8.480 (1) Å, β = 98.87 (1)°, U = 2561 Å^3, space group $P2_1/a$, Z = 4, D_c = 1.38 g cm^{-3}. Of the 3821 independent reflections ($\theta \leq 60°$) measured on a diffractometer using Cu$-K_\alpha$ radiation, 535 were classified as unobserved The structure was solved by direct methods and refined to give an R value of 0 039

References and Footnotes

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4. The compositions of all new compounds were confirmed by elemental analyses Structural assignments were based upon the results of high resolution mass spectrometry and ^{1}H n.m r spectroscopic evidence.
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8. Although the chance that diastereotopic *N*-methyl groups in asymmetric conformations remain accidentally equivalent at low temperatures is remote in spectra recorded at 220 MHz, the possibility cannot be discounted
9. The assignment of the three AB systems, A1B1, A2B2, and A3B3 was confirmed by decoupling experiments.
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11. Indeed, when (5) is crystallised from methanol alone, there is evidence for inclusion compound formation associated with an orthorhombic space group, *Pbca* The crystals are relatively unstable and rapidly craze on loss of solvent of crystallisation

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