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Synthesis and X-Ray Structural Determination of New Aniline Derivatives of 2,4,6,8-Tetraazabicyclo[3.3.0]octanes; Anomeric Effect in N-C-N Moiety and Implications of Solvent Polarity on ^{1}H-NMR Patterns.

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Abstract: The condensation of aniline with glyoxal and formaldehyde in stoichiometric ratio, leads to 2,4,6,8-tetraphenyl-2,4,6,8-tetraazabicyclo[3.3.0]octane (1f) with formic acid as catalyst. Nine substituted derivatives of 1f have been prepared in high yield by this synthetic method. X-ray analysis revealed the existence of an anomeric effect, $n_N \rightarrow \sigma^*_{C\text{-}N}$ in N-C-N moieties manifested by reduction in N-pyramidality and short C-N bond lengths. Moreover, ^{1}H-NMR studies showed the dependency of methylenic protons splitting pattern on solvent polarity.

INTRODUCTION

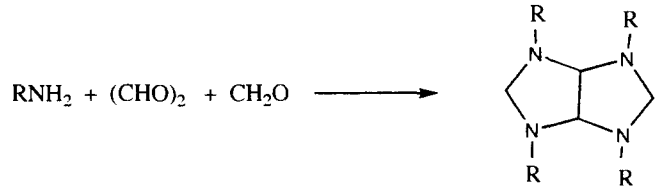
Several substituted benzylamine and alkylamines of 2,4,6,8-tetraazabicyclo[3.3.0]octane have been synthesized either via hydride reduction of glycoluril derivatives or by a direct one pot condensation of glyoxal and formaldehyde with amines[1-5]. In addition, probing the anomeric effect in N-C-N systems and its implications on structure, reactivity and conformational behaviour have been the subject of extensive studies during the past years[6-7]. The general concept of anomeric effect involves a stabilizing interaction between a lone pair on N and an antiperiplanar σ^* orbital of the adjacent C-N bond ($n_N \rightarrow \sigma^*_{C\text{-}N}$) best described as "negative hyperconjugation"[8].

In this account we report results obtained in the synthesis of new aniline derivatives of 2,4,6,8-tetraazabicyclooctanes and on the X-ray structural determination, to probe substituent effects in the anomeric N-C-N moiety of five membered fused rings and to show implications of solvent polarity on ^{1}H-NMR patterns.

RESULTS

Condensation was performed with formaldehyde, glyoxal and aniline and its derivatives via a direct, one pot reaction to 2,4,6,8-tetraaryl substituted 2,4,6,8-tetraazabicyclo[3.3.0]octanes 1f-q. Substituents include 4-methyl, 3-methyl, 3,4-dimethyl, 3,5-dimethyl, 4-methoxy, 4-ethoxy, 4-chloro, 4-bromo and 4-iodo. These previously unreported compounds separated from the reaction mixture in highly pure crystalline form in 71-93% yield. Reactions are fast and complete in a few hours. Best yields are obtained at pH=9-9.5 but drastically reduced under highly basic or acidic conditions

10<pH<7. Reactions stay incomplete at 0° C giving a mixture of 1, diol 2 and tetramine 3.



1a: R = CH_3-	1f: R = C_6H_5-	1K: R = 4-$MeOC_6H_4$-
1b: R = C_2H_5-	1g: R = 4-$CH_3C_6H_4$-	1m: R = 4-$EtOC_6H_4$-
1c: R = i-C_3H_7-	1h: R = 3-$CH_3C_6H_4$-	1n: R = 4-ClC_6H_4-
1d: R = CH_3CO-	1i: R = 3,4-$(CH_3)_2C_6H_3$-	1P: R = 4-BrC_6H_4-
1e: R = Ar-CH_2-	1l: R = 3,5-$(CH_3)_2C_6H_3$-	1q: R = 4-IC_6H_4-

The structure of all derivatives have been characterized by IR, NMR and MASS spectroscopic methods and elemental analysis (Tables 1,2 and 3). The position of methylenic and methinic carbons are distinguished by performing DEPT ^{13}C-NMR experiments. The isolated 1f was further characterized by X-ray crystallography (Figure 1). Condensation of glyoxal with other anilines proceeds in the same fashion with the exception of the ortho derivatives. Careful skeletal analysis reveals that the ortho substitution suffer from increased steric crowding near nitrogen of the ring, thereby inhibiting bicyclic ring closure[2-4].

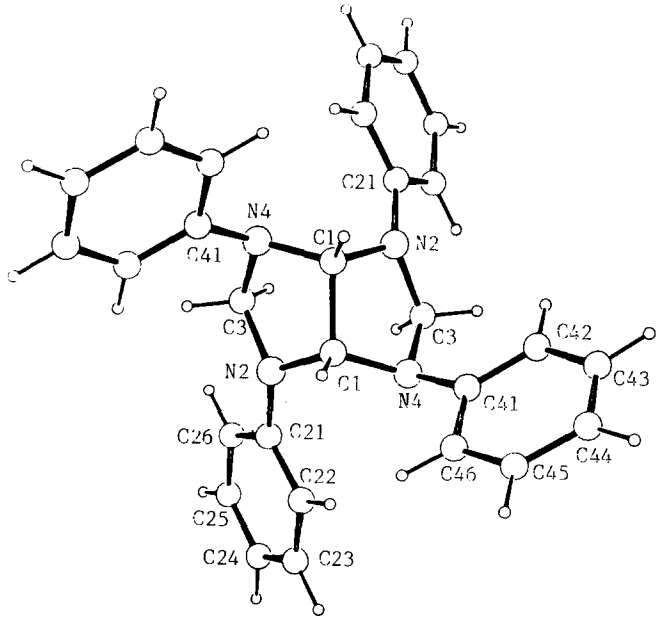


Figure 1. Molecular Projection of 1f. Selected bond distances (Å) and angles (°):
C_1-C_1 1.559(4), C_1-N_2 1.465(3), C_1-N_4 1.453(4), N_2-C_3 1.464(4), N_4-C_3 1.454(4), N_2-C_{21} 1.392(4), N_4-C_{41} 1.426(4), C_1-N_2-C_3 109.8(2), C_1-N_2-C_3 123.0(2) C_3-N_2-C_{21} 119.9(2), N_2-C_3-N_4 104.3(2), C_1-N_4-C_3 103.2(2), C_1-N_4-C_{41} 116.1(3), C_3-N_4-C_{41} 118.0(2), N_2-C_1-N_4 114.1(2), N_2-C_1-C_1 101.5(3), N_4-C_1-C_1 105.8(2).

Table 1: Synthesis of 2,4,6,8-tetraaryl 2,4,6,8-tetraazabicyclo[3.3.0]octanes 1f-q

					Element. Analys.					
					Calc.			Found		
No.	M.P. C°	Rec. Solv.	Yield	Formula	C	H	N	C	H	N
1f	210-211	CH_3CN	85	$C_{28}H_{26}N_4$	80.38	6.22	13.4	80.08	6.126	13.6
1g	194-196	$C_6H_5CH_3$	92	$C_{32}H_{34}N_4$	81	7.1	11.82	80.6	7.1	12.2
1h	180-181	$C_6H_5CH_3$	82	"	"	"	"	80.63	6.97	12.17
1i	207-208	C_6H_6	87	$C_{36}H_{42}N_4$	81.4	7.9	10.55	81.37	7.91	10.54
1l	221-223	$C_6H_5CH_3$	86	"	"	"	"	81.39	7.9	10.54
1k	162-163	CH_3CN	82	$C_{32}H_{36}N_4O_4$	71.29	6.68	10.4	71.3	6.69	10.39
1m	158-158.5	"	93	$C_{36}H_{42}N_4O_4$	72.64	7.06	9.42	72.63	7.05	9.425
1n	219-220	DMSO	84	$C_{28}H_{22}N_4Cl_4$	60.39	3.97	10.06	60.3	3.91	10.05[a]
1p	210-210.5	C_6H_6	71	$C_{28}H_{22}N_4Br_4$	45.78	3	7.63	45.71	2.97	7.62[b]
1q	181(dec.)	$C_6H_5CH_3$	80	$C_{28}H_{22}N_4I_4$	36.44	2.39	6.07	36.43	2.39	6.0[c]

a)Calc. for Cl 25.49% found 25.57% b)Calc. for Br 43.54% found 43.56% c)Calc. for I 55.05 found 55%

Table 2: ^{1}H-NMR spectral data of 2,4,6,8-tetraaryl 2,4,6,8-tetraazabicyclo[3.3.0]octanes

No.	Solv.	Phenyl Subs.	CH_2(ring)	CH (ring)	Aryl
1f	DMSO d_6	-	4.65,4.82(AB_q, 4H, J=7.50)	6.37(s, 2H)	6.70-7.16(m, 20H)
1f	$CDCl_3$	-	4.80(s, 4H)	6.01(s, 2H)	6.80-7.20(m, 20H)
1g	DMSO d_6	2.14(s, 12H)	4.58,4.75(AB_q, 4H, J=7.91)	6.19(s, 2H)	6.78,6.96(dd, 16H)
1g	$CDCl_3$	2.29(s, 12H)	4.73(s, 4H)	5.88(s, 2H)	6.83,7.08(dd, 16H)
1h	DMSO d_6	2.19(s, 12H)	4.62,4.79(AB_q, 4H, J=7.59)	6.34(s, 2H)	6.53-7.15(m, 16H)
1h	$CDCl_3$	2.27(s, 12H)	4.77(s, 4H)	5.86(s, 2H)	6.66-7.23(m, 16H)
1i	DMSO d_6	2.18(s, 24H)	4.57,4.73(AB_q, 4H, J=7.93)	6.15(s, 2H)	6.60-6.96(m, 12H)
1i	$CDCl_3$	2.19(s, 24H)	4.70(s, 4H)	5.86(s, 2H)	6.63-7.05(m, 12H)
1l	DMSO d_6	2.18(s, 24H)	4.60,4.73(AB_q, 4H, J=7.80)	6.27(s, 2H)	6.41,6.60(s, 12H)
1l	$CDCl_3$	2.24(s, 24H)	4.72(s, 4H)	5.94(s, 2H)	6.52,6.57(s, 12H)
1K	"	3.76(s, 12H)	4.53,4.71(AB_q, 4H, J=7.12)	5.72(s, 2H)	6.78,6.83(s, 16H)
1m	"	1.37(t, 12H) 3.87,4.05(AB_q, 8H)	4.52,4.71(AB_q, 4H, J=7.10)	5.69(s, 2H)	6.61(s, 16H)
1n	DMSO d_6	-	4.58,4.81(AB_q, 4H, J=7.80)	6.39(s, 2H)	6.92,7.19(dd, 16H)
1n	$CDCl_3$	-	4.65,4.76(AA′, 4H, J=6.91)	5.94(s, 2H)	6.78,7.21(dd, 16H)
1p	$CDCl_3$	-	4.65,4.75(AA′, 4H, J=7.04)	5.94(s, 2H)	6.72,7.33(dd, 16H)
1q	$CDCl_3$	-	4.69(s, 4H)	5.94(s, 2H)	6.60,7.51(dd, 16H)

Table 3: ^{13}C-NMR spectral data of 2,4,6,8-tetraaryl 2,4,6,8-tetraazabicyclo[3.3.0]octanes

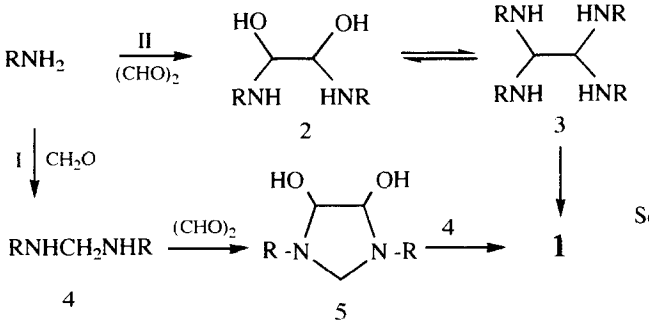
No.	Solv.	Phenyl Subs.	CH_2(ring)	CH(ring)	Aryl
1f	DMSO d_6	-	68.43	75.86	115.79, 119.41, 129.37, 146.54
1g	$CDCl_3$	20.86	69.01	79.34	117.06, 129.84, 130.15, 144.67
1h	"	21.44	69.32	79.72	117.31, 130.04, 130.09, 144.67
1i	"	19.45,20.75	69.23	79.94	108.32, 114.94, 119.28, 128.67, 130.66
1l	"	22.21	66.72	79.28	115.26, 122.52, 139.39, 147.06
1k	"	55.07	78.37	88.43	114.22, 117.45, 140.49, 152.85
1m	"	15.60,64.55	70.48	81.75	116.13, 119.46, 141.47, 154.05
1n	DMSO d_6	-	69.43	75.86	117.45, 123.44, 129.16, 145.11

DISCUSSION

The crystal structure for compound 1f represents the completion of a series of X-ray structure determinations for the completely saturated 2,4,6,8-tetraazabicyclo[3.3.0]octane ring system. The data indicate progressive anomeric effect and confirms previous suggestions as evidenced by shortened bond lengths N_1-C_{21}=1.39A° and distorted C-N-C bond angles: C_1-N_2-C_3=109.8°, C_1-N_2-C_{21}=123° and C_3-N_2-C_{21}=119.9°. These results suggest an increase in P-character of nitrogen and reduction in N-pyramidality. The stereoelectronic factors that governs N-C-N moieties also suggest an increase in stabilizing $n_{N4} \rightarrow \sigma^*_{C\text{-}N2}$ interaction manifested by the bond lengths and angles[6-7]: N_2-C_1 = 1.465 A°, N_4-C_1 = 1.453 A°, N_2-C_3 = 1.464 A°, N_4-C_3 = 1.454 A°, N_2-C_1-N_4 =114.1° and N_2-C_3-N_4 = 104.3°. These strong $n_N \rightarrow \sigma^*_{C\text{-}N}$ anomeric interactions on the two fused five membered rings invoke substantial changes upon chemical shift and splitting pattern at ^{1}H-NMR spectra. Methinic protons of 1f exhibit a signal at 6.01 ppm in $CDCl_3$ shifted downfield from those of 1a, 1c and 1e (2.37, 1.87 and 1.64 ppm respectively). X-ray crystallography shows a racemic orientation of 1f, but ^{1}H-NMR data indicate a fast equilibrium by nitrogen inversion of racemic moieties. In DMSO d_6 as solvent, methylenic protons of 1f appear as AB quartet (4.64,4.82 ppm, J=7.50 Hz) to indicate a cis conjucture of the ring; but in low polarity solvents such as $CDCl_3$ and C_6D_6 a singlet at 4.80 ppm is observed. Upon gradual addition of $CDCl_3$ to an NMR sample of 1f in DMSO d_6, the AB quartet collapses first into an AA′ and finally to a singlet with complete removal of side bands. This observation suggests sensitivity of methylenic protons to solvent polarity and existence of an additional interaction with polar solvents. To investigate the effect of substituents on splitting pattern of ^{1}H-NMR methylenic signals, substituted 2,4,6,8- tetraazabicyclo[3.3.0]octanes 1g-q were synthesized and their NMR signals were compared. Derivatives 1g-l with activating methyl substituents show a singlet for methylenic protons in $CDCl_3$ similar to 1f. Conversely methoxy and ethoxy derivatives 1k and 1m give an AB quartet, while halogen series give an AA′ pattern (1n-p) and a singlet (1q) in $CDCl_3$. We attribute this phenomenon to the resonance ability of substituents and to their unshaired pair contributions which is competing with nitrogen non-bonded electrons for back donation to aromatic ring. It is apparent that the former effect

outweighs the latter so that an increase in P-character of nitrogens may result in a better observation of diastereotopic protons while the rate of nitrogen inversion is relatively reduced[6]. Although a strong interaction of nitrogens with nonpolar solvents is not expected, solvent dependence in polar solvents (e.g. DMSO) arises when solvation of N limits both the extent of ring conjugation and nitrogen inversion. Conceivably, we observe an AA' or AB patterns, depending upon solvent polarity and the extent of its interaction. The data clearly indicate that any change in proton chemical shift may be the result of a differential effect arised from substituent effects mediated by solvation of N and fast conformational changes[9].

In scheme 1 are shown plausible mechanisms for condensation of glyoxal with aromatic amines and formaldehyde.



Scheme 1

Reaction Path I represents a thermodynamic condition for formation of 1d[1]. In activated amines however, pathway II is more favorable through a kinetic condition[10]. An exception to the general pattern of the reaction of anilines was p-nitro aniline which formed intermediate 4, thus favoring pathway I.

EXPERIMENTAL SECTION

General. Melting points were determined on an Electrothermal Model 9100. IR(KBr) spectra were taken on a Shimadzu model 4300 spectrometer. NMR spectra were recorded on a Brucker-80 MHz and Varian-500 MHz spectrometers. MASS analysis of the product was conducted on a Shimadzu-QP 1000 EX and Finnigan-matt 8430 GC-MASS instruments. Elemental analysis were done with a C, H, N, O Rapid-Hereaus analyzer.

Synthesis of 2,4,6,8- tetraphenyl 2,4,6,8-tetraazabicyclo[3.3.0]octane 1f. A solution of aniline (4.66g, 50 mmol), formic acid (0.112g of 98% aqueous solution, 2.12 mmol), and 2-propanol (50 mL) were prepared. To this solution at 25°C while being continiously stirred, formaldehyde (2.03g of 37% aqueous solution, 25 mmol) was added. Then glyoxal (1.8125g of 40% aqueous solution, 12.5 mmol) was gradually added in a period of ten minutes. The solution was stirred for one hour at 25°C until precipitates were formed. The precipitates were then filtered and the filterate concentrated to get residual precipitates. Overall yield 4.46g (85.36%) of crude product. Recrystallization in acetonitrile yielded white pure crystals of 1f, mp 210-211°C. Condensation of other aniline derivatives with glyoxal and formaldyhde was conducted under similar conditions to that described for the preparation of 1f. The reaction was successful with 4-methyl, 3-methyl, 3,4-dimethyl, 3,5-dimethyl, 4-methoxy, 4-ethoxy,

4-chloro, 4-Bromo and 4-Iodo anilines to give compounds 1f-q. For optimum results solution must be kept at 25° C while being continiously stirred (Tables 1,2,3).

Crystal data and structure solution. $C_{28}H_{26}N_4$, FW=418.25, clear, colorless crystals (recrystallized from acetonitrile/DMSO solvent) was used for data collection on an Enraf-Nonius CAD4 diffractometer at the Hoffman - LaRoche laboratories using graphite monochromated CuK_α radiation and ω-2θ scans. Orthorhombic crystals in a F2 dd space group, a = 5.712(1) Å, b = 19.342(2)Å, c = 39.168(3)Å, z = 8 (1 molecule/ asymmetric unit), D(x-ray, calcd.) = 1.285cm^{-3}, CuK_α = 5.6cm^{-1}. Of the 900 independent reflections for $\theta<60°$, 726 were considered observed [$1>3.0\sigma(1)$]. The structure was solved by a multiple solution procedure with the aid of the program Multan 11/82, and was refined by full matrix least squares. The nonhydrogen atoms were refined anisotropically. The final discrepancy indices are R=0.034 and RW=0.041 for the 719 observed reflections. The final difference map had no peaks greater than ±0.1 eÅ^{-3}. Atomic coordinates and temperature factors, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre.

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