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SYNTHESIS AND X-RAY STRUCTURAL DETERMINATION OF 2,4,6,8- TETRAPHENYL- 2,4,6,8- TETRAAZABICYCLO [3.3.0] OCTANE

Farnia, S. Morteza *
Kakanejadifard, Ali
Department of Chemistry, Faculty of Sciences, Tehran University,
Tehran, Iran.
Karimi, Sasan
Department of Chemistry, Hunter College, New York
New York, 10021, USA
Todaro, Louis J.
Hoffmann- LaRoche Inc. Nutley, New Jersey 07110-1199, USA

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ABSTRACT : *Condensation of glyoxal, formaldehyde and anilines lead to the formation of 2,4,6,8- tetraphenyl and substituted phenyl 2,4,6,8- tetraazabicyclo [3.3.0] octanes. The reactions are sensitive to pH and temperature. Ortho derivatives of anilines do not participate in this condensation. X- ray structural determination reveals a cis- dienvelope geometery about the two fused rings.*

KEY WORDS : *Polyaza Polycyclic Derivative, 2,4,6,8- Tetraphenyl- 2,4,6,8- Tetrazya Bicyclo [3.3.0] Octane- Cis Dienvelope Geometery, X-Ray Structural Analysis.*

INTRODUCTION :

Recent upsurge of interest in the synthesis of 2,4,6,8- tetraazabicyclo [3.3.0] octanes is mainly due to their application as drug substitute and preparation of high energy materials [1]. Several 2,4,6,8- tetraaza -n- alkyl- 2,4,6,8 - tetraazabicyclo octanes with N - methyl, ethyl and isopropyl substitutents have been synthesized by reduction of the substituted glycolurils *(1)* with lithium aluminum hydride [2-4]. The nitro derivatives such as *(2d)* are not yet synthesized,

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* Corresponding author

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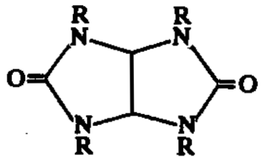
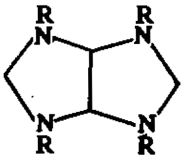
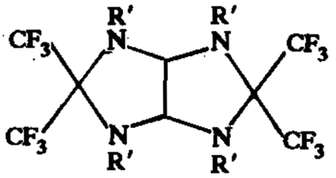


(1)



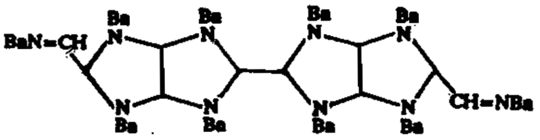
(2a): R = CH_3
(2b): R = C_2H_5
(2c): R = i-C_3H_7
(2d): R = NO_2
(2e): R = $C_6H_5CH_2$



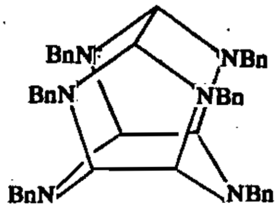
(3a): R′ = H
(3b): R′ = NO_2

however, recent investigations have shown that electron withdrawing groups like- CF_3 at positions *3* and *7* increase the stability of the tetranitro derivative as in *(3b)*[1].

Recently we have reported the synthesis of 2,4,6,8- tetrabenzyl- 2,4,6,8- tetraazabicyclo [3.3.0] octane *(2e)* from glyoxal, formaldehyde, and benzylamine [5]. Besides benzylamine was shown to condense with glyoxal to give mixtures of *(4)* and *(5)* [6,7].



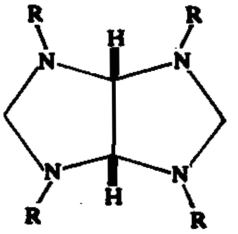
(4) : Bn = $C_6H_5CH_2-$



(5) : Bn = $C_6H_5CH_2-$

In extension of our continued efforts here-in we disclose the facile condensation of glyoxal formaldehyde and anilines to give 2,4,6,8- tetraaryl- 2,4,6,8- tetraazabicyclo [3.3.0] octanes. This reaction proceeds in the presence of catalytic amounts of formic acid providing white crystals of *(2f–2k)* according to the following equation.

$$4RNH_2 + 2CH_2O + (CHO)_2 \xrightarrow[i\text{-}C_3H_7OH]{H_3O^+}$$



(2f) : R = C_6H_5-
(2h): R = $4-CH_3C_6H_4-$
(2i) : R = $3-CH_3C_6H_4-$
(2k): R = $4-ClC_6H_4-$

EXPERIMENTAL :

Materials :

Glyoxal, formaldehyde and amines were obtained from *Merck*, Inc. and all were synthesis grade.

Instruments :

Ms analysis of the product was conducted on a *Finnigan Matt* 8430 GC-MS spectro- graph. NMR experiments were run on a *Varian* 500 MHz and *Brucker* 80 MHz spectrometers. The IR(KBr) spectra were recorded on a *Shimadzu* 4300 FT-IR spectrophotometer. All elemental analysis were done with a C, H, N, O, rapid Hereous analyzer and melting points were determined with a Gallenkamp instrument.

Methods :

Synthesis of 2,4,6,8- tetraphenyl- 2,4,6,8- tetraazabicyclo [3.3.0] octane (2f)

A solution of aniline (4.66g, 50mmol), formic acid (0.112g, 2.12mmol), and isopropyl alcohol (50mL) were prepared in a 250mL flask. To this solution at 25°C while being continiously stirred formaldehyde (2.03g, 37%, 25mmol)was added. Then glyoxal was gradually added (2.43g, 30%, 12.5mmol) in a period of ten minutes. The solution was stirred for one hour at 25°C and then at 50°C for ten minutes. The solution was cooled subsequently to 0°C untill white precipitates were formed. The precipitates were then filtered and the filtrate concentrated to get residual precipitates. Overall yield: 4.46g (85.36%) of crude product, MP 203-207°C. Recrystallization in acetonitrile yielded white pure crystals of *2f*, MP 208-210°C.The condensation of other aniline derivatives with glyoxal and formaldehyde was conducted under similar conditions to that described for the preparation of *2f*. The reaction was successful with 4- methyl, 3- methyl and 4- chloroanilines to give compounds *(2h-2k)*.

For optimum results solutions must be kept at 50°C while being continiously stirred. Recrystallization solvents are either toluene or mixtures of methylacetate and acetone.

Synthesis of 2f from -1, 1', 2, 2' tetrakis (Phenyl amino) ethane (8)

To a solution of tetramine 8(4.92g, 12.5mmol) in 50mL THF and formic acid (0.112g, 88%, 2.15mmol) at 10°C was added formaldehyde (2.03g, 37%, 25mmol)gradually in a period of ten minutes. After stirring for 15 minutes white precipitates appeared. The slurry was stirred for an additional sixty minutes at 30°C followed by filtration. Overall yield: 3.82g (73%) of crude product MP 206 - 210°C. Recrystallization in acetonitrile yielded white pure crystals of *2f*. See summaries of data in Table (1-3).

Table 1 : Synthesis of 2,4,6,8- Tetraaryl 2,4,6,8- Tetraazabicyclo [3.3.0] Octane (2f-2k).

							elemental analysis					
							Calcd			Found		
No.	phenyl subs.	MP°C	cryst	yield	mol.formula	mol. weight	C	H	N	C	H	N
2f	–	208-210	CH_3CN	85.36	$C_{28}H_{26}N_4$	418.25	80.38	6.22	13.4	80.08	6.126	13.6
2h	4-CH_3	194-196	$C_6H_5CH_3$	92	$C_{32}H_{34}N_4$	476	81	7.1	11.82	80,6	7.1	12.2
2i	3-CH_3	179-181	$C_6H_5CH_3$	82.2	$C_{32}H_{34}N_4$	476	81	7.1	11.82	80.63	6.97	12.17
2k	4-Cl	214-216	$CH_3COOCH_3/(CH_3)_2O$	83.53	$C_{28}H_{22}N_4Cl_4$$^{(a)}$	556.4	60.39	3.97	10.06	60.3	3.91	10.05

a: Calculated for Cl: 25.49%; Found : 25.57%

Table 2 : ^{1}H-NMR spectral data of 2,4,6,8- Tetraaryl 2,4,6,8- Tetraazabicyclo [3.3.0] Octane (2f-2k).

No.	Solvent	Phenyl-sub.	CH_2(ring)	CH(ring)	Aryl
(2f)	DMSO-d_6	—	4.65-4.82 (ABq , 4H , J= 7.52)	6.37(S , 2H)	6.7-7.16(m , 20H)
(2f)	$CDCl_3$	—	4.72 (S , 4H)	6.37(S , 2H)	6.7-7.2(m , 20H)
(2h)	DMSO-d_6	2.20(S , 12H)	4.61-4.78(APq , 4H , J=7.41)	5.89(S , 2H)	6.8-7.2(m , 16H)
(2h)	$CDCl_3$	2.21(S , 12H)	4.7(S , 4H)	5.90(S , 2H)	6.8-7.2(m , 16H)
(2i)	DMSO-d_6	2.17(S , 12H)	4.57-4.75(APq, 4H , J=7.43)	5.87(S, 2H)	6.55-7.12(m , 16H)
(2i)	$CDCl_3$	2.17(S , 12H)	4.66(S , 4H)	5.87(S , 2H)	6.55-7.12(m , 16H)
(2k)	DMSO-d_6	—	4.58-4.80(ABq, 4H , J=7.75)	6.39(S , 2H)	6.9-7.2(m , 16H)

Table 3 : ***^{13}C-NMR spectral data of 2,4,6,8- Tetraaryl 2,4,6,8- Tetraazabicyclo [3.3.0].***

No.	Solvent	Phenyl-subs.	CH_2(ring)	CH(ring)	Aryl
(2f)	DMSO-d_6	–	68.517	75.737	115.792 , 119.413 , 129.368 , 146.545
(2h)	$CDCl_3$	20.86	69.01	79.34	117.06 , 129.84 , 130.15 , 144.67
(2i)	$CDCl_3$	21.082	69.325	79.724	117.314 , 130.04 , 130.09 , 144.67
(2k)	DMSO-d_6	–	69.428	75.861	117.449 , 123.437 , 129.157 , 145.107

X- ray Diffraction Analysis of 2f

$C_{28}H_{26}N_4$, FW= 418.25 clear, colorless crystals (recrystallized from acetonitrile/DMSO mixed solvent) was used for data collection on an Enraf- Nonius CAD_4 diffractometer at the *Hoffman- LaRoche* Laboratories using graphite monochromated Cu Kα 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 (1molecule/ asymmetric unit), D(X-ray, calcd)=1.285cm^{-3}, (Cu Kα)= 5.6cm^{-1}. The size of the crystal used for data collection was approximately 0.11 × 0.14 × 0.24mm. The data were not corrected for absorption. Of the 900 independent reflections for $\theta < 60°$, 726 were considered observed [$I > 3.0\sigma(1)$].

The structure was solved by a multiple-solution procedure with the aid of the program Multan 11/82 [13], and was refined by full-matrix least squares. Seven reflections which were strongly affected by extinction, were excluded from the final refinement. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the structure- factor calculations but their parameteres were refined. 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 ±0.1e Å^{-3}.

Atomic scattering factors are from International Tables for X-ray crystallography (1974). Tables of atomic coordinates, bond distances and angles, and anisotropic thermal coordinates are available as supplementary materials.

RESULTS AND DISCUSSION :

Formic acid (0.1%mol) is added to the reaction mixture to keep the pH in the range of 9-9.5. The reaction is fast and is completed in a few hours. Crystalline precipitates *(2f-2k)* from the reaction mixture in 82-92% yield are formed. Best yields are obtained at pH=9-9.5 but drastically reduced under highly basic or acidic conditions (10<pH <7). The yield is sensitive to the reaction temperature and optimum results are obtained in the range 25- 50°C. The reaction stays incomplete at 0°C giving a mixture of diol *(6)* and tetramine *(8)*. The isolated *(2f)* was characterized by NMR, IR, MASS and X-ray crystallography (Table 1).

IR spectra shows the absence of N-H and C=O bands. Characteristics of the proton spectra are a singlet for the two ring methine protons at 6.369 and two doublets of methylene protons(ABq) at 4.637-4.837(DMSO-d_6,J= 7.52) (Table 2). The ^{13}C-NMR spectra reveals a signal for the two ring methinic carbon atoms at 75.737 ppm. Also seen is the signal corresponding to two ring methylenic carbons at 68.517 ppm. The position of methylenic and methinic carbons are distinguished by performing DEPT and INEPT-^{13}C-NMR experiments. It is interesting to note that in $CDCl_3$ the methylenic protons appear as singlet which is attributed to the effect of solvent (Table 3).

X-ray crystallographic analysis was used to establish the solid state structure of *(2f)*. The crystal structure confirms the expected cis conformation (Fig. 1). The four phenyl groups are oriented in such a way that half of the molecule

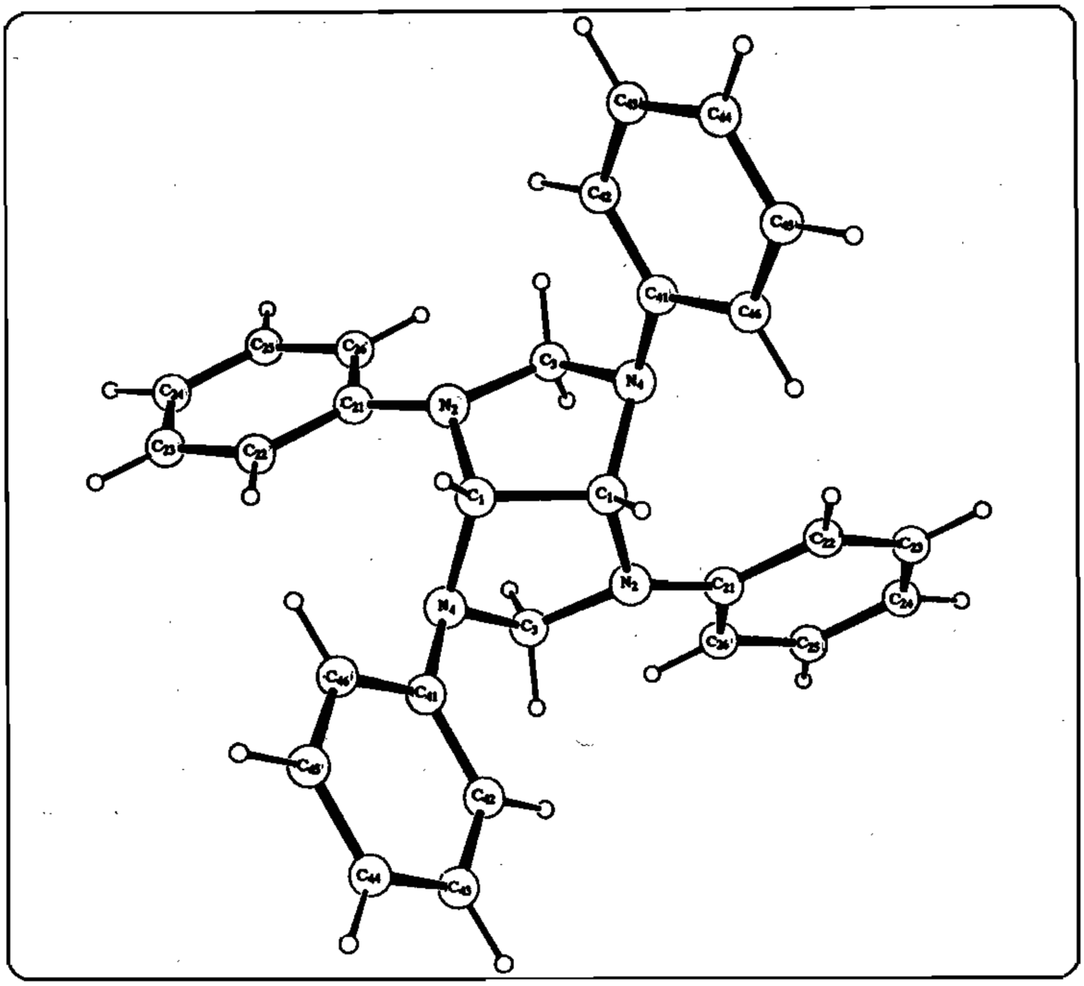
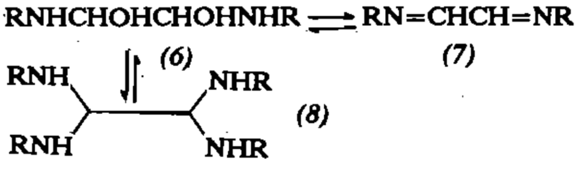


Fig. 1 : Computer generated view of 2,4,6,8- Tetraphenyl 2,4,6,8- Tetraazabicyclo [3.3.0] Octane (2f)

is related to the other half by a two fold rotation axis and the orientation of the two fused five-membered rings with respect to one another is folded- planar. Noteworthy is the sharpening of the N-C-N bond angles and shortening of the N_2-C_{21} bond distances required for the observed geometry and conjugation of aromatic π- system to the five membered ring. The bond angles at N2 and N4 (defined as the angle between the N-ipso aromatic carbon bond and the adjacent C-N-C ring plane) are 29.3° and 31.5° respectively which are deviated from pure sp^2 and sp^3 hybridization by about 25 degrees (ideally 0° for sp^2 and 54.8° for sp^3).

The formation of tetraazabicyclo octane *(2f-2k)* is believed to first go through diol *(6)* and diammine *(7)* which is then rapidly cyclized to 2 [5, 8-11].



The condensation of glyoxal with other derivatives of aniline proceeds in the same fashion with the exception of the ortho derivatives. Careful skeletal analysis reveals that the ortho substituted derivatives suffer from increased steric crowding near nitrogen of the ring, thereby inhibiting bicyclic ring closure [1,12].

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