HETEROCYCLES, Vol. 75, No. 9, 2008, pp. 2235 - 2242. © The Japan Institute of Heterocyclic Chemistry
Received, 7th March, 2008, Accepted, 17th April, 2008, Published online, 21st April, 2008. COM-08-11382

SYNTHESIS AND CHARACTERIZATION OF 2,3,5,6-TETRAPHENYL-PYRAZINE-*N, N*-DIOXIDE: NEW NITRONE DIMER SPECIES

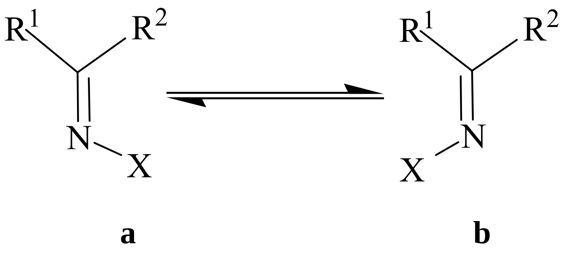
Ali Hashem Essa,[a]* Zeki A. Nasir Al-Shamkhani,[a] Abraham F. Jalbout,[b] and Ali Jameel Hameed[a]

*[a] Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq
[b] Instituto de Quimica, Universidad Nacional Autonoma de Mexico, Mexico D.F.
Email: alihashemalyunis@yahoo.com
Tel: +9647801255033

Abstract – The synthesis, characterization and physical properties of 2,3,5,6-tetraphenylpyrazine-*N,N*-dioxide presently are reported. A specific reduction mechanism of an oxime using zinc with NH_4Cl to yield hydroxylamine was performed. This was followed by a condensation reaction with sulfuric acid that leads to 2,3,5,6-tetraphenylpyrazine-*N,N*-dioxide. The product was characterized by means of IR, UV, ^{1}H-NMR and ^{13}C-NMR spectroscopy which were complemented by theoretical computations.

INTRODUCTION

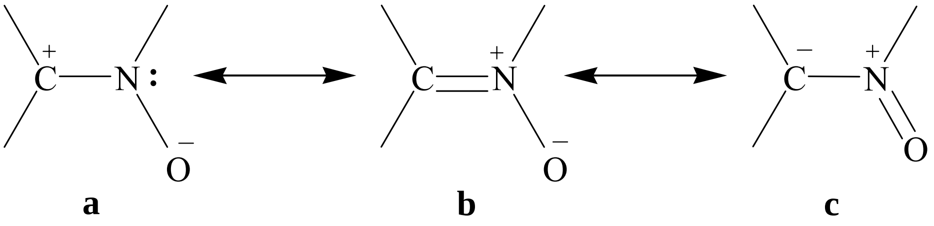
The chemistry of *N*-oxides has been the focus of research in several years.[1] A wide range of mono, di and tri substituted derivatives of *N*-oxides have been prepared and physically characterized. The majority of these are isolated colorless solids or oily compounds. It soon became known that the color solids produced were aliphatic. On the contrary, the oily compounds were indeed aromatic. Further IR measurements demonstrate the existence to different forms of *N*-oxide.[2,3] The isomeric forms synthesized are identical to the *cis* and *trans* alkenes. In relation to the *N*-substituted aldimines, the structure a in Scheme 1 (R^2 = H, X = alkyl or aryl) has the hydrogen atom on the same side of the double bond as the *N*-substituent which is thermodynamically more stable. This is designated as the anti isomer and the other configuration (Scheme 1b, R^2 = H, X = alkyl or aryl) is the less stable *syn* isomer.[2]



(R^2 smaller than R^1)

Scheme 1

The nitrone structure is traditionally viewed as a resonance hybrid of three canonical forms[4, 5] depicted in Scheme 2. The most significant form (based on reactivity) is the extended carbonyl structure a. The nitrones should be subject to electrophilic attack at the oxygen atom and nucleaphilic attack at the carbon atom as is observed in the laboratory.



Scheme 2

Solutions of many organic *N*-oxide compounds (R – C = N→ O) in organic solvents leads to interesting behavior. In these solutions the (N → O) group is bonded to a carbon atom which depends on the nature of the organic group (R), temperature and concentration.[6]

Scant spectroscopic information on the internal nitrone group in comparison to the external nitrone group[7] is available. In this work, we have prepared and analyzed the UV, IR and NMR spectra of 2,3,5,6-tetraphenylpyrazine-*N,N*-dioxide.

The favored preparative protocol of 2,3,5,6-tetra phenyl pyrazine *N,N*-dioxide involves the condensation of 2-hydroxybenziloxime with sulfuric acid as a catalyst. This reaction is based on converting the benzil to benzildioxime then finally to 2-hydroxylamine benziloxime by a reduction scheme using zinc powder and NH_4Cl.

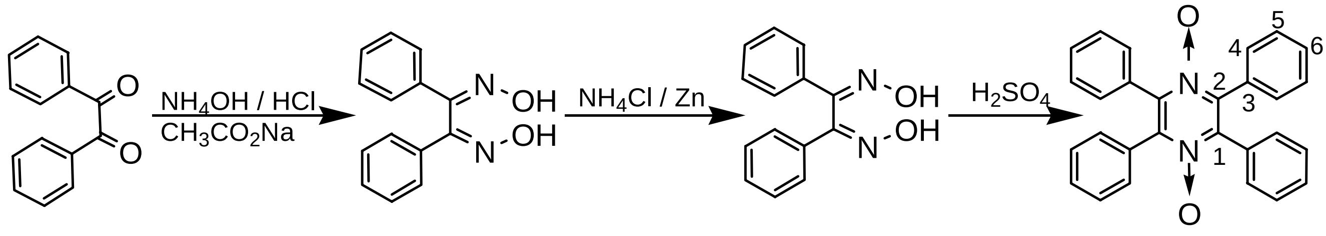
Recent spectroscopic evidence on substituted aromatic *N*-oxide compound has yielded information on the effect of substitution nitrone.[8] The ground and excited electronic states for both isomers of the nitrone were identified from absorption spectra. What is interesting to note is the determination of the nature of the bonding forces in the cis structure. This was performed to gain further insight into the rate of trans formation.

Various methods have been reported regarding the synthesis of aliphatic or aromatic *N*-oxide compounds.[9-11] Related species of this type were prepared by photolysis and oxidation of aldehydes or ketones. Compounds resulting from such a procedure are identified as aldonitrones or kitonitrones respectively.

The utility of hydroxylamine oxime condensation for the synthesis of nitrone (*N*-oxide) is not impaired by its susceptibility to steric hindrance.[12] This approach is exemplified by a standard method for the synthesis of cyclic nitrone, and has been used with particular success for the general synthesis of the synthetically important pyroline-*N*-oxide.

RESULTS AND DISCUSSION

The synthesis of 2,3,5,6-tetraphenylpyrazine-*N,N*-dioxide is represented in Scheme 3. The preparative formation of an oxime is well known.[13] Poor yields were obtained with sodium acetate in the diketone, and we found it utile to compare this to the ketone. We obtained over 86% yields of oxime by using this method. The reduction of dioxime carried out by the addition of freshly zinc powder to the mixture of 1,2-diphenylethane-1,2-dionedioxime and NH_4Cl was successful.



1 **2** **3**

Scheme 3

Acid catalyzed condensation with carbonyl compounds has been reported to result in the formation of imidazole oxide derivatives.[14,15] The acid catalyzed condensation occurs when hydroxylamine oxime is treated with concentrated sulfuric acid. This reaction may involve the elimination of the hydroxylamine along with an accompanying oxidation mechanism (the major product is the pyrazine-*N,N*-dioxide (R_f = 0.32)).

N-oxide is a white crystalline compound that dissolves in $CHCl_3$ and acetone solvents. This compound does not yield isomers in an aqueous acidic or basic medium. In contrast to the aromatic *N,N*-dioxide, the whole aliphatic nitrones revealed no tendency to dimerize.[16] The relative stability of pyrazine-*N,N*-dioxide may therefore be related to conjugation with the aromatic rings. The stabilization of the 1,2-ethanedinitrone N(O):CH.CH:NO group occurs only when the aromatic rings can become coplanar with it.[17] However, the nature of the dimerization oxidation remains to be explored.

Elimination of hydroxylamine oxime (preformed by a suitable condensation reaction) leads to a crucial step in a number of synthetic methods leading to nitrone. Perhaps the simplest and most general method of this type is an extension of oxime formation by hydroxylamine oxime condensation. Nitrone formation from a simple aromatic ketone is uncomplicated by the tendency of the product to undergo subsequent dimer condensations.

The existence of synthesized molecules in either solution or solid state can be verified by electronic and infrared spectra. In the current report, the electronic spectra were recorded at rt and exhibit two bands. The first transition band (π- π^*) is accounted to the double bond of an aryl residual but the other transition (π - π^*) is ascribable to an *N*-oxide group.

The substance was assigned to the dinitrone (*N,N*-dioxide) structure based on spectroscopic evidence.[8] The value observed on the UV absorption maximum at 249 nm for the mono group is comparable to the value of the di group which reaches a maximum of 295 nm (i.e 1,2-ethanedinitrone).[8]

Many groups[8, 18] have assigned the N-O stretching frequency in the 1100-1300 cm^{-1} range as a strong band. This IR assignment is based on the R group attached at imine group site.

The characteristic band in infrared spectrum of the pyrazine-*N,N*-dioxide compound at 1558 and 1228 cm^{-1} indicates the presence of the C=N and N-O groups respectively. The elemental composition suggests the absence of two carbonyl groups and hydroxyl groups in the dimer species.

The ^1H NMR spectrum exhibits two resonance regions 7.5 and 6.7 ppm, the first region of resonance signals due to the proton of aromatic ring, which was analogous in chemical environment. The other region is caused by $CDCl_3$ solvent.

^{13}C NMR spectroscopy has provided important information on the nature of the *N*-oxide compounds, that yielded six lines. Four lines were generated by carbon atoms of the aromatic ring in addition to the two lines of the cyclic pyrazine.[19] The remainder of the lines were attributed to the $CDCl_3$ solvent.

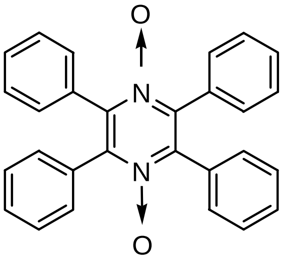
The geometry of the six membered ring of the pyrazine-*N,N*-dioxide implies that the steric hindrance of the nitrone group be reduced. This effect is lower when compared with that for the hindrance observed in nitroso benzene.[20]

COMPUTATIONAL STUDY

Some electronic details about the system considered is given in Table 1. The geometry optimization at the AM1 and PM3 methods yields a non-planar structure as the stable form with C1 symmetry for 2,3,5,6-tetraphenylpyrazine-*N,N*-dioxide.

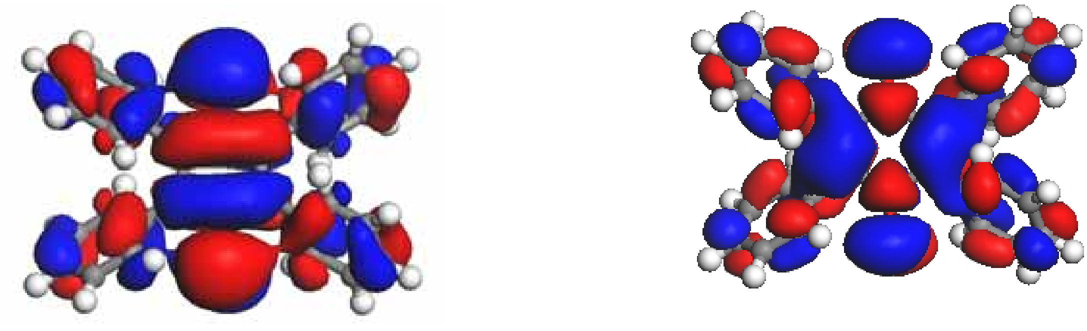
The calculated frontier bonding molecular orbitals (MO) of 2,3,5,6-tetraphenylpyrazine-*N,N*-dioxide (HOMO shown in Figure 1) is largely localized on the N→O fragment. The electronic character of 3 is also of interest with respect to its reactivity, especially towards nucleophilic agents such as olefins.

Table 1. Physical properties of 2,3,5,6-tetraphenyl pyrazine-*N,N*-dioxide.



Quantity	Values		
	AM1	PM3	DFT
No. of electrons	154	154	218
No. of doubly occupied levels	77	77	109
No. of total orbitals	148	148	328
No. of primitive gaussians	-	-	540

The calculated LUMO (electron acceptor orbital) of 2,3,5,6-tetraphenylpyrazine-*N,N*-dioxide is seen to be substantially localized along the C-C axis of the pyrazine unit (Figure 1). Overall, the net positive charge is calculated to be greatest at the nitrogen atom (+0.4). Complex 3 could thus be anticipated to act as an *N*-centered electrophile. This means that the nitrone groups undergo cycloaddition reactions with alkenes, a phenomenon observed in many practical reactions.[20,21]



HOMO **LUMO**

Figure 1. DFT-calculated 3D HOMO (-0.158708eV) and LUMO (-0.074850eV) of 2,3,5,6-tetraphenylpyrazine-*N,N*-dioxide

Isosurface of the electrostatic potential (ESP) for the molecule is shown in Figure 2. Dark (green) colors indicate negative ESP regions and light (violet) colors indicate positive ESP regions. These figures represent how the oxygen atoms have more negative ESP regions in comparison with other atoms. This signifies that oxygen atoms undergo protonation reaction with acidic reagents.[22]

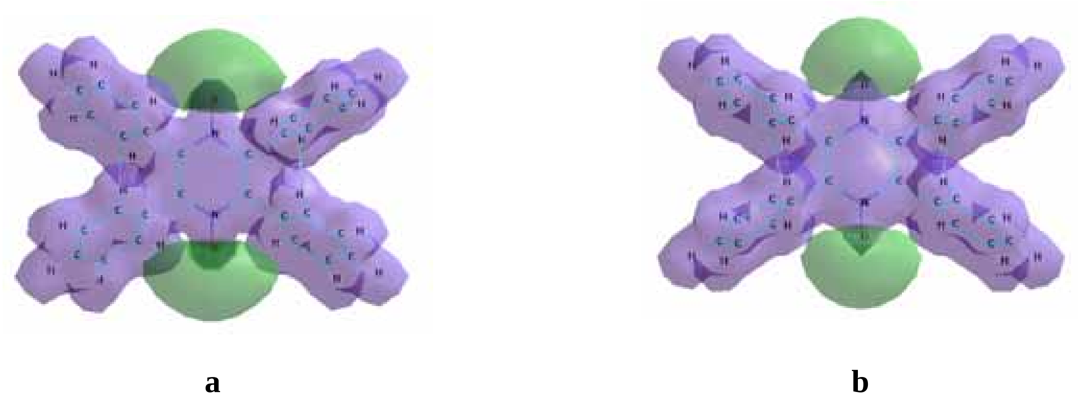


Figure 2. Isosurface of the electrostatic potential in the spatial vicinity of the 2,3,5,6-tetraphenylpyrazine-*N*,*N*-dioxide. a: AM1 b: PM3 levels of theory.

EXPERIMENTAL

2.1. Preparation of 1,2-diphenylethane-1,2-dionedioxime compound **1**.

Dissolve (0.7 g, 0.02 mol) of hydroxylamine hydrochloride and 4 g of crystallized sodium acetate in 10 mL of water in a small flask, warm the solution to about 40 °C and added (2.1 g, 0.01 mol) of benzil. Stopper the vessel securely with a cork and shake vigorously for a few minutes. The dioxime soon separates as a crystalline solid, cool in ice and filtration. Wash with a little cold water. Re-crystallize from light petroleum. mp 236-237 °C (decomp). (lit.,[23] mp 238 °C).

2.2. Preparation of 2-Hydroxyamino-1,2-diphenylethanonoxime compound **2**.

To a solution of EtOH (100 mL) in water (10 mL) was added 1,2-diphenylethane-1,2-dionedioxime (1.2 g, 0.05 mol) and NH_4Cl (1.4 g, 0.02 mol). While the mixture was stirred, freshly activated zinc powder (10.2 g) was added over 15 min. (the temperature rise to 45 °C). After 1 h solution was filtered and treated with acetic acid to give the crystalline acetic acid salt, which could be readily regenerated to the free white crystals of 2-hydroxyamino-1,2-diphenylethanonoxime mp 147-148 °C.

2.3. Preparation of 2,3,5,6-tetraphenylpyrazine- *N*,*N*-dioxide **3**.

A finally crystals sample of 1.5 g 2-hydroxyamino-1,2-diphenylethanonoxime was introduce in a small portions at a time to 10 mL of concentrated sulfuric acid at 0 °C with mechanical stirring. The slurry was gradually warmed to ambient temperature and allowed to stir for 36 h, made basic with 2N NaOH solution and extracted several times with EtOAc. Wished with light petroleum, afforded yellow oil compound. Recrystallized from $CHCl_3$. A white crystal of product was obtained. mp 262-264 °C. Elemantal analyses: Anal. Calcd for $C_{28}H_{20}N_2O_2$: C, 80.77; H, 4.81; N, 6.73%. Found: C, 81.15; H, 4.28; N, 7.22%. Ultraviolet absorption in $CHCl_3$ λ_{max} 297 and 252 nm. Infrared absorption (KBr, cm^{-1}) 3001 (CH), 1641(C=C), 1558 (C=N), 1228(N-O), 1097(C-N). ^1H NMR (400 MHz, $CDCl_3$) δH (ppm) 7.5s

(5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (ppm) 146 C1, 135 C2, 127 C3, 125 C4, 124 C5, 126 C6.

2.4. Spectrophotometric measurement

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer, 400.13 MHz for proton and 100.13 MHz for carbon, in $CDCl_3$ as a solvent. Infrared spectra were recorded on a Shimadzu FTIR model 8400. Ultraviolet spectra were recorded on a Spectro Scan 80D UV-Visible Spectrophotometer. Finally, CHN analysis was carried out on Shimadzu 8011.

2.5. Computational Methods

Geometry optimizations were carried using a conjugate gradient method (Polak-Ribiere algorithm)[24] by applying the semi-empirical molecular orbital (MO) theory at the level of Austin Model 1 (AM1) and the PM3 model[25,26] within the restricted Hartree-Fock (RHF). The convergence has been set to 0.001 kcal mol^{-1}. The AM1 and PM3 computations have been done on the hyperchem release 7.5 for Widows[17] running on Windows XP Workstation in Pentium IV PC.

All of the Density Functional Theory (DFT) electronic structure calculations were performed using the DMol[25-28] numerical-based density-functional computer software implemented in the Materials Studio Modeling 3.1 package from Accelrys, Inc. Geometrical optimizations and frequency calculations were carried out with the B3LYP general-gradient potential approximation in conjunction with the double-numerical plus diffusion basis set (all-electron core treatment) was employed (denoted as DND). The calculations were performed with an SCF tolerance level of 1.0 X 10^{-6} and global orbital cutoffs of 5.5 angstroms.

ACKNOWLEDGEMENTS

The authors are grateful to Prof. B. G. Gowenlok, School of Chemistry, University of Exeter, for carrying out the NMR spectra.

REFERENCES

1. a) L. I. Smith, *Chem. Rev.*, 1938, **23**, 193. b) R. C. Brown "*N*-Oxide and Nitrones in Organic Chemistry of Aliphatic Compound," Oxford Clarendon Press, Oxford, 1994, **28**, 260.
2. C. G. McCarty, "The Chemistry of the Carbon-Nitrogen Double Bond," ed. by S. Patai, Wiley Interscince, New York, 1970, Chapt. 9, pp. 363-464.
3. J. Hamer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 474.
4. E. Breuer, "The Chemistry of Amino, Nitroso and Nitro Compound and Their Derivatives," ed. by S. Patai, Wiley Interscince, New York, 1982, **1**, 459.

5. G. R. Delpierre and M. Lamcher, *Quart. Rev.,* 1965, **19**, 329.
6. S. Franco, F. L. Merchan, P. Merino, and T. Tejero, *Synth. Commun*., 1995, **25**, 2275.
7. A. Dodoni, S. Franco, F. Junquera, F. L. Merchan, P. Merino, and T. Tejero, *Synth. Commun*., 1994, **25**, 2523.
8. A. F. Abbas, MSc Thesis, University of Basrah, 2002.
9. S.-I. Murahashi, *Angew. Chem., Int. Ed. Engl*., 1995, **34**, 2443.
10. K. A. Kandeel and A. S. Youssef, *J. Molecules*, 2001, **6**, 512.
11. T. L. Feving, S. M. Bowen, D. A. Janowick, B. K. Jones, H. R. Munson, D. F. Ohleweiler, and E. T. Design, *J. Med. Chem*., 1976, **36**, 4988.
12. D. St. C. Black and A. B. Bascacci, *Aust. J. Chem*., 1996, **29**, 2561.
13. Vogel's "Text book of Practical Organic Chemistry," 3rd ed., Longman, NewYork, 1974, **45**.
14. L. B. Volodrski and Y. G. Pntakin, *Tetrahedron Lett* , 1968, **9**, 1067.
15. M. L. Scheinbaum, *J. Org. Chem.,* 1970, **35**, 2790.
16. J. E. Baldwin and N. Rogers, *Chem. Commun.,* 1965, **1**, 425.
17. M. Lamchen and T. W. Mittag, *J. Chem. Soc.* (C), 1966, 3300.
18. L. A. Al-Rubaie, M.Sc, Thesis, University of Basrah, 1999.
19. E. Ochiai, "Aromatic Amine Oxide," Elsevier, New York, 1967, 425.
20. T. K. M. Shing, W. F. Wong, T. Ikeno, and T. Yamada, *Org. Lett*., 2007, **9**, 227.
21. T. Kano, T. Hashimoto, and K. Maruoka, *J. Am. Chem. Soc*., 2005, **127**, 11926.
22. D. A. Fletcher, B. G. Gewenlock, and K. G. Orrell, *J. Chem. Soc., Perkin Trans. 2,* 1998, 797.
23. J. D. Brady and S. F. Muer, *J. Chem. Soc*., 1967, 220.
24. C. C. J. Roothaan, *Rev. Mod .Phys*., 1951, **23**, 69.
25. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc*., 1985, **107**, 3902.
26. W. Thiel, *QCPE*, 1982, **63**, 438.
27. Hyperchem TM release 7.52. Windows Molecular Modeling System, Hypercube, Inc. and Autodesk, Inc. Developed by Hypercube, Inc.
28. B. Delley, *J. Chem. Phys.,* 1990, **92**, 508.