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N-Dealkylation of Dialkylanilines: Role of Oxidizing Agents on Product Selectivity

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Abstract

Large varieties of pharmaceuticals metabolize involving dealkylation of their important functional groups. N Dealkylation of Tertiary amines is one of the most important biochemical processes of Cytochrome P-450, which play major role in Drug metabolism. Efficiency of pharmaceutical compounds depends on their metabolic patterns inside the body. Development of newer and better drugs requires understanding of their metabolism under different reaction conditions. Having keen interest in study of N-Dealkylation process, We are herein reporting investigation into the role of oxidising species on N-Dealkylation of dialkyl anilines, NN Dimethylaniline (NDMA) and NNdiethylaniline (NDEA) with metal complexes as catalyst Dialkylanilines gave corresponding N-dealkylated and monoxygenated compounds as products with molecular oxygen as oxidizing agent. Replacement of molecular oxygen with Tetraethyl ammoniumperiodate (TEAPI) as oxidant using same set of reactions, gave N- alkyl formanalide as major product. TEAPI shifted the selectivity of products towards the mono oxygenated product as compared to molecular oxygen. TEAPI facilitates oxygen atom transfer to the substrate and tilts the product selectivity towards N-alkyl formanalide formation

Keywords

Dealkylation, Metal Complex, TEAPI, Molecular Oxygen

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1. Introduction

Dealkylation of tertiary amines is a biologically as well as commercially important process [1-4]. It plays a significant role in crude oil refining [5]. Dealkylation is also used for production of pharmaceuticals for human as well as animal consumption [6]. Large varieties of pharmaceuticals metabolize involving dealkylation of their important functional groups [7-8]. Almost 70% of drug metabolism in our body, is carried out by cytochrome P-450 enzymes [8], N-dealkylationbeing one of the most significant and vitalreaction involved due to its apparent ease. [9-11]. Dealkylation of tertiary amines finds direct application in design and study of metabolism of drugs and this process is at the key focus of many researchers [12]. The dealkylation of different tertiary amines using metal complexes as catalysts in presence of different oxidants, has been reported already While the role of the the metal complexes in product formation and efficiency of the reaction has been thoroughly investigatedl [13-14]. The role of oxidizing species and their influence on the product formation has not been reported so far.

Investigation into the role of oxidizing species on N-Dealkylation of dialkyl anilines, NN Dimethylaniline (NDMA) and NNdiethylaniline (NDEA) with metal complexes as catalyst is being reported here..

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2. Method and Materials

Tertiary amines, NN Dimethyl aniline (NNDMA) andNNDiethyl aniline (NNDEA), were purchased commercially and purified before use. [15] Solvents acetonitrile, benzene, and ethyl acetate were also purified before use. Other reagents i.e. 2,6-di-*tert*-butyl-4-methylphenol, butyl vinyl ether, sodiumperiodate, and tertraethylammonium bromide were obtained from commercial sources and used directly.

2.1. Synthesis of Tetraethyl Ammonium Periodate (TEAPI)

TEAPIwas synthesised by stirring a solution of tetraethyl ammonium bromide (2.1g in 5ml H_2O) with sodium periodate solution (2.1g in 20ml water) for half an hour. The precipitate obtained was filtered, washed and dried thoroughly over phosphorous pentoxide. [16]

$$(C_2H_5)_4NBR + Na10_4 \rightarrow (C_2H_5)_4N10_4 + Nabr.)$$

The substituted metalorphyrin complexes, having electronegative substituents at the β-pyrrole position and O-phenyl position Viz; metal (octabromo-terraphenylporphyrin, M(OBP)Cl), 2,6, dichloro tetraphenylporphyrin (M(2,6,ClTPP)Cl) and octachlorooctabromo-tetraphenylporphyrin M(OCOBP)Cl), were prepared using a modified literature procedure. [17-18]. Products of dealkylation were characterized by spectroscopic methods like NMR and Mass spectroscopy along with routine analytic techniques.

2.2. Procedure for N-Dealkylation

Dealkylation reaction using molecular oxygen and TEAPI as oxidants were carried out by using our previously reported procedures [14]. In a typical procedure, 5mmols of Tertiary amine (NNDMA, NNDEA) and 10 mmol of TEAPI oxidant [Molecular oxygen], was taken in 10 ml of acetonitrile in a round bottomed flask, fitted with reflux condenser. 0.01 mmol of catalyst [Fe (OBP) Cl], [Fe(OCOBP) Cl] [Fe(2,6,Cl,TPP) Cl] was added to reaction mixture. The Contents were refluxed at 60° for 7 hrs. Aliquots were taken out periodically to check consumption of starting material using pre-heated TLC plates till reaction was complete. The solvent was removed and remaining solution subjected to column chromatography over silica gel. Benzene and Ethylacetate were used as eluants. In a typical method for product separation, using TEAPI as oxidant, only benzene was used at the beginning of the process, when a yellowish oily substance eluted out first which was identified as N-methlyformanalide (m-p. 240°C). Further elution with benzene resulted in the separation of yellow brownish gum, which remained unidentified. The column was then eluted with a 90:10 V/V mixture of benzene, ethylacetate when a reddish brown solution started eluting out. Solvent evaporation left behind a brownish oily substance (b.p. 194°). It was found to contain mainly N-methlyl aniline. Unreacted NNDMA eluted out at the end. Besides the above products an unidentified sticky mass was also obtained when the column was eluted with a 60:40 mixture of benzene ethylacetate. This mass failed to crystallize and could not be purified hence remained uncharacterized. The yield of this unidentified product was extremely low.

The experimental procedure using molecular oxygen as oxidant was same as described above. The product obtained were characterized by spectroscopic (H' NMR, using JOEL-JNN-EX-90; and Mass spectroscopy using JOEL, DX-300 analyser) and analytical methods. Elemental analysis using carlo-ERBA equipment. Wherever required products were compared with authentic samples as well.

2.3. Dealkylation Reaction in Presence of Additives

Effect of additives like 2,6 ditertertiary. butyl- 4 methyl phenol and butyl vinyl ether on the product formation was studied, by adding 1mmol of the additive to the reaction mixture containing 10 mmol of substrate with 0.001 mmol of catalyst and oxidant (molecular oxygen /TEAPI) and refluxing the same for ten hours. The products were subjected to column chromatography and analyzed by spectral analysis.

3. Results

The products obtained from dealkylation reaction of NNdimethyl aniline and NN diethyl aniline using molecular oxygen andTEAPI as oxidant are given in Tables 1 and 2 respectively.

Table 1. Oxidative dealkylation of NN-dialkylaniline with molecular oxygen.

S.No	Catalyst	Product (m mol) *			
		2	3	4	5
A. NNDMA					
1	Fe(OCOBP) Cl	2.80	2.1	0.20	1.070
2	Fe (2,6,Cl_2TPP) Cl	1.6	1.40	0.40	0.95
3	Fe (OBP) Cl	2.89	2.06	0.625	0.9
4	Fe(OBP)Cl[a]	Nil	-	Nil	Nil

S.No	Catalyst	Product (m mol) *			
		2	3	4	5
5	Fe(OBP) Cl[b]	2.81	2.00	0.52	0.85
B. NNDEA					
	Fe (OCOBP) CL	1.10	1.3		
	Fe (2,6 Cl TPP) Cl	1.21	1.8		
	Fe (OBP) CL	1.19	2.4	Yellow oily mass	

5 mmol amine with 10 ml Acetonitrile in Molecular oxygen, refluxed at 60° for 10hrs.
[b]Reaction in presence of 2,6, di ter. butyl 4methyl phenol.

NNDMAgave*N*-methyl aniline (2), *N*-methylfomanilide (3) asmajorproduct, and *N*-(4-dimethylaminobenzyl)-*N*-methylaniline (4) and 4-4'-methylene bis(*NN*-dimethylaniline) (5) as minor products. The latter too products are formed as a result of dimerisationreaction. (Figure 1)

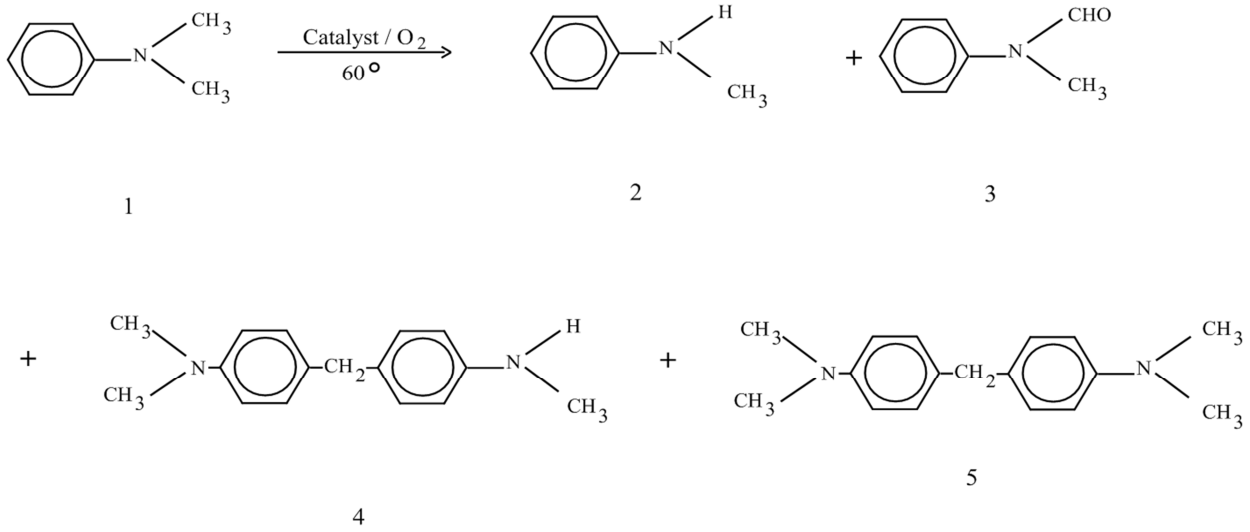

Figure 1. Dealkylation of NNDMA using Molecular oxygen.

NNdiethyl aniline gave corresponding de-ethylated compounds as products when subjected to dealkylation under similar reaction conditions. The yield of products formed shows variation as the catalyst is changed from less halogenated catalyst complex to more halogenated complex.

When TEAPI was employed as oxidizing agent NNDMA and NNDEA produced the corresponding monodealkylated and mono-oxygenated compounds as major products (Table 2, Figure 2). A brownish residue, which remained unidentified, was also observed in some reactions. Change of the catalyst effected the yield of products formed in these reactions as well. The yield of products improved as we move from a less halogenated catalyst to more halogenated one. In the same manner as observed in case of reactions carried out in presence of molecular oxygen. When the reaction was carried out in the absence of the catalyst complexes, while the remaining conditions were unaltered, no significant product formation could be observed, even after 10 hrs. of reaction.

Table 2. N-Dealkylation of Tertiary amines with TEAPI.

S.No	Substrate	Catalyst	Product mmol		
			2	3	other
		Fe (OBP) Cl	1.0	3.5	
1.	NNDMA	Fe (OCOBP) Cl	1.8	2.6	Yellowish brown unidentified
		Fe (2.6 Cl TPP) Cl	1.1	2.0	
2.	NNDMA*	Fe (OBP) CL	1.1	3.1	
3	NNDMA**	No catalyst	--	--	Trace of sticky mass.
		Fe (OBP) CL	1.1	2.8	
3.	NNDEA	Fe (OCOBP) CL	0.9	1.9	Yellow oily mass
		Fe (2,6 Cl TPP) Cl	1.0	1.8	

5 mmol amine + 10 mmol TEAPI in 10 ml Acetonitrile refluxed at 60° for 7hrs.
*Reaction in presence of 2,6, di ter. butyl 4methyl phenol

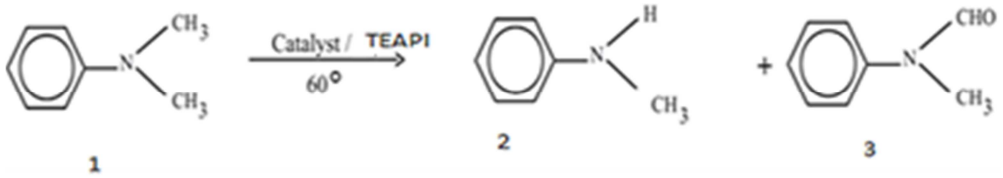

Figure 2. Dealkylation of NN Dimethylaniline using TEAPI.

4. Discussion

The results show the important role-played by catalysts in the process under investigation. The Comparative data of the products obtained from various reactions is given in Table 3.

Comparison of two sets of dealkylation reactions with respect to oxidizing agent used, led to observation that under similar reaction conditions NNDMA gave N-methyl aniline(2), N-methyl formanalide and traces of dimerised products 4 and 5 as products with molecular oxygen as oxidant while as replacement of molecular oxygen with TEAPI shifted product selectivity towards N-methyl formanalide (3) as major product along with N- methyl aniline(2). This shift in product selectivity towards product 3 was observed with other sets of reactions as well. This observation suggests that oxidizing species plays an important role in reaction mechanism and influences product formation. Table 3 TEAPI facilitates transfer of oxygen atom to the substrate molecule.

Table 3. Comparative study of products of dealkylation of NNDMA with Molecular oxygen and TEAPI.

S.No.	Oxidant used	Catalyst used	Products (mmols)			
			2	3	4	5
1	TEAPI	Fe (OBP) Cl	1.0	3.5	_	_
		Fe (2,6,Cl_2TPP) Cl	1.1	2.0	_	_
		Fe (OCOBP) Cl	1.8	2.6	_	_
2	Molecular Oxygen	Fe (OBP) Cl	2.89	2.06	0.625	0.9
		Fe(OCOBP) Cl	2.80	2.1	0.20	1.070
		Fe (2,6,Cl_2TPP) Cl	1.6	1.40	0.40	0.95

Oxidativedealkylation of tertiary amines by cytochrome P-450-dependentmono-oxygenase is either initiated by a one-electron transfer process from the tertiary amine to the active oxidizing species{ET}[19-20]] or by hydrogen atom abstraction of the amine by oxidant as reported{HAT} in some reactions. [21]. Figure 3

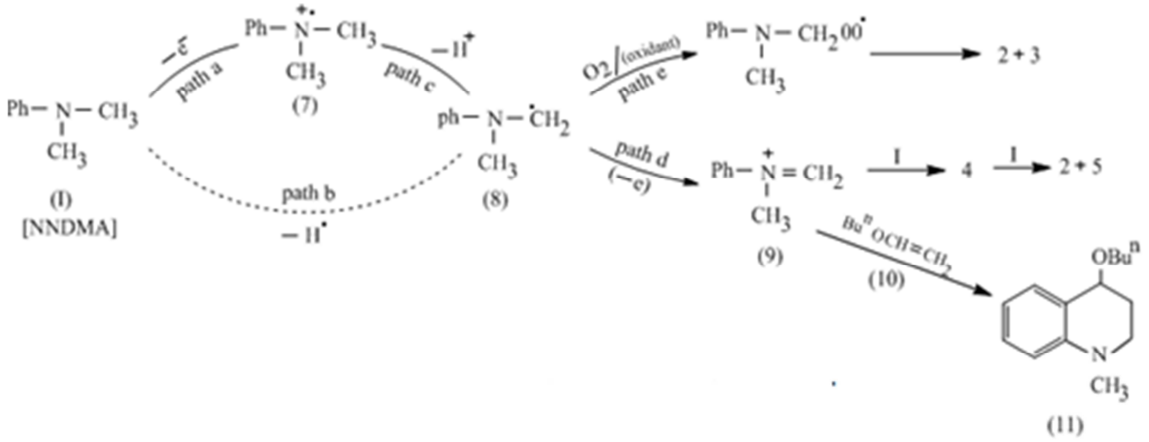

Figure 3. Mechanism of N-dealkylation of Tertiary amines.

Based upon the investigation of the reaction of NNDimethyl aniline in presence of of 2, 6-di-*tert*-butyl-4-methyphenol and *Butyl Vinyl Ether*. We have suggested one electron transfer route as the most preferred mechanism [14]. This is due to the fact that there is no significant change in product formation in presence of 2, 6-di-*tert*-butyl-4-methyphenol which is a hydrogen atom abstractor it rules out hydrogen atom abstraction pathway of mechanism. The proposed mechanism and involves a one-electron oxidation of the tertiaryamine I to give an iminium cation radical 7 (Path a). [21, 22]. The cation radical loses a proton to produce radical 8 (Path c). The radical 8 reacts with the oxidant TEAPI/oxygen (Path e), resulting in the formation of oxygenated radical, which accounts for the formation of products 2 and 3. The formation of the dealkylated product 2 has also been explained in a previous study [21] via an

alternative route (path-d). The radical 8 loses an electron to form imminium cation 9 which in turn forms bases of formationdimerised products 4 and 5. The shift in product selectivity towards monoxygenated product Nmethyl formanilide, in presence of TEAPI as oxidant, suggests that TEAPI facilitates transfer of oxygen to the substrate which results in formation of product 3. Molecular oxygen on the other hand, facilitates the formation of radical 9 which in turn forms bases of formation of dimerised products 4 and 5. As shown in Figure 3.

5. Conclusion

The aforementioned results show that:-

Molecular oxygen efficiently oxidizes tertiary amines to N-dealkylated and monooxygenated products.

TEAPI shifts the product selectivity towards monooxygenated product due to easy transfer of oxygen to substrate molecule. Use of selective oxidizing species can be exploited to get desired products under controlled reaction conditions. The comparative study is helpful in having a deeper insight into this biologically important reaction. Comparison of this process with other oxidizing species is under investigation.

References

[1] N. Kasi, M. SookSeo, K. Jinheung, N. Wonwoo, *Inorg. Chem*. 2007, 46, 293−298.

[2] C. Walch. *Enzymatic Reaction Mechanism*, Freeman CO., San Fransisco, 1979.

[3] N. Murugesan, S. M. J. Hecht, *Am. Chem. Soc.* 1985; 107: 493–500.

[4] A. de. Klerk*, Fischer Tropsch Refining, John Wiley* 2012.

[5] J. P. Speight *Environmental Organic Chemistry for Engineers, Chap. 3* Butterwork Heinmann (Elsevier) 2017.

[6] J. H. Cooley, E. J. Evain, *Synthesis* 1989, 1 (and the references therein). doi: 10.1055/S-1989-27129.

[7] L. Que, R. Y. N. Ho, *Chem. Rev.* 1996, *96*, 2607. doi: 10.1021/CR960039F.

[8] F. P. Guengerich. *Chem. Res. Toxi.* 2008; 21: 70–83.

[9] H. Dong, R. L. Helning, E. L. Thummel, AE, Rettle, S. D. Nelson, *Drug Matabolism and Deposition* 2008; 28: 1397–1400.

[10] R. E. McMohan. *J. Am. Pharm. Assoc.* 1947; 55: 267–271.

[11] M, Stilborova, H. H. Shmeiser E. Frei. *Phytochem.* 2000; 54: 353–362.

[12] R. S. Mane, B. M. Bhange, J. Org. Chem. 2016, 81 (12), 4974-4980.

[13] D. Bhat, N. Sharma*, Aust. J. Chem.* 2017, *70*, 233–236.

[14] D. D. Agarwal, D. Bhat, *J. Porphyrins Phthalocyanines* 2016, 20: 689–693.

[15] A. I. Vogel, *Text Book of Practical Organic Chemistry* 1978.

[16] D. Bhat, *Asian Chem. Lett.* 2006, *10*, 157.

[17] P Bhyrappa, V. Krishnan. *Inorg. Chem*. 1991; 30: 239.

[18] V. Krishana, D. D. Agarwal, G. Bhayrappa, R. Rastogi, *Indian J. Chem., Sect. A: Inorg., Phys., Theor. Anal.* 1998, *37*, 918.

[19] R. P. Hanzlik, R. H. Tullman, *J. Am. Chem. Soc.* 1982, *104*, 2048. doi: 10.1021/JA00371A055.

[20] T. L. Macdonald, K. Zirvi, L. T. Burka, P Peyman, F. P. Guengerich, *J. Am. Chem. Soc.* 1982, 2050. doi: 10.1021/JA00371A056.

[21] J. R. Lindsay Smith, D. N. Mortimer, *J. Chem. Soc., Perkin Trans. 1*1986, *2*, 1743. doi: 10.1039/P29860001743.

[22] F. P. Guengerich, T. L. Macdonald, *Acc. Chem. Res.* 1984, *17*, 9. doi: 10.1021/AR00097A002.