



Feasibility of Room Temperature Reduction of Aromatic Carbonyl and Nitro Compounds by Zn/dil. HCl-Et₂O System: An Experimental and DFT Study

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This experimental study is about the feasibility of the room temperature reduction of the ether soluble aromatic carbonyl/nitro compounds by atomic hydrogen. The atomic hydrogen is produced by the novel Zn/dil. HCl-Et₂O reducing system (wherein dil. HCl is slowly added to the ethereal solution of Zn and substrate). This study resulted in single or mixture of anticipated reduced products in different yields. The DFT study with B3LYP/6.311g++ (d,p) basis set revealed that the stability of the first formed free radical (energy factor) and the homo nuclear nature of the carbonyl and nitro group (charge factor) decide the yield. It is also found that the presence of -M group at *o*- or *p*- position to the carbonyl/nitro group results in the favourable modification of above-mentioned factors. The above-mentioned factors also explain the preferential reduction of nitro group when it is present along with carbonyl group. The free radical mechanism was confirmed by the formation of pinacol coupled product in one instance. In one of the reduction reactions, an unreported compound *viz.* the dimer of *o*-amino benzaldehyde was obtained in good yield.

Keywords: Charge factor, Energy Factor, Homonuclear, Pinacol coupling, Atomic hydrogen.

INTRODUCTION

Reduction is one of the frequently used reactions in organic synthesis and a vast variety of reducing agents have been introduced for this achievement [1]. The reduction of nitro compounds is of paramount importance for the preparation of amino derivatives in the organic synthesis. The synthesis and biological evaluation of aromatic amines are also active and most important areas of research and their chemistry by derivative formation is widely studied [2,3]. Likewise, the conversion of carbonyl compound to alcohol or alkane is important in pharmaceutical industries as the transformation changes the hydrophilicity of the compound. A plethora of reducing agents is available for the reduction of aromatic carbonyl/nitro compounds, some reagents claim to be chemo selective [4-10].

There are many reducing agents reported in the literature for the reduction of carbonyl/nitro group, but a non-catalytic reagent, which can perform the task at room temperature with simple work up technique and with commonly available non toxic chemicals, have not been reported. The solvent chosen was ether, as it is easily recoverable and suitable for room temperature reaction and dissolves most of the organic compounds.

Zn/dil. HCl-Et₂O system is a commonly available reducing system, capable of slow *in situ* generation of hydrogen. The excess of zinc can be filtered and reused. At room temperature

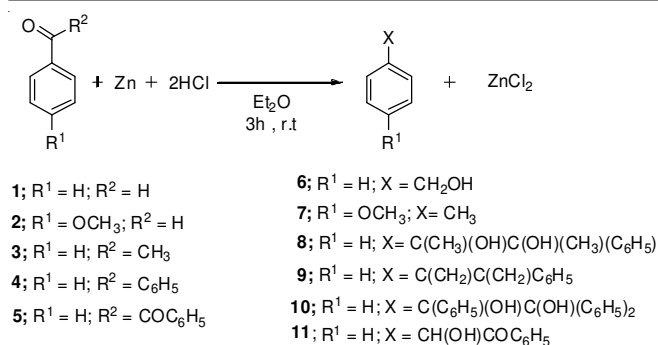
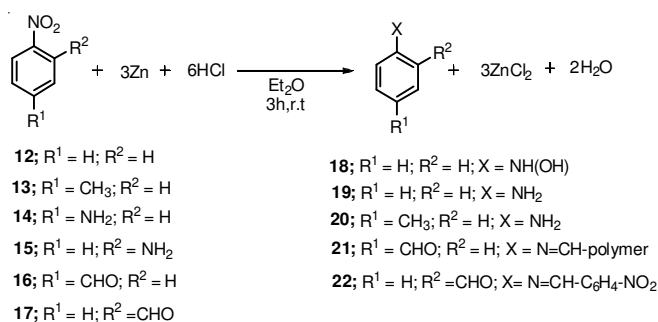
the velocity of the liberated hydrogen gas can be controlled, by controlling the rate of addition of the dil. HCl to the Zn suspension in the organic phase.

The aims of the investigation, are to study the feasibility of room temperature reduction of the ether soluble aromatic carbonyl and nitro compounds by Zn/dil. HCl-Et₂O system, to explore the theoretical reasoning for the experimental results by performing DFT study of the energies of the geometry optimized structures of the substrates and the possible free radical intermediates and to suggest a plausible mechanism for the reduction of aromatic carbonyl and nitro compounds by Zn/dil. HCl-Et₂O system.

EXPERIMENTAL

The general schemes for the reduction of aromatic carbonyl and nitro groups by the Zn/dil. HCl-Et₂O system are given in **Schemes I** and **II** respectively and the details of the various products formed are given in Table-1.

All the reagents and substrates were purchased from commercial sources with the best quality and were used without further purification. SiO₂ was used in the form of silica gel 60 (70-230 mesh ASTM) and was purchased from Merck company. IR and ¹H NMR spectra were recorded on Thermo Nicolet Nexus 670 FT-IR and Bruker Avance DPX-400 MHz

**Scheme-I:** Reduction of aromatic carbonyl compounds **1-5****Scheme-II:** Reduction of aromatic nitro compounds **12-17**

spectrometers, respectively. The products were characterized by a comparison with authentic samples (melting or boiling points) and their ¹H NMR or ¹³C NMR or IR spectra. TLC was applied for the purity determination of substrates, products and the reaction mixture by using silica gel 60 F₂₅₄ aluminum sheet.

As the starting materials for the investigation are known compounds, the experiments are performed in a higher scale for the ease of qualitative identification of the products. 0.2 mol of zinc dust was added to a solution 0.05 mol aromatic carbonyl compound in 150-200 mL of diethyl ether, taken in a 500 mL 2 necked round bottom flask. To the stirred zinc suspension of the ethereal solution of the substrate, 150 mL of very dilute HCl of the concentration 0.3 mol per 150 mL is added very slowly through the addition funnel at the rate of 50 mL/h which is the optimum rate of addition for the optimum velocity of the generation of hydrogen for the maximum yield, tested by several trial runs and monitored by TLC (8:2) hexanes and ethyl acetate system as eluant. To compensate the loss of solvent due to evaporation, 20 mL of ether was added at end of each hour.

After the completion of the reaction, the zinc was filtered off and usual work up resulted in the crude. The mixture NMR of the crude was obtained to determine the product to reactant ratio (conversion percentage) and in the case of formation new compound, isolated yield was determined. In the case of the reduction of nitro compound the amount of zinc and HCl was scaled up by 3 times to match the stoichiometric requirement.

As most of the substrates and products involved in our study are known compounds, the NMR data of the mixture are compared with the NMR of the authentic samples available with SDBS [11] and with the NMR of the starting materials available. In some mixture NMR, the residual solvent (diethyl ether) signal occur at 1.16-1.19 and 3.42-3.47 ppm, in ¹H NMR

and at 15.2 and 65.9 ppm in ¹³C NMR. The spectral data of the unreported compound **22** are given below:

2-(4-Nitrobenzylideneamino)benzaldehyde (22): Pale yellow low melting solid, mp 25 °C; ¹H NMR (400 MHz, CDCl₃) δ 10.35 (s, 1H, aldehydic proton), 9.10 (s, 1H, alkenic proton), 8.05-6.95 (m, 8H, aromatic protons) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 194.0, 188.2, 156.0, 154.6, 134.1, 133.7, 131.3, 130.9, 129.6, 129.4, 124.37, 119.7, 124.43, 114.9 ppm.

To compensate the loss of the atomic hydrogen atoms generated as hydrogen molecules (bubbles) without effecting reduction, the stoichiometric ratios of the zinc and acid was scaled up for the optimum yield. The scaled up ratio of the acid was lesser than that of Zn, to avoid residual acid medium and loss of acid sensitive products to the aqueous phase. The acid of the required concentration was prepared by using brine solution to minimize the loss of water soluble products to the aqueous phase. By this technique, it was found that the amount of product in the organic phase was increased by two folds (mixture NMR evidence) without the regular workup.

The technique of adding dil. HCl in drops by using addition funnel/burette to organic phase containing zinc and substrate dispersed in ether, at the rate of 50 mL/h provides a steady velocity of hydrogen generation and more contact time for atomic hydrogen to effect reduction on the substrate. The rate of addition was optimized after several trial runs, by running TLC with hexanes/ethyl acetate (8:2) as eluent.

The present investigation is aimed only at finding the feasibility of the reduction of aromatic carbonyl/nitro group and the extent of reduction possible, under given the set of experimental condition, so the technique used to calculate the yield was to cull the ratio of unreacted substrate and the products formed (percentage of conversion), from the ¹H mixture NMR of the crude product. It was done on the basis of the peak area integration of the aromatic protons or the characteristic protons of the substrate/products.

The principle for spectral assignment for the aromatic protons is that, when an carbonyl group is converted to alcohol/alkane, or when a nitro group is converted to hydroxyl amine or amine, the aromatic protons of the products appear slightly up field in comparison to the aromatic protons of the substrate (starting material) as most of the product formed are known compounds. The products aromatic peaks are identified by comparing them with the authentic spectra available in NMR data base [11].

RESULTS AND DISCUSSION

The results of this investigation of reduction of aromatic carbonyl and nitro compounds by Zn/dil. HCl-Et₂O system are presented in the Table-1.

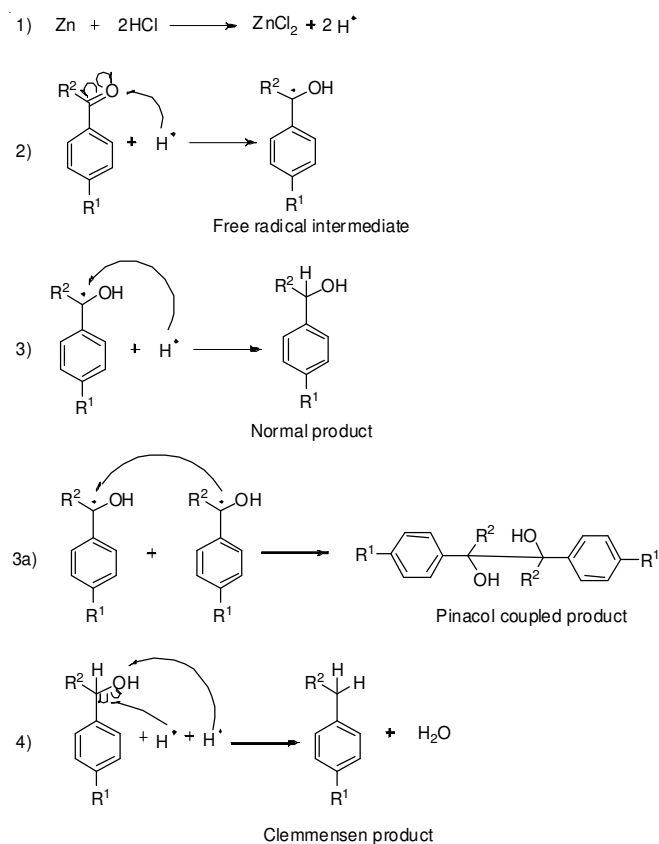
Based on studies of Turro and others [12], we suggest a plausible free radical mechanism (**Schemes III and IV**) for the room temperature reduction of aromatic carbonyl and nitro compounds by Zn/dil. HCl-diethyl ether system.

The mechanism for the carbonyl reduction (**Scheme-III**) is suggested to account for the three types of products (normal, coupled and clemmenson) formed. The first step is the slow generation atomic hydrogen (free radicals) or the 'nascent hydrogen'. The Zn metal suspended in the organic phase,

TABLE-1
DETAILS OF THE REDUCED PRODUCTS OF THE AROMATIC CARBONYL (1-5) AND NITRO COMPOUNDS 12-17

Entry	Substrates	Products	Name	Yield* (%)
1	1	6	Phenylmethanol	42
2	2	7	1-Methoxy-4-methylbenzene	4
3	3	8 & 9	2,3-Diphenylbutane-2,3-diol & buta-1,3-diene-2,3-diylidibenzene	13
4	4	10	1,1,2,2-Tetraphenylethane-1,2-diol	42
5	5	11	2-Hydroxy-1,2-diphenylethanone	25
6	12	18 & 19	N-Phenylhydroxylamine & aniline	33
7	13	20	<i>p</i> -Toluidine	5
8	14	—	—	0
9	15	—	—	0
10	16	21	Iminobenzylidene polymer	90**
11	17	22	2-(4-Nitrobenzylideneamino)benzaldehyde	90**

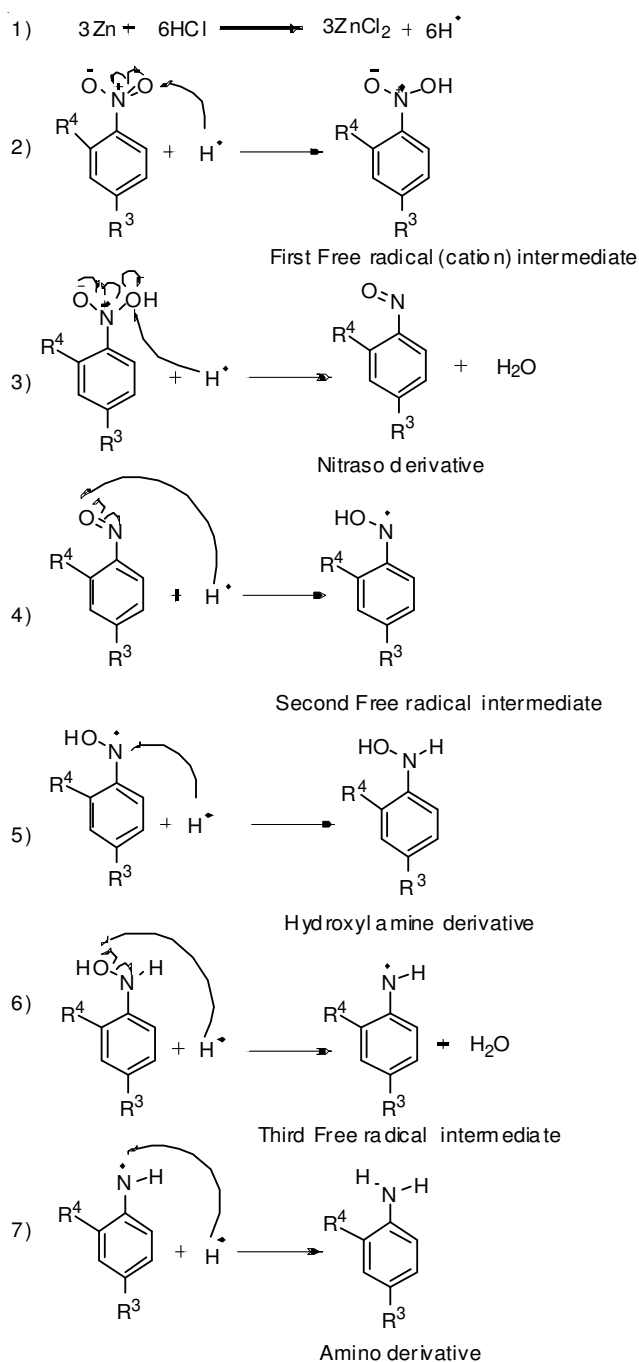
*Culled from ¹H mixture NMR spectra; **Calculated based on the isolated yield.



Scheme-III: Mechanism for the carbonyl reduction

transfers electrons to H⁺ ions of the falling dil. HCl drops to reduce them to atomic hydrogen. The hydrogen free radicals, before combine to form H₂ molecule (gas) and bubble out, they induce the homolytic fission of the carbonyl π bond with the generation of carbon and oxygen radicals. As it is a room temperature reaction, the π bond of the carbonyl group cannot undergo heterolytic fission (ionic mechanism) in the absence of a energetically favourable nucleophile like H⁻ ion *etc.* In the second step, the hydrogen free radical combines with the oxygen free radical (which is less stable) to form the hydroxyl carbon free radical species as intermediate whose stability should decide the further course of reaction.

Similar steps are involved in the reduction mechanism of nitro compounds (Scheme-IV), It is well documented that the conversion of NO₂ group to NH₂ group involves 'N=O' and



Scheme-IV: Mechanism for the nitro group reduction

'-NHOH' intermediate. The suggested free radical mechanism accounts for the production of hydroxyl amine. The second step (**Scheme-IV**), which is similar to the second step of carbonyl reduction, the π bond of the nitro group under goes homolytic fission under the influence of the hydrogen free radical to yield the nitrogen radical cation and oxygen free radical. The generated hydrogen free radical attacks the oxygen free radical of the substrate to generate a hydroxyl nitrogen radical cation of the substrate first free radical (cation) intermediate whose stability decides the further course of the reaction.

We consider the formation of benzo pinacol by the pinacol coupling of the free radicals of the substrate **4**, in large yield serves as the evidence for the suggested mechanism for carbonyl reduction. The evidence for the suggested free radical mechanism for the nitro group reduction is the formation of the hydroxylamine intermediate for the substrate **12**, usually reduction by using metal does not stop at intermediate stage, but the use of mild reagent, such as the one used, can produce mixture of intermediate products also. Moreover, we have used the same reducing system for reducing carbonyl and nitro groups. Liu *et al.* [13] have also reported the *N*-arylhydroxyl amines by the use of Zn-CO₂/H₂O system.

The success of the carbonyl/nitro group reduction by our reducing system depends as three factors:

- The homonuclear nature of the carbonyl group and nitro group, the electro negativity of the carbonyl carbon and oxygen and nitro group nitrogen and oxygen in the given substrate.
- The stability of the free radical intermediate formed in the second step of both mechanisms.
- The concentration and rate of addition of the dil. HCl.

The faster addition or the use of concentrated acid will generate large concentration of the hydrogen free radicals which will recombine to form H₂ gas and will bubble out without effecting reduction. Of the three factors, the third factor can be controlled experimentally, but for the knowledge of first two factors, one has to resort to the theoretical study. As DFT study is popular and more accurate, we have decided to perform DFT calculation. We have optimized the geometries of substrates (**1-5** and **12-17**) and the their first formed free radical intermediates mentioned in **Schemes III** and **IV** by using Gaussian 03 program. The optimization was done by B3LYP (Becke, 3-parameter, Lee-Yang-Parr) method with 6.311g ++ (d,p) basis set. The energies of the geometry optimized structures are summarized in Table-2. The difference in the energies of the substrate and free radical (energy factor), gives in sight to the stability of the radicals and hence taking care of the second factor. From the Geometry optimization of the substrates, the partial charges on each the atom of the substrates (Mullikan charges) are obtained. The difference in the Mullikan charges for carbon and oxygen of the carbonyl group and nitrogen and oxygen of the nitro group (charge factor) gives insight into the homo nuclear nature of the groups.

Thus, there are two factors envisaged: 1) Energy factor 2) Charge factor. The charge factor is important for the homolytic cleavage of the carbonyl and nitro group. The energy factor is important for the subsequent formation of free radicals needed for the progress of the reaction. Higher the energy factor more stable is the free radical intermediate, because energy factor

TABLE-2
ENERGIES OF THE GEOMETRY MINIMIZED
SUBSTRATES (**1-5**) AND (**12-17**) AzND THEIR FREE RADICALS

Substance	Energy (hf) (DFT-6311g ++ (d,p))	Energy (kJ/mol)
Benzaldehyde	-345.66920379	-907554
Benzaldehyde-FR	-346.23573214	-909042
Anisole	-460.22823165	-1208329
Anisole FR	-460.79130200	-1209808
Acetophenone	-385.00178859	-1010822
Acetophenone-FR	-385.56579451	-1012303
Benzophenone	-576.77159850	-1514314
Benzophenone-FR	-577.35344980	-1515841
Benzil	-690.12893287	-1811934
Benzil-FR	-690.71256956	-1813466
Nitrobenzene	-436.87472610	-1147015
Nitrobenzene-FR	-437.46035854	-1148552
4-Nitrotoluene	-476.20367999	-1250273
4-Nitrotoluene-FR	-476.78823310	-1251808
4-Nitroaniline	-492.25620264	-1292419
4-Nitroaniline-FR	-492.83758052	-1293945
2-Nitroaniline	-492.25642811	-1292419
2-Nitroaniline-FR	-492.83793181	-1293946
4-Nitrobenzaldehyde	-550.22867204	-1444625
4-Nitrobenzaldehyde-aldehyde-C-FR	-550.80362843	-1446135
4-Nitrobenzaldehyde-nitrogen-N-FR	-550.81890792	-1446175
2-Nitrobenzaldehyde	-550.21882762	-1444600
2-Nitrobenzaldehyde-aldehyde-C-FR	-550.80688319	-1446143
2-Nitrobenzaldehyde-nitrogen-N-FR	-550.81204534	-1446157

indicate much lower is the energy of the free radical when compared to the substrate (*i.e.* $E_{\text{substrate}} - E_{\text{Free radical}}$) from which it is produced. As the substrates involved are different, the energy factor is normalized for comparison. The normalization was done by dividing the energy factor of substrate by the number atoms of the substrate and is called 'effective' energy factor. The charge factor indicates the homo nuclear nature of the carbonyl/nitro group, It is arrived by adding the magnitudes of 'unlike' charges or by subtracting the magnitudes of 'like' charges on the C and O atoms in the case of carbonyl group on the N and O group on the nitro group of the substrates, the charge factor is the approximate measure of the electro negativity difference of the atoms at reaction site of the substrate, the lesser the difference, more is the homo nuclear nature of the (π) bond present between the atoms and hence more likely is the homolytic fission of (π) bond in second step of the suggested mechanism (**Schemes III** and **IV**). The energy and charge factors obtained from DFT studies are given in Table-3. For handy comparison 1/charge factor called α and 'effective' energy factor called β are also given in Table-3 along with yield and remarks. A scrutiny of data given in the Table-3 reveals that for the yield of the reduction products to be high, the value of either one of the two factors (α and β) or both of them should be high. If both the factors are less, the yield will be less and the pattern of change of α and β is summarized in the remarks column of the Table-3. The anomalous behaviour of the substrates **5**, **16** and **17** are due to the occurrence of consecutive elimination (**5**) or polymerization reactions (**16**

TABLE-3
ENERGY DIFFERENCE OF THE GEOMETRY OPTIMIZED SUBSTRATES (1-5) AND (12-17) AND THEIR FREE RADICALS (ENERGY FACTOR) WITH CHARGE FACTOR OF THE SUBSTRATES ALONG WITH YIELD

Compound name	Energy difference k.J/mol (energy factor)	Charge difference (charge factor)	Energy factor (effective) α	1/Charge factor β	Yield (%)	Influencing factor (s)
Benzaldehyde	1487	0.094	106	10.6	42	α & β more
Anisole	1478	0.191	92	5.2	4	α less, β very less
Acetophenone	1481	0.018	87	55.6	13	α very less, β moderate
Benzophenone	1528	0.005	64	200.0	42	α very less, β very high
Benzil	1532	0.302	59	3.3	25*	α & β very less
Nitrobenzene	1538	0.118	110	8.5	33	α & β more
4-Nitrotoluene	1535	0.140	90	7.1	5	α & β less
4-Nitroaniline	1526	0.144	85	6.9	0	α & β very less
2-Nitroaniline	1527	0.248	85	4.0	0	α & β very less
4-Nitrobenzaldehyde C-FR	1550	0.147	97	6.8	90*	α & β more
2-Nitrobenzaldehyde C-FR	1557	0.138	97	7.2	90*	α & β more

*With consecutive elimination/polymerization reaction.

and 17) of the reduction products respectively. The values in the Table-3 are presented in the form of graphs Figs. 1-3 to depict the possible linear correlation between the yield and stability of the free radical; yield and homo nuclear nature of carbonyl and nitro group.

Apart from the theoretical reasoning of the yield (α and β factors), It was observed that the free radical (intermediate) which can be delocalized more (more canonical structures)

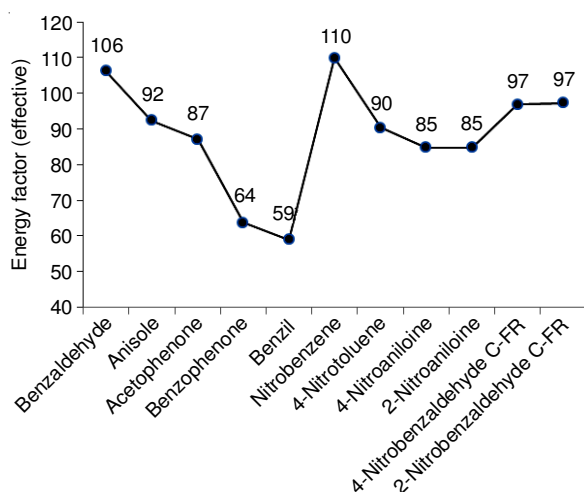


Fig. 1. Relationship between effective energy factors of the substrates

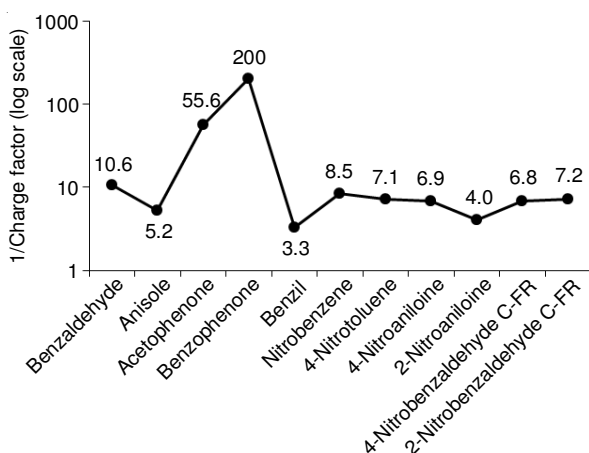


Fig. 2. Relationship between 1/charge factors of the substrates

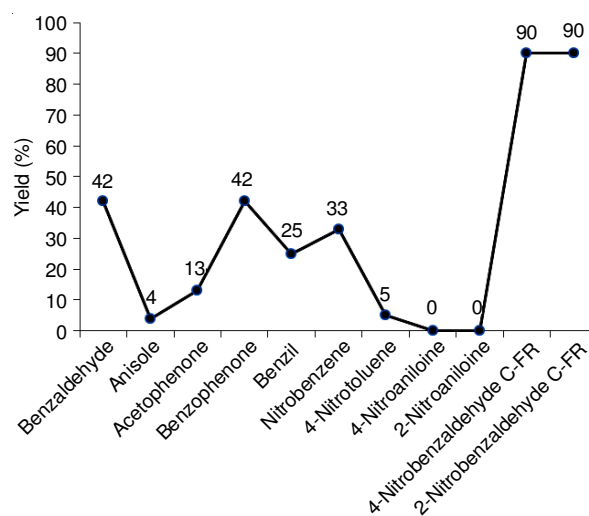


Fig. 3. Relationship between yield percentages of the substrates

are more stable, resulting in high yield of reduction product. This fact is reflected in the yields of substrate **4**, **16** and **17**. Very less yield was obtained in the case of substrate **7** and no yields were observed in substrates **14** and **15** with electron donating group. In the case substrates **16** and **17**, the DFT study shows that the aldehyde free radicals are of high energy than the nitro group free radical, so in those cases, it is the nitro group which gets reduced and not the CHO group, leading to chemo selective reduction. So the reducing agent system is chemo selective, with the free radical mechanism.

Conclusions

The investigation of the feasibility of the room temperature reduction of the aromatic carbonyl and nitro group by our novel Zn/dil. HCl-diethyl ethereal system highlights the following factors:

- The reduction is surprisingly by hydrogen free radical (contrary to Clemmenson ionic reduction mechanism) and is possible under the given set of experimental conditions. The DFT study reasons out that the yield of the reduction depends on both the stability of the free radical generated (in the second step of the suggested mechanisms), denoted as effective energy factor α and the charge factor (Mullikan charges) β which makes the ' π ' bond of both the nitro and carbonyl group

amenable for homolytic fission which is a precondition for the free radical reactions.

- For high yield, both the energy factor α and the charge factor β must be more, for moderate yield any one of the two factors must be more. If both the factors are low then the yield is observed to be low.

- Apart from energy factor and charge factor, the presence of electron withdrawing (-M) group in the 'para' or 'ortho' position to the carbonyl/nitro group, also facilitates reduction, as it indirectly affects the energy and charge factor. An electron withdrawing group pulls the electron away from the more electronegative oxygen of the carbonyl/nitro group and making the charge factor favourable. It also helps in the delocalization of the free radical formed in second step of the suggested mechanism and thereby making energy factor also favourable.

- In the course of our investigation an unreported dimer formed by the iminobenzylidene coupling of the 2-amino benzaldehyde in good yield and we have also reported the new method for the room temperature preparation of the iminobenzylidene polymer formed by self condensation of 4-amino benzaldehyde.

It is reported based on the theoretical and experimental evidences that the present investigation involves free radicals. So in the future probe, reduction of more substrates can be studied and it can be performed by changing the experimental conditions suitable for free radical reactions, such as use of ordinary/UV light, radical initiator, *etc.* to increase the yield of the reduction products.

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