Special Paper

DIIMIDE — A NOVEL INTERMEDIATE

S.M. Abdul Hai, A. Wadood Qureshi and (Miss) Asifa Begum

*PCSIR Laboratories, Karachi 39*

Diimide $(NH = NH)$ also referred to as diazene[33] (for a review of monosubstituted diazenes[33]) is a member of a class of labile organic intermediates. It is very useful synthetically for selective hydrogenation of various sensitive multiple bonds. Its use has gained popularity over the recent past on account of its easy handling and absence of complications that come across in other hydrogenation methods. Its usefulness is even more enhanced on account of its selective nature. One can carry out reductions of nonpolar bonds without disturbing the polar multiple bonds in the same molecule. Its effectivity is unhampered by the presence of sulphur in the molecule. Aromatic nuclei are also not affected by this reagent. It is even superior to metal-catalyzed reductions as it does not cause a *cis-trans* isomerizations of substrates being hydrogenated. Its individual existence has been established by spectroscopic data obtained at liquid nitrogen temperature. In the liquid and gaseous states, diimide disproportionates to give nitrogen and hydrazine. This process is very fast and does not permits its isolation. Therefore, it is always generated *in situ* in the presence of a substrate.

Fortunately a chemist has a choice of a variety of methods and substrates from which it can be obtained, and luckily the behaviour of the reducing agent so formed is completely independent of its origin. Deuterium diimide $(DN = ND)$ is a nice source for the introduction of deuterium in a molecule, as it does not affect its other functional groups.

Modes of Generation

By Oxidation of Hydrazine.[1,15] The reduction proceeds only in the presence of an oxidant. Corey *et al.*[1] have demonstrated the catalytic role of copper ion for oxidation of hydrazine, which results in the increased rate of reductions of multiple bonds. Copper ion has also been used as a catalyst in the presence of hydrogen peroxide as oxidant for reductions with hydrazine.
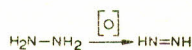
Evidence based on the IR and mass spectral data leads one to believe that diimide is the species responsible for the reduction, and there is reason to believe that it requires acid catalysis. Substituted phenylhydrazines on heating in the presence of an alkali also lead to metastable diimide.
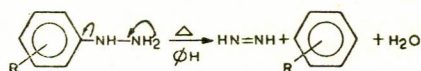

By Thermolysis of Potassium azodiformate.[1–3,12] This is the most classical of all known methods. Alkali salts of azodicarboxylic acid which can be easily prepared by hydrolysis of azodicarboxamide undergo decomposition in warm water to give diimide which on account of its high potential energy reacts
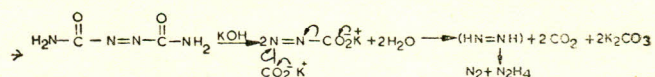

with itself to give nitrogen and hydrazine. If an olefin is present in the reaction mixture, it undergoes reduction to an alkane. A large excess of the reagent is required. The reaction is subject to general acid catalysis.

From Sulphonyl and Acyl hydrazides.[3,4,16] Certain sulphonyl and acyl hydrazides on treatment with alkali yield diimide by a β-elimination. Again 100% excess of the reagent is required. The fate of the diimide is the same as stated above in the absence of a hydrogen acceptor. One can also generate it rapidly at 0°C by alkaline decomposition[4] of chloroacetyl hydrazine hydrochloride (m.p 150°C decomp.)
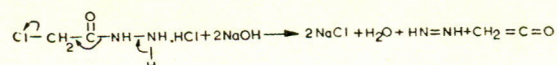
In the absence of a hydrogen acceptor diimide disproportionates into nitrogen and hydrazine and the latter is acetylated by the ketene.

Thermolysis of Anthracine-9,10-biimine.[5] Anthracene-9,10-biimine is an effective reductant for azo and mono and disubstituted olefinic linkages. This method is very handy as it does not require any acid
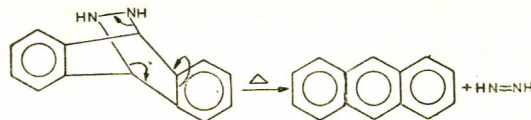

or base catalysis. The reaction can be carried out simply by heating the reagent with the olefin in ethanol. On decomposition it gives anthracene and diimide. The yields of hydrogenated products are just as good as described in above methods. This is relatively a milder method as it lacks drastic effects of acid or base catalysis. Again 2–8 fold excess of the reagent has to be employed.

By the Alkaline Decomposition of Chloramine or Hydroxylamine-o-sulphonic acid. One can also make diimide by the alkaline decomposition of chloramine[6]

or hydroxylamine-o-sulphonic acid.[6,7] Both the reactions are believed to proceed via an 'azene' which dimerises to diimide. This postulate seems to be quite reasonable in view of the fact that similar reactions of metastable azenes such as these are known.[11]
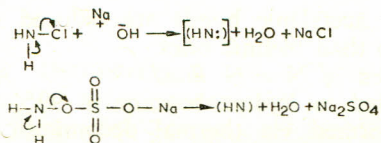

By the Decomposition of 1,1-Dihydroxyazocyclo-hexane. Cyclohexanone,[25] in an alkaline medium reacts with hydroxylamine-o-sulphonic acid to give 1,1-dihydroxyazocyclohexane. This substance is not very stable and undergoes decomposition even at room temperature to give cyclohexanone, nitrogen and hydrazine.
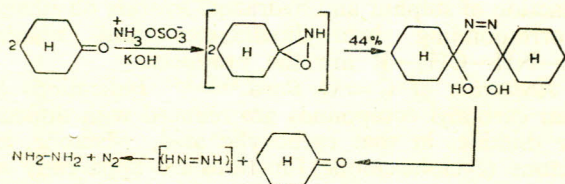

That the reaction proceeds via diimide is confirmed from the fact that if carried out in the presence of quinone or azobenzene then hydroquinone or hydrazobenzene is obtained.

By Conversion of Hydrazobenzene. N-Benzylaziridine-2-carboxylic acid hydrazide on heating in methanol results in ring opening with evolution of a gas.[13] Azobenzene if present is converted to hydrazobenzene. The reductant is reasonably assumed to be
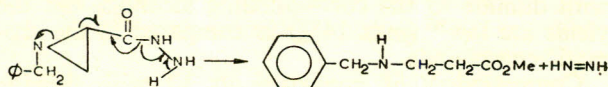
diimide. The ketene formed in the ring opening is esterified by MeOH.

In all the above-mentioned methods one has to employ a large excess of the reagent to dispel the affects of a parallel competing reaction of its disproportionation to nitrogen and hydrazine.

$$2HN = NH \longrightarrow N_2 + N_2H_4$$
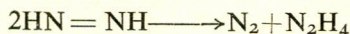
The metastable diimide generated by any one of the above stated methods transfers a pair of hydrogens to symmetrical carbon–carbon double bonds and other multiple bonds in stereospecific *cis* manner,[1,5] whereas more polar functional groups such as nitrile, NO₂, C=N, S=O and C=O do not respond as readily.

Reactions

The following representative examples will illustrate the usefulness of the intermediate. Yields are generally high.

Reduction of C=C Bonds. Sclareol is converted to dihydrosclareol by diimide generated from the thermal decomposition of anthracene-9,10-biimine.[5]
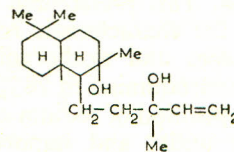

Sclareol

Lithocholic acid is obtained in 79% yield by the treatment of 3,α-hydroxy-△-cholenic acid[11,12] from the same reagent.[5]
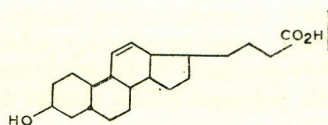
Similarly *trans*-cinnamic acid, maleic acid, fumaric acid, *cis*-4-cyclohexene-1,2-dicarboxylic acid and *t*-stilbene are reduced in 81, 87, 80, 45 and 88% yield respectively.

Diimide generated by the oxidation[1a] (O₂ or H₂O₂) of hydrazine in the presence of CuSO₄ catalyst reduces various multiple bonds in good yields.
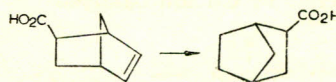
Thus gibberellic acid is converted to tetrahydrogibberellic acid in 74% yield.
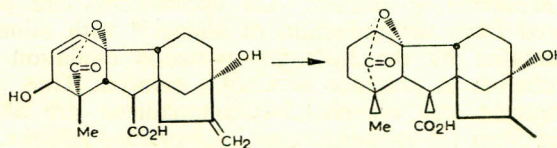
Gibberellic acid

Cholesterol is converted to cholestanol by air oxidation of hydrazine in presence of Cu ion[1a] in 20% yield.

Similarly *exo*-△⁵-norbarnene-2-carboxylic acid is reduced to *exo*-norbornane-2-carboxylic acid in 82% yield[1a]

Certain unsaturated fatty acids are converted to the corresponding hydrogenated products[14] by diimide generated by air oxidation of hydrazine.

Cis-cinnamic acid is obtained by the reduction of phenylpropiolic acid with diimide generated by basic decomposition of N,N-dimethyl-N-phenylhydrazinium chloride.[15] Contrary to the expectation, 7-substituted norbornadienes give anti-7-substituted norbornenes instead of the *syn*-isomer.[17]
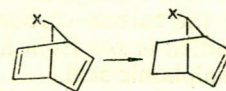
Reductions with deuteriodiimide lead to the introduction of deuterium in *exo,exo* configuration. Reaction of norbornadiene also shows the introduction

of *exo*-deuterium. This preferential reduction of *syn* double bond is the characteristic reaction of 7-substituted norbornenes and norboradienes. Quinine is converted to dihydroquinine in 78% yield by diimide from acid decomposition of sodium azodicarboxylate.[3]

The synthetic utility and importance of diimide is shown by the following illustration: Cyclododecene is obtainable only by long and cumbersome synthetic routes, and that also gives a mixture of stereoisomers. *Cis, trans, trans*-1,5,9-cyclododecatriene is smoothly reduced to the corresponding saturated cyclododecane by catalytic hydrogenations. But with diimide (generated by air oxidation of hydrazine in the presence of $CuSO_4$ catalyst, *cis*-cyclododecene is easily obtained in 79% yield by selective reduction of *trans* bonds only[18,19] as shown by IR spectrum. Reductions of other cyclic polyenes follow similar course.[19] This


1,5,9-cyclodo-   Cyclodocene
decatriene.
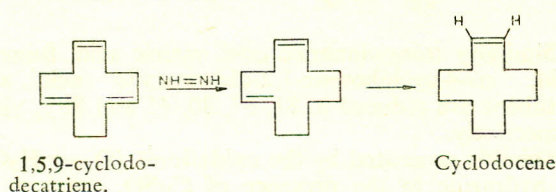
indicates the considerable differences in reactivity between *cis* and *trans* double bonds towards diimide.

*Reduction of Allenes.* *Cis* cycloalkenes are prepared from the reduction of allenes[20] with diimide generated by the hydrogen peroxide oxidation of hydrazine in presence of $CuSO_4$ catalyst. Thus *cis*-2-nonene and *cis,-cis*,1,5-cyclononadiene are obtained from 1,2-nonadiene and 1,2,6-cyclononatriene.
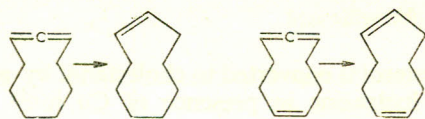

Reduction of $C \equiv C$. 2-Butyne-1,4-diol is converted to butane-1,4-diol in 40% yield with diimide[1a] generated by hydrogen peroxide oxidation of hydrazine in presence of Cu ion catalyst.
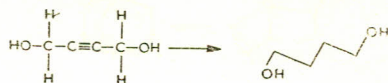

Similarly diphenylacetylene[1a] gives 1,2-diphenyl ethane by the air oxidation of hydrazine with Cu catalysis.
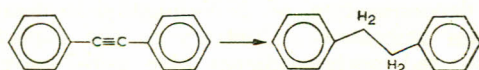
Compounds of the type I and II are selectively hydrogenated[21] only at the carbon–carbon multiple bond, with diimide generated *in situ* from hydroxylamine or hydroxylamine-*o*-sulphonic acid.

I   II $R=CO_2H$; O_2N-
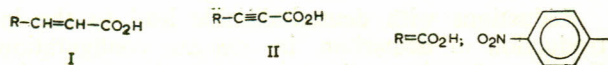
Reduction of III with diimide[1b] gives IV in 40% yield.

III   *Cis* IV
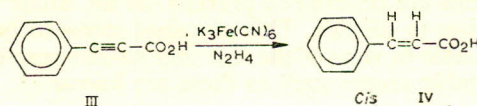
Generally acetylenic bonds are reduced with much more ease than olefinic ones.

Reduction of $N = N$ *Bond*.[4,5,8,13,25] Azobenzene is converted to hydrazobenzene in 99% yield with diimide formed via thermal decomposition of anthracene-9,10-biimine.[5] Similar conversions are also effected by potassium azodicarboxylate.[3] Azobenzene is also reduced by diimide produced from thermal decomposition of N-benzyl-aziridine-2-carboxylic acid hydrazide.[13]

Reduction of $C = N$ *Bond*.[23] The $C = N$ bonds in benzoylhydrazones and the Schiff bases R—N=CHR, are reduced with diimide generated by the reaction of sulphur and hydrazine hydrate on ethanol. Corresponding benzoylhydrazines and s-amines R—NH—CH_2—R are the products.

Reduction of $C = O$ *Bond*.[8,24,25] Indications are that carbonyl compounds are reduced with difficulty by diimide, in that carboxylic acid, γ-lactone, and ketone (cyclohexanone) functions are apparently untouched.[8]

Various aromatic aldehydes[24] bearing substituents such as —OMe and —NO_2 are reduced by diimide generated by the acid decomposition of potassium azodicarboxylate. The yields are generally pretty good (62–84%) except in case of *p*-nitrobenzaldehyde. In the latter case it goes down as low as less than 5%. Reductions are accompanied by a side reaction of formation of corresponding azines.

Aliphatic carbonyl compounds undergo reductions with diimide to the corresponding alcohols, but the yields are low[26] (max 14%) as compared to the aromatic compounds.

Compound V is converted to VI with diimide obtained from thermal decomposition of tosylhydrazine as well as from anthracene-9,10-biimine.

X, CH=CH;—CH_2—CH_2—
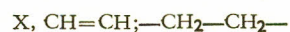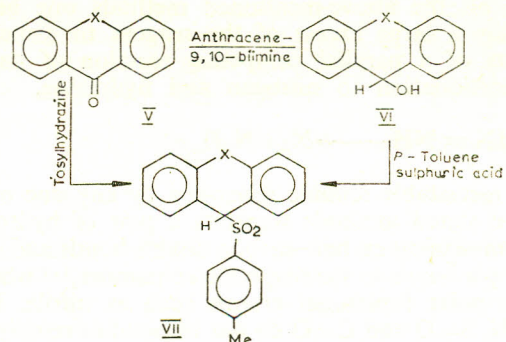
Surprisingly enough the $C = C$ bond is left intact.[28] With tosylhydrazine, a reagent which on thermal decomposition gives diimide, compound VII is obtained. There is evidence for reaction to follow the path V→VI→VII. It is proposed that reduction of ketones may occur with tosylhydrazine in the above-

mentioned manner, only if the carbonyl group is sufficiently innert to nucleophilic attack by tosyl-hydrazine to permit the formation of diimide by thermal reaction.

Mechanism

The transfer of hydrogen from diimide to a multiple bond is an exothermic[1a] ($\sim$70 kcal/mole) process. It should, therefore, be highly favoured energetically and should, require low activation energy.

The overall reaction is of second order. The rate of the reaction may be correlated with the Hammett's free energy relationship, and its ρ-value[14] (—0.95) indicates that the reaction would be aided by electron donors at the reaction site, i.e. multiple bonds. This is quite in agreement with the reduction of carbonyl linkage,[24] wherein the reaction does not proceed readily with *p*-nitro substituent on the phenyl ring. In case of *p*-chloro substituent which is electron donating by resonance, the reaction proceeds with much more facility. In aromatic carbonyl compounds it is observed[24] that the reduction proceeds most readily where the charge on the carbon atom of the carbonyl linkage can be delocalized. The later process facilitates the formation of the transition state, which, as is indicated by low ρ-value, should be of negligible ionic character. In the absence of this delocalization the reaction site would definitely be comparatively more polar. Although the differences in the yields[24] of hydrogenated products are not too large, but it is significantly clear that the reduction is highly facilitated in cases where lone-pair of electrons are available to feed the electron deficient reaction site in the transition state. On the other hand in case of *p*-substituted cinnamic acids[29] practically no difference in the relative rates of hydrogenation is observed. Both these observations can be rationalized by the postulate that the transition state is weakly polar and much more similar to the starting materials then to the products. Noteworthy are the examples of *p*-nitrocinnamic acid and *p*-nitrobenzaldehyde. In the former case no noticeable effect due to the presence of nitro group is observed, while in the latter case the reduction proceeds with much more difficulty and side reactions are accompanied owing to the low reactivity of the carbonyl substrate towards diimide and resultant disproportionation of the latter to nitrogen and hydrazine which subsequently reacts with carbonyl compound to give azine. This difference may be explained by the fact that the carbonyl linkage being polar in character, there is already charge separation in the ground state, and if an electron withdrawing group is in resonance with it, then polarity of the bond will be increased further as the charge density on the carbonyl carbon will be further decreased. This will have deleterious effect on the reduction reaction by diimide. On the other hand in substituted (in the *para* position only) cinnamic acids no such charge separation is inbred in the parent molecule, so there is no question of its further enhancement by a substituent.

In a study of selective hydrogenation[27] where such olefins were selected wherein the approach of diimide would afford the thermodynamically less stable of the two possible products, it was found that the reaction follows the pathway in which steric hindrance is the least, leading to the kinetically controlled final product instead of thermodynamically more stable end product. Thus olefins with large side chains such as α-pinene, β-pinene, camphene and 2-norbornene-2,3-dicarboxylic acid, give marked steric control of the reduction. On the other hand olefins with moderate steric crowding at the reaction site, e.g. 2,3-dimethyl-cyclohexene, 2-methylmethylenecyclohexene, and 4-*t*-but-methylene cyclohexene exhibit much less stereochemical control of the reaction.

Bicyclo(2.2.1)heptene and 1-pentene are found to be more reactive than 1,2-dimethylcyclohexene by a factor of 3.8×10^4 and 1.9×10^3 respectively. This also indicates steric approach control since there would be no hindrance to the approach by hydrogen atoms from the exo side, as also discussed above for 7-substituted norbornadienes.[17] This property explains the highly selective nature of diimide, and puts it in the category of *cis*-addition reagents such as osmium tetraoxide and potassium permanganate.

The relative velocities of the reductions found[29] for various olefinic linkages such as fumaric acid 100, undecyclenic acid 46, maleic acid 10, methyl fumaric acid 3, methyl maleic acid 0.7, *t*-cinnamic acid 10, *cis*-cinnamic acid 3, *p*-dimethylaminocinnamic acid 8 and *p*-chlorocinnamic acid 8–9, also support the concept of steric approach control,[8] in diimide reductions.

From the available data one can generalize:

(a) Acetylenes and mono or disubstituted double bonds are reduced with much ease and trisubstituted with more difficulty.

(b) It is generally found that where the steric effects in an olefin are pronounced, reduction is markedly subject to steric approach control, whereas if bulk effects are moderate much less steric discrimination is observed. The reaction sequence is kinetic controlled. Thermodynamic stability of the product does not[27] entirely govern the course of the reaction.

(c) *Trans* double bonds are easily reduced than *cis*. This is because the substituent effects of *cis*-olefin increase as the bond angle contracts toward tetrahedral angle of 109° in the transition state, which may add to steric interference.

(d) These observed differences are due to the torsional strain, bond angle bending strain, and α-alkyl substituent effects.

(e) It should, however, be noted that the steric effects (non-bonded) for addition of hydrogen to multiple bonds are small. On the other hand both polar and resonance effects are important contributors to the reactivities of diimide reductions of alkenes.

(f) Various experimental conditions have considerable influence on the course of the reaction.[9] Thus air does not have any deleterious effects on the reaction, while it is found to be extraordinarily sensitive to water. Even small quantities of which have strong adverse effect in non-hydroxylic solvents, but surprisingly no such effects are noticeable in hydroxylic solvents. Solvent effects are quite substantial. Their efficacy decreases in the order pyridine > dioxane DMSO > MeOH > EtOH > n-butanol. The magnitude of the solvent effects is increased with the decrease in the substrate reactivity which is decreased by the

presence of electronegative atoms, such as halogens or heteroatoms on the olefinic bond, as it will cause charge separation, however small it may be, by cumulative inductive and resonance effects.

(g) It is also observed[8] that reductions of symmetrical multiple bonds, e.g. $C = C$ and $N = N$, proceed readily, whereas more polar functional groups (e.g. $C = N$, $C \equiv N$, $S-C-S$, $S = O$, $C = O$ and NO_2) are not at all or are reduced with difficulty. Thus the following substrates are substantially if not completely unattacked by diimide; acetonitrile, benzonitrile, nitroethane, nitrobenzene, benzalaniline, benzyl sulphide, dimethylsulphoxide, benzyl disulphide, and the ethylene dithioketal of cyclohexanone.

For the time being the only reasonably safe conclusion that can be drawn from the available data, is that the attack of diimide on a multiple bond is electrophilic in nature and that it synchronously transfers a pair of hydrogens to it in a very highly stereospecific *cis* manner[1b,5,10] leading to a six-membered transition state of negligible ionic character.

Geometry. Diimide was originally supposed to exist predominantly in the *cis* bent configuration in the solid state at 77°K, as was indicated by its IR. The stability of one or the other form has not so far been established experimentally. Results of various types of calculations do not agree either in frequencies or number of bonds and no satisfactory explanation or correlation has so far been made of all the six fundamental vibrations of this molecule.[30] The spectral data does not provide any evidence for or against the presence of unsymmetrical form of diimide.

No clear conclusion can be drawn about the stability of any one of the stereoisomers of this molecule. Equally renowned workers have come up with molecular orbitals calculations favouring the stability of either of the structures.

Thus Herzberg[31] is of the opinion that diimide should take the *trans* form in ground state and the calculations[31] of electron density, difference in the total relative energies, and the splitting of lone-pair levels show the *trans* form to be more stable. Lehn, and his coworkers have estimated *trans* diimide to be more stable than *cis* by 10.5 kcal/mole. Low absorption coefficient of diimide also favours the *trans* structure. Gorden[32] and his coworkers, on the other hand estimate *cis* N_2H_2 and *cis* N_2F_2 to be more stable than the corresponding *trans* stereoisomers. On the basis of above observations and the relative reactivities of various alkenes towards diimide generated from various substrates it is reasonable to believe that the unsymmetrical form of diimide $N^+H_2=N^-$, either participates to a negligible degree in reductions of multiple bonds or that various substrates lead to the same rapidly equilibrating mixture of isomeric forms of diimide. Generally it is assumed that the unsymmetrical diimide has negligible or no kinetic effects on the reductions of multiple bonds.

In the absence of any reliable data for or against

any one of the stereoisomers, one will have to wait for some conclusive evidence to answer the question about the molecular geometry of this *meta*-stable molecule. This is, however, of purely theoretical interest, and does not preclude a chemist to utilize the synthetic potential of the intermediate in any way.

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