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FRONTIERS OF FORMAZANS CHEMISTRY: A REVIEW

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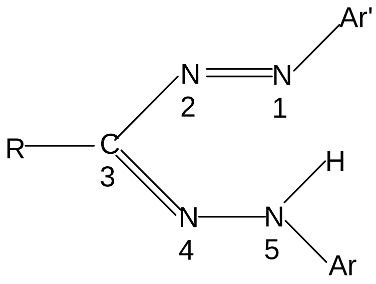
ABSTRACT

In this review, an emphasis has been laid on methods of synthesis, characterization, plausible structure, physical and chemical properties of formazans. Various aspects of the formazan chemistry such as, their solvatochromic behaviour, analytical and pharmacological activities, use of formazans as naked eye colorimetric chemical sensors, redox behaviour using electrochemical method and other various applications of differently 3-substituted formazans have been unraveled. The review revealed that the characteristic skeleton (I) of the formazan moiety enabled it to be used as a potential functionalized molecule, delivering various useful applications.



I

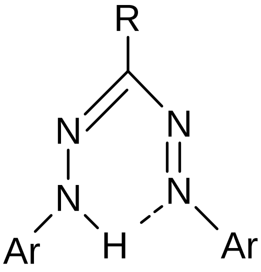
Functionalized Structure of Formazan

KEYWORDS: Formazan, tetrazolium salt, tautomerism, diazonium salts, solvatochromism, naked eye chemical sensor.

INTRODUCTION

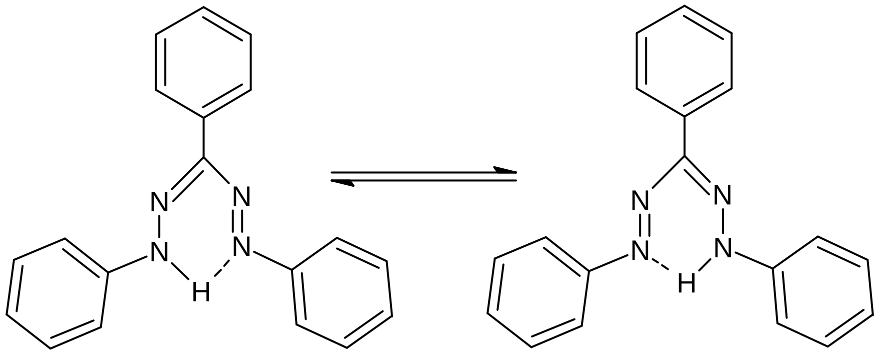
This review encompasses various aspects of chemistry of formazans ever since their discovery. Formazan chemistry has been evolving since 1892 when Pechmann[1] and Bamberger[2] synthesized the first representatives of this class of compounds. Friese in 1875, prepared a formazan by the reaction between benzene diazonium nitrate and nitro methane and named the product as phenylazomethane.[3] The condensation reactions of phenylhydrazine were also studied.[4-6] Many workers have reported synthesis of number of formazans with aryl diazonium salts but the structure of formazans could not be established for long.[7-9]

The action of various aliphatic compounds containing active methylene groups with diazonium salts in alkaline medium was studied in depth which prompted Claisen10 to suggest a structure (II) for the class in 1892.



II

Extensive work in the field of formazans was carried out by Pechmann[11-13] and Bamberger[2] who proposed the term “formazyl” for the equivalent described above. Pechmann prepared the compounds of this type by different methods. These compounds were found to exhibit tautomerism[12-14] and their oxidation products were studied.[14-15] The compounds obtained by the oxidation of the formazyls were described as “tetrazolium compounds”. The tautomerism in formazans was described by Wedekind[16] and was carried further by Lapworth.[17] Though not very successful, these studies paved a direction for Hunter and Roberts[18] who in 1941 established beyond doubt that for several pairs of formazans the structures were identical rather than being tautomeric. It was suggested that formazans were resonance hybrids with a chelated hydrogen-bridge structure. As a result internally co-ordinated hydrogen bonded structure which is capable of existing in two mesomeric forms as shown below was proposed. Hence the Formazan molecule seems to be a resonance hybrid of these Forms (III and IV).



III IV

Mesomeric forms of Formazans

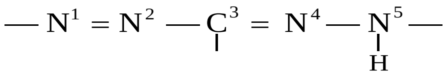
Kuhn and Jerchel[19] confirmed the mesomeric character of formazans. However much progress in the field of Chemisty of formazans took place after 1939, when Lakon,[20] before Kuhn and Jerchel[21] found that colorless tetrazolium salts are very sensitive to biological reduction processes and got converted to intensely colored formazans.

Kuhn and his co-workers are accredited for the substantial advancements in the study of formazans and ever since extensive work has been carried out in this direction.

In 1941, Hunter and Roberts produced metal complexes from formazan compounds.[22] Wizinger and Biro[23] introduced other complex forming groups into formazans which lead to the discovery of metallized formazans dyes.

Definition

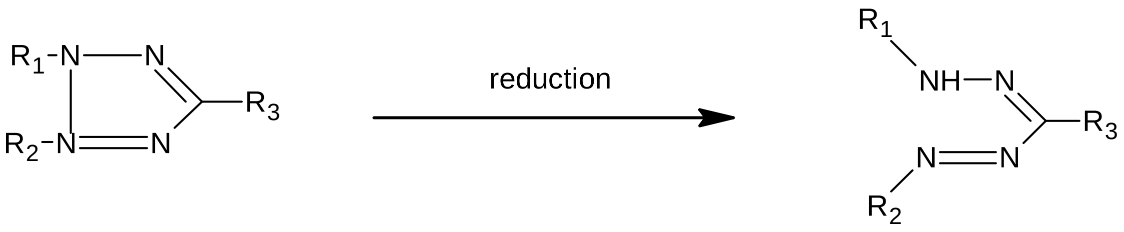
Formazans are the water-insoluble, colored azo-hydrazone compounds containing the characteristic chain of atoms in the molecule.



$$—N^1=N^2—\underset{|}{C^3}=N^4—\underset{\underset{H}{|}}{N^5}—$$

Most commonly 1, 5-substituents are aryl or heteroaryl groups. The 3-position or the meso position can be occupied by a variety of substrates (*e.g.* aryl, heteroaryl, H, -OH, -SR, halogen, $-NO_2$, -CN and alkyl) The 1, 5-diphenyl and 1,3,5-triphenyl derivatives were discovered almost simultaneously by Von Pechmann[1] and Bamberger[2] in 1892.

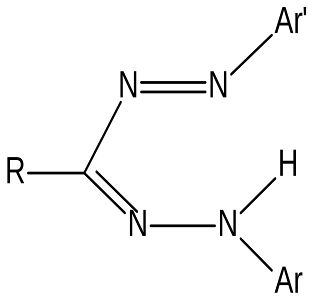
Formazan dyes are artificial chromogenic products obtained by the reduction of tetrazolium salts (V and VI). They possess a variety of colors varying from dark blue to deep red to orange, depending on the type of tetrazolium salt used as the substrate for the reaction.



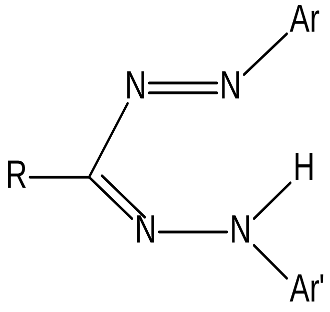
V **VI**

Nomenclature

The pioneer literature in this field is highly confusing because of different systems of nomenclature suggested by the British, American and German workers. The two general structures VII and VIII for a formazan lead to possible names for a formazan where the Ar and Ar′ are not alike.

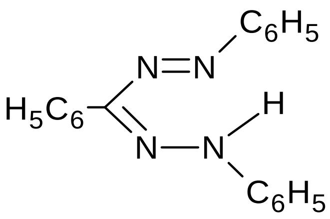


VII

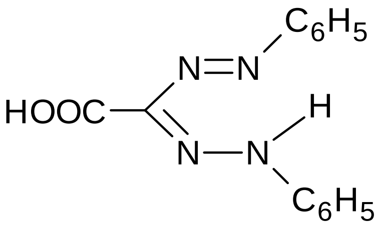


VIII

Initially the formazans were named on the basis of the structure of the radical $C_6H_5-N=N-\underset{|}{C}=N-NH-C_6H_5$ which were called as "Formazyls". Accordingly IX and X were called formazylbenzene and formazylcarboxylic acid, respectively.



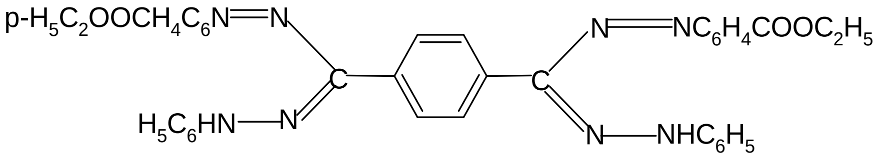
IX



X

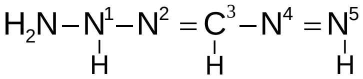
This system of nomenclature was retained by Mitchell[24] in his monograph, British Chemical Nomenclature. In the earlier reports of Chemical Abstracts[25], formazans have been called as derivatives of "Formazyl" radicals. But the problem arises in naming the formazans in which *N*-phenyl groups have been replaced by other groups that cannot be named as substituted phenyls (*e.g.* naphthyls). The naming of diformazans also becomes a tough task, when followed the above system of nomenclature.

The present system of nomenclature solves the problem of naming of formazans by calling the hypothetical, fundamental compound $HN^1=N^2-C^3H=N^4-N^5H_2$ as the formazan and by numbering the atoms in the compound as represented above. Hence the compound VII and VIII can be named as 1, 3, 5-triphenylformazan and 3-carboxy-1,5-diphenylformazan respectively. It must be noted that the numbering of atoms in formazans can be proceeded from either direction. The modern method is more versatile and appropriate to describe the structures of formazans, which can be extended even to diformazan (XI).



XI

However, the modern German system[26] now seem to be the most readily accepted. This system takes hypothetical compound (XII) as its fundamental unit, which is called formazan.



$$H_2N-\underset{H}{N^1}-N^2=\underset{H}{C^3}-N^4=\underset{H}{N^5}$$

XII

Hypothetical Formazan

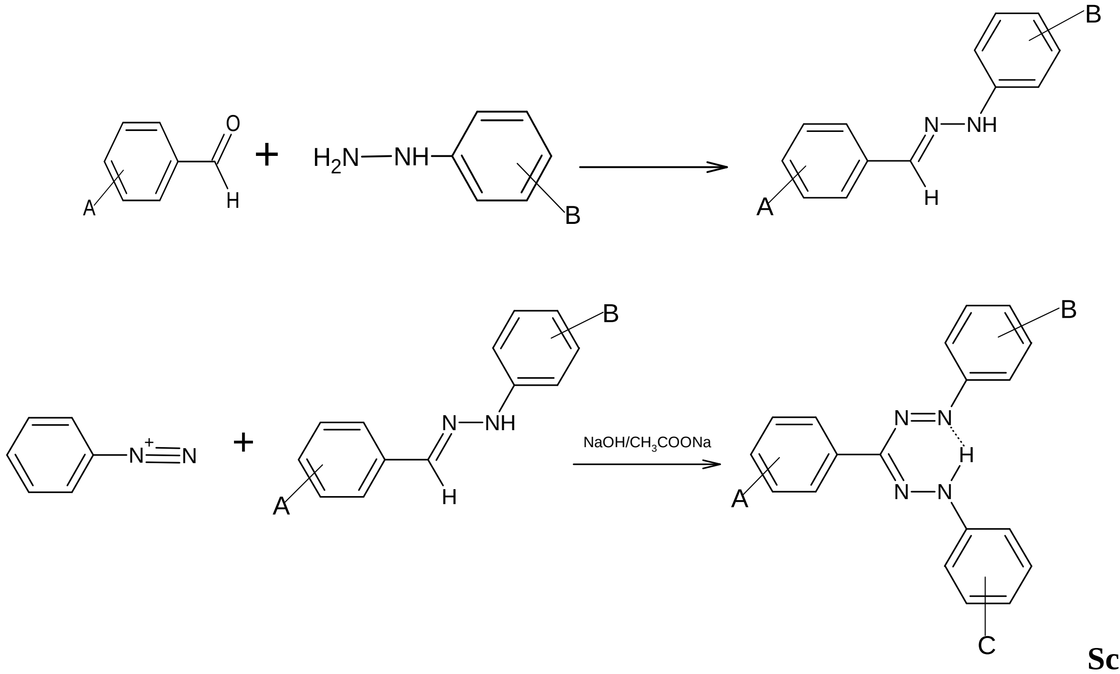
The numbering, 1 to 5, may be applied arbitrarily from either end but this does not lead to confusion. This method of naming the series is presently accepted by the Journal of the Chemical Society.[27] "Formazan" is a Chemical Abstracts recognized keyword and has the registry number 504-654.

1.4 Synthesis of Formazans

Nineham[28] during his extensive study of the chemistry of formazans put forth a comprehensive account of the classical methods of synthesis of formazans. However, there has been significant improvement in these methods of preparation which allows better yield in the given conditions. The various methods of preparation of formazans are.

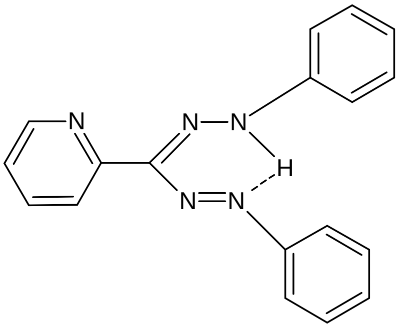
By the Reaction of Diazonium Salts on Arylhydrazones

This is the standard procedure for the preparation of triaryl formazans. This methods involves the condensation of aromatic and aliphatic aldehydes with phenyl hydrazones and the coupling reaction of the resulting hydrazones with diazonium salts (scheme - I).



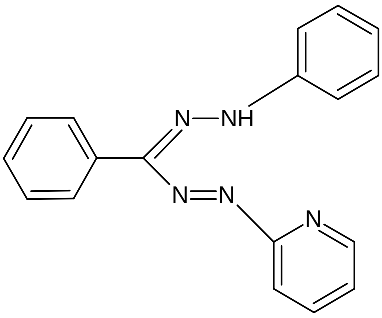
Scheme - I

The coupling reaction serves as a very important tool for the synthesis of formazans of differently substituted aldehydes, hydrazines and amines. Heterocyclic derivatives of aldehydes, hydrazone and amine are also used to synthesize the formazans. For example Frolovo et al.[29] synthesized 1,5-diphenyl-3-(pyridyl) formazan (XIII) with pyridine carbaldehydephenylhydrazone.



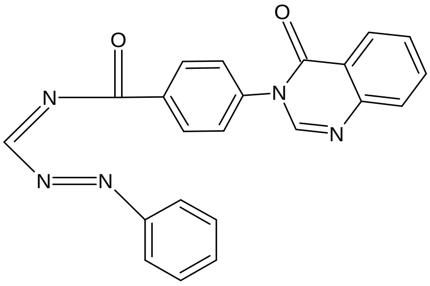
XIII

Marriappan et al.[30] synthesized the hetarylformazan derivatives (XIV) by the reaction of benzaldehyde phenylhydrazone with substituted aromatic and heteroaromatic amines (1-phenyl-3-phenyl-5[aryl/hetaryl].

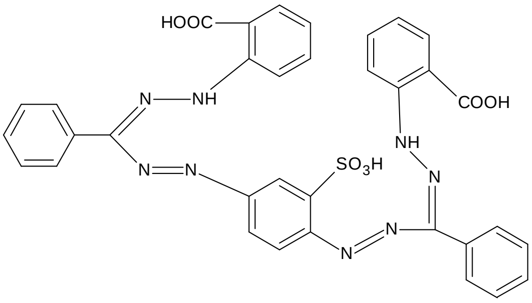


XIV

Babu and Nadendla[31] used anthranilic acid as a starting material and synthesized (XV) 3-(4-hydrazinobenzoyl)-2-methyl-3-quanizolin-4-one.



XV



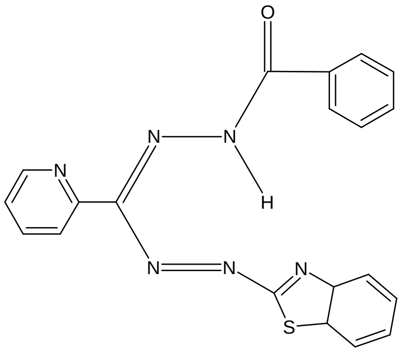
XVI

When compound containing two amino groups such as phenyldiamine was used in formation reaction of formazans, bis-formazans were obtained as a result of two side diazotisation. For example, 1,4-bis-[3,3'-phenyl-5,5'- (o-carboxyphenyl)-formaz-1-yl]-benzene-o-sulphonic acid was prepared by 2,5-diaminobenzene sulphonic acid (XVII).

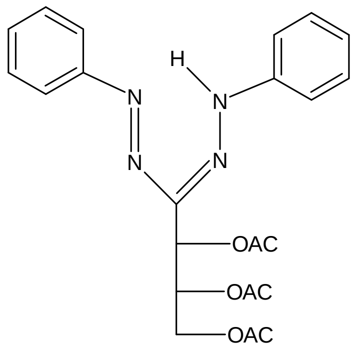
Desai[32] prepared heterocyclic formazans (XVII) using diazonium salt of 2-amino-benzothiazole and thiophene-2-aldehyde benzoylhydrazone.

Mady et al.[33] synthesized pent-2-enose formazans (XVIII) which were synthesised with monosaccharide instead of aldehyde.

Bisformazans can be obtained using phenylinediamine as a consequence of two side diazotization.[34]



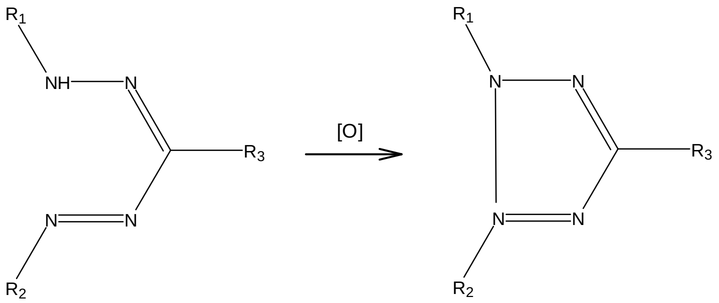
XVII



XVIII

By the Reduction of Tetrazolium Salts

The tetrazolium –formazan couple (XIX) is a special redox system acting as oxidant or a proton acceptor.[35] Tetrazolium salts upon reduction give formazans but the method does not have any practical utility from synthesis point of view.



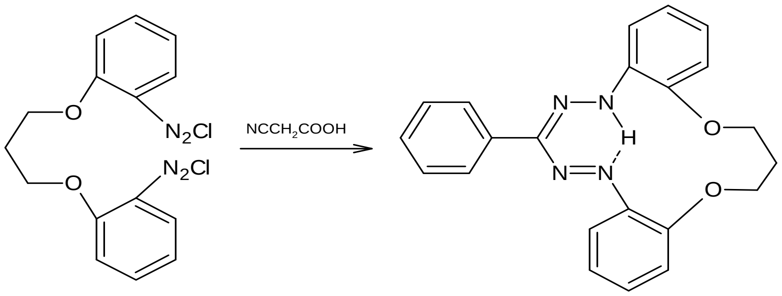
XIX

In 1941 Kuhn and Jerchel[36] studied the biological application of the process. Formazan/tetrazolium system is described as marker of vitality.[37-39]

By the Reaction of Diazonium Salts on Compounds Containing Active Methylene Groups

Diazonium salts when coupled with compounds containing active methylene groups such as aldehydes, ketones, nitroalkanes, cyanoacetic ester, malonic acidesters etc. yield formazans.[28, 35]

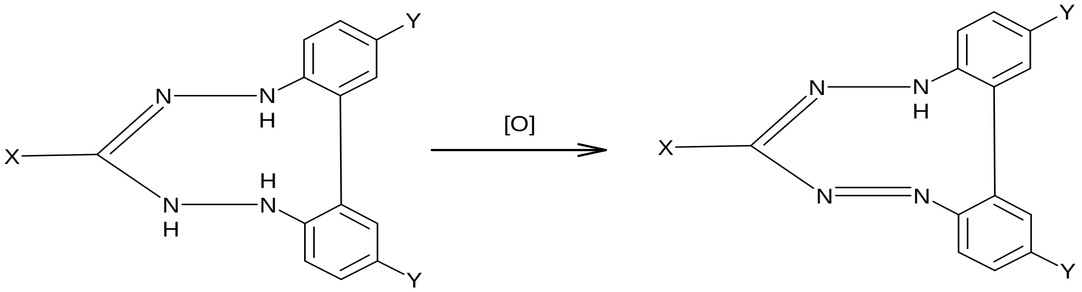
Macrocyclic crown formazans (XX) have been prepared by this method using pyruvic acids and aryl pyruvic acids[40] in 1994.



XX

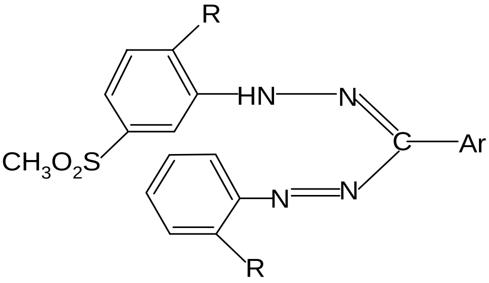
By the Modification of the Substituents Present in Formazans

A change in the functional group substituted in a molecule converts the formazan into another formazan *e.g.* nitro groups can be converted into amines, ester group can be hydrolysed into carboxylic acid, nitriles can be hydrolysed into carboxylic acid, carboxylic acid have been esterified through silver salts and decarboxylation of C-carboxyl group has been reported.[28] There have been very few additions to the synthetic methods available in recent years. Jerchel and Edler[41] have described a novel class of formazans, designated as cycloformazans (XXI) which are obtained by air oxidation of cyclic amidrazones.



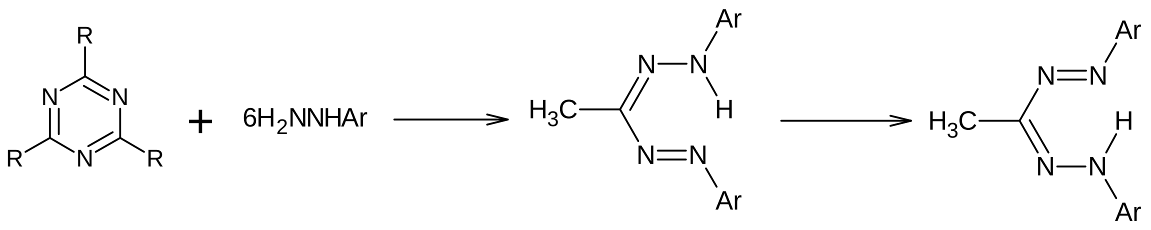
XXI

Zeigler[42] reported a new procedure for the preparation of arylformazans (XXII) in excellent yields by coupling of ArCHXY (XY being electron attracting substituents) in succession with two diazotized amines or aminophenol. The new method is superior to previous one.[43]



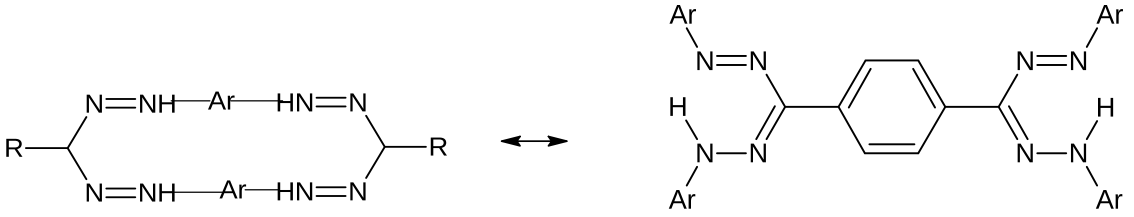
XXII

Formazans with 3-positions either unsubstituted or bearing methyl or phenyl substituents can be prepared by reactions of 1,3,5-triazines with hydrazino compounds[44] as shown in the scheme - II.



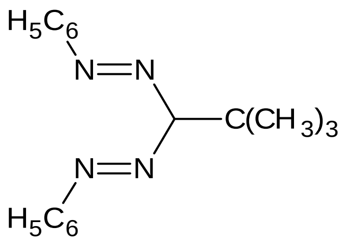
Scheme - II

The preparation of pseudobisformazans (XXIII) by coupling 2-arylazomethylene-1,3-dimethylbenzidazolines with diazotized benzidines in pyridine[45] represent another slight variation of the usual synthetic procedure. No monoformazans are obtained, but the pseudobisformazans tautomerise readily in acid to give the bisformazans.

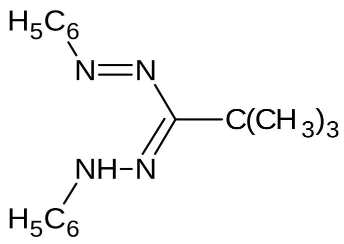


XXIII

In an analogous reaction,[46] tert-butylbis-(phenylazo)-methane (XXIV) on treatment with strong base tautomerise to give formazan (XXV).



XXIV



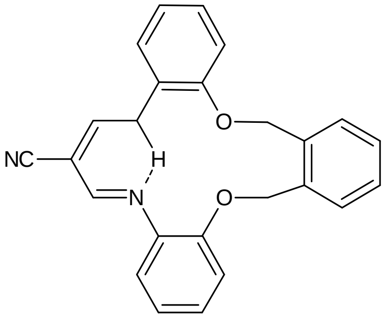
XXV

Kumar and Shanker[47] synthesized cyclic formazans by azo type coupling of dialdimines with 4,4'-diphenylenebis (diazonium chloride)

Synthesis of Crown and Spiro-linked Crown Macrocyclic Formazan

In 1994 Ktritzky et al.[48-50] synthesized the first lariat crown formazan using a phase transfer assisted coupling reaction with active methylene group and studied the complexion ability of such formazans. They found that the high rigidity of the formazans reduces their complex forming tendency.

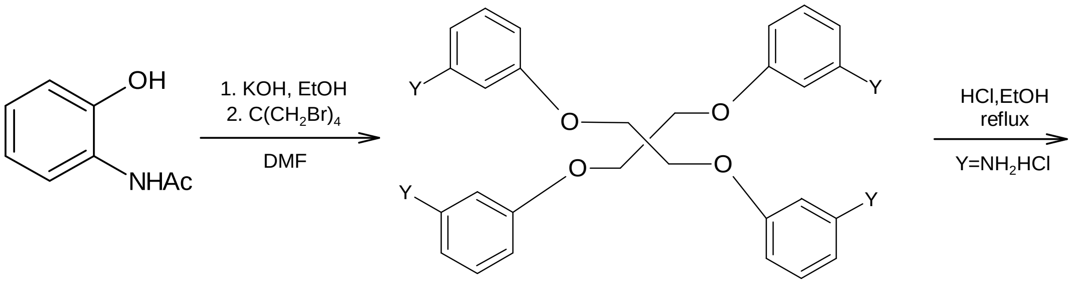
Many macro cyclic formazans have been synthesized (XXVI) and their applications in selective metal extraction and determination have been studied. Such applications depend mainly on the cavity size of the macro cyclic crown formazans as well as on the substituents on the macro cycle.

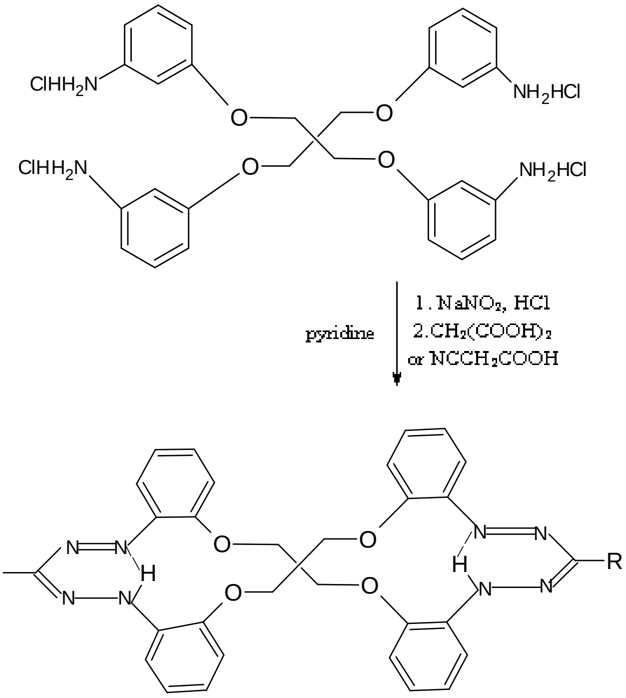


XXVI

Recently, interest has been directed toward the synthesis of multi-site crown compounds. These multi-site molecular receptors are capable of binding two or more guest metal cations. They have been used in the spectrophotometric determination of lithium and as carriers in cesium ion selective electrodes.

Abbas and Elwahy[51] synthesized the spiro linked crown formazans (XXVII) by diazotization of tetrakis amine hydrochlorides followed by their coupling with malonic acid or cyanoacetic acid in pyridine.

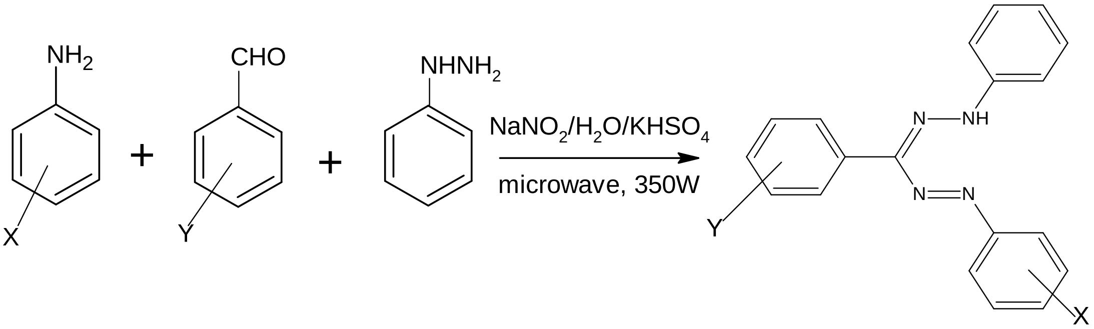




XXVII

Microwave mediated solvent free one-pot synthesis

An alternative green method for the synthesis of formazans in the absence of mineral acids, buffer solutions and volatile organic compounds was developed by Pranab Jyoti Das *et al.*[52] One pot solvent free synthesis of formazans was carried out by mixing 4-nitroaniline, benzaldehyde, phenylhydrazine, $NaNO_2$. $KHSO_4$ and deionised water. The homogeneous mixture was subjected to microwave irradiation at 350W power. The product was obtained in short time in high yield. (scheme-III)



Scheme-III: Microwave mediated solvent free synthesis of formazan.

Physical Properties of Formazans

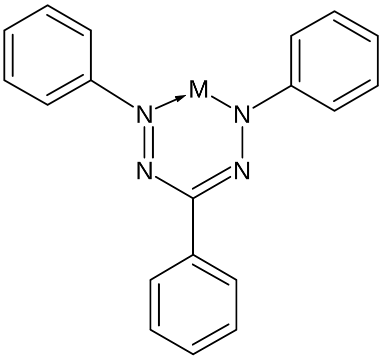
Formazans generally are water insoluble, varied colored solids of relatively low melting point. Most of the triarylformazans tend to melt in the range of 70-215°C. They are characterized by intense colors ranging from yellow-orange through most of the visible light to an intense purplish-black. At the same time, they exhibit brilliant reflex colors and their appearances are very striking.

Substituents affect the color of the formazans. Formazans with aliphatic substituents (hydrogen, methyl, carboxyl etc.) attached to carbon-3 have lighter (yellow-orange) colors while the aryl derivatives bear brighter (deep red) colors. Formazans are water insoluble, except where specifically solubilizing functionality has been introduced in the molecule. However most formazans dissolve in a wide range of common organic solvents like chloroform, acetone etc., bis-formazans of high molecular weight seem to have no appreciable solubility in any other solvent but nitrobenzene.[53]

Formazans may behave as weak acids as well as bases; both of the resulting salts may be hydrolyzed in the cold.[54]

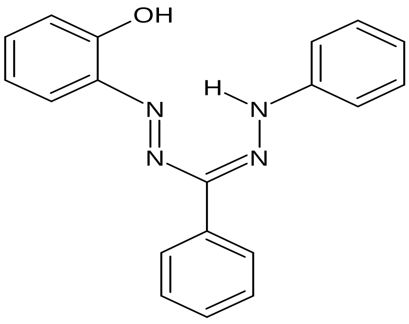
Synthesis of Metal Complexes of Formazans

In 1941, Hunter and Roberts[18] established that 1,3,5-triphenylformazan functions as a bidentate ligand and forms complexes having 2:1 stoichiometry with divalent copper, nickel, and cobalt. These complexes were found to be less stable towards acids (XXVIII).



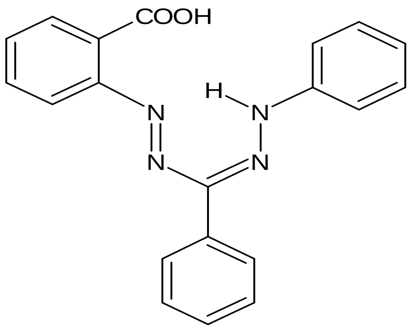
XXVIII

The formazans as ligands have been successfully explored in complex formation reactions. In an endeavor to obtain metal complexes of enhanced stability, Wizinger[55,56] investigated the scope of formazans to function as tri and tetradentate ligands. 1-(2’-hydroxyphenyl) (XXIX) and 1-(2’-carboxyphenyl)-3,5-diphenyl (XXX) formazans form intensely colored bicyclic compounds 1:1 stoichiometry with divalent copper and nickel.[57,58] A considerable shade change occurs on metal complex formation, and the products have enhanced stability towards acids in comparison with metal complexes of bidentate formazans (XXXI and XXXII).



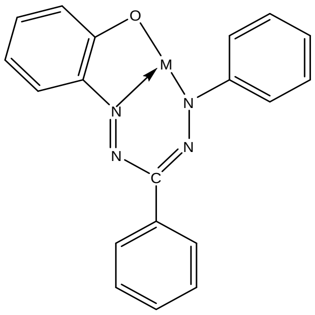
Orange Red

XXIX



Red

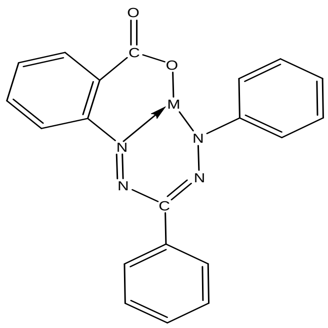
XXX



M= Cu, Violet

M= Ni, Brownish green

XXXI



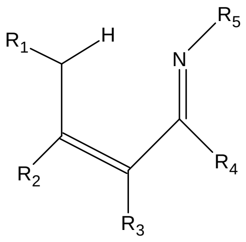
M= Cu, Violet

M= Ni, leaf green

XXXII

In contrast to copper and nickel, divalent cobalt does not form complexes analogous to those of copper and nickel. Various dyestuffs and applications have been claimed for 1:1 metal complexes of tridentate formazans.

Gilroy et al.[59] showed that formazans are close structural analogues of β-diketiminates (XXXIII), possessing two additional nitrogen atoms in their backbone, so scientists chose them as ancillary ligand.



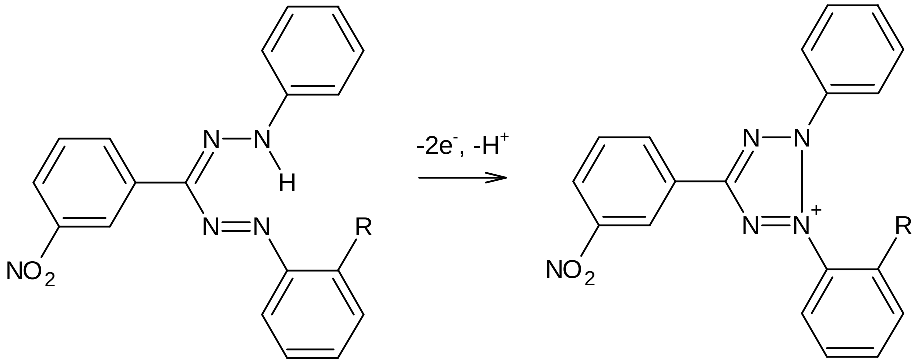
XXXIII

The coordination chemistry of formazans has been extensively explored over the past 60 years, but remains an underdeveloped field. Irving et al.[60] and Dale[61] studied bis- formazan complexes of nickel. Cyclometallated ruthenium complexes were studied by Doff[62] and Ni^{2+} complexes of sulphur containing macro cyclic formazans were studied by Alcock and Tasker.[63]

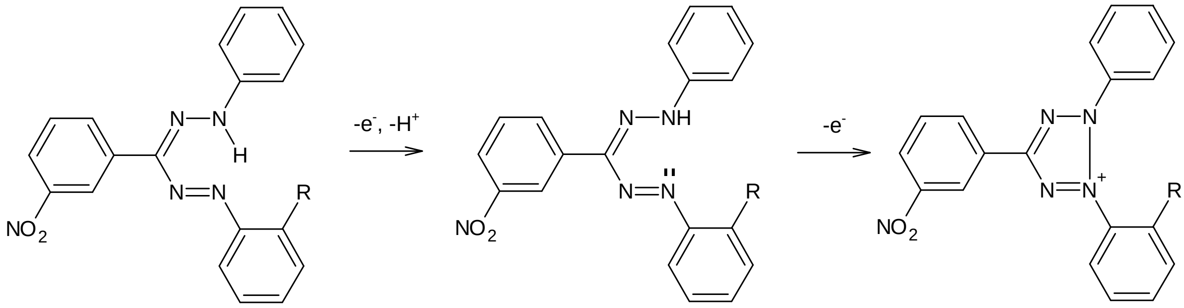
Gilroy[64] synthesized complexes of Fe^{3+}, Co^{3+}, Ni^{2+} and Pd^{2+} metals using 3-cyano-1,5-diphenylformazans and 3-nitro-1,5-diphenylformazans. There have been almost no systematic investigations into the metal complexing tendency of formazans. The metal binding properties of the formazans are associated with noticeable color changes as a result of which they find immense applications as dyes or as metal sensing agents.[65]

Anthryl formazans were tested for their metal complexing tendency using Cu^{2+}, Zn^{2+} and $Cd^{2+}$by Uchiumie et al.[66] With the use of 1H1 NMR and IR analysis and the measurements of magnetic moments an attempt to attribute the chemical structure to both isomers of 1:2 type iron complex of 1-(5'-nitro-2'-hydroxyphenyl)-3-cyano-5-(4''-sulphonamidophenyl) formazan has been made.[67-69] Tezcan and his co-workers[70-75] synthesized metal complexes of formazans with iron and investigated their structural properties, magnetic properties and stability constants depending upon their pH value.

Ni^{2+} complexes of formazans were prepared and characterized by Tezcan et al.[70-72] and the electrochemical investigations were carried out using cyclic voltammetry, linear sweep voltammetry and chronoamperometry. The structures of these formazans were elucidated by elemental analysis GCMS, FTIR and their spectral behavior were investigated using ^{1}HNMR, ^{13}CNMR and UV-visible spectral data. The peak potentials ($E_{\text{oxidation}}$ and $E_{\text{reduction}}$), number of electron transferred (n), diffusion coefficients, heterogeneous rate constants were obtained. The oxidation mechanism occurred in a single step two electron or one electron transfer to disproportionation reaction or dimerization reaction following the radical step formation (scheme - IV and V).

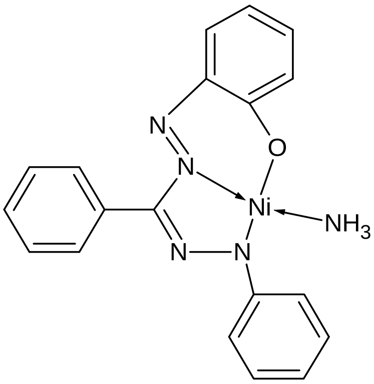


Scheme - IV

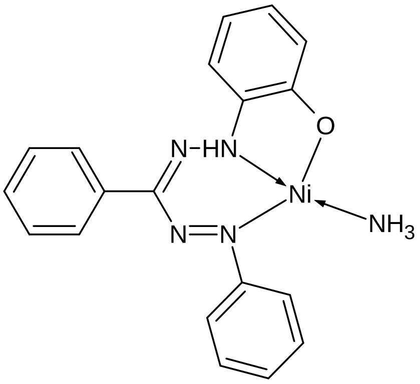


Scheme - V

Balt et al.[76-77] carried out kinetics studies of complex formation between copper (II) and 1-(2-hydroxyphenyl)-3,5-diphenylformazns in an ammonical ethanol-water mixture brought out evidence for a stepwise coordination of tridentate ligand to the metal ion. In 1980 they also reported kinetics and mechanism of complex formation between 1-(2-hydroxyphenyl)-3,5-diphenylformazans (XXXIV) and ammineaqua nickel (II) complexes (XXXV) and they determined that the intermediate is isolobal which in contrast to the more stable isomeric form has five membered formazan ring.



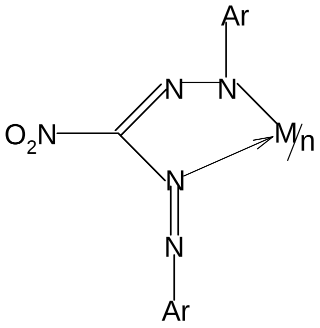
XXXIV



XXXV

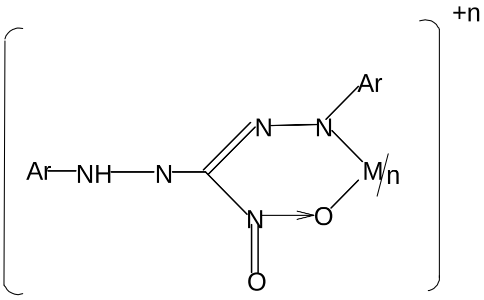
Nitika et al.[65] reported cobalt (III) chelates of 3-nitro-1,5-diarylformazans for the first time and proposed that the symmetrical 3-nitro-1,5-diarylformazans are versatile complex forming agents as the chelation may occur through.

i) Nitrogen 1 and 4 of the formazan group giving structure XXXVI capable of existing in cis or trans geometry.



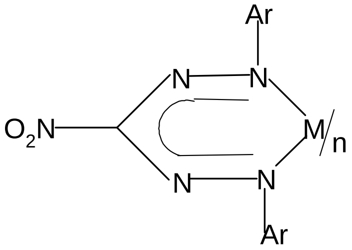
XXXVI

ii) One of the oxygen atoms of the nitro group and one of the four nitrogens of the formazans of giving structures XXXVII and.



XXXVII

iii) Nitrogens 1 and 5 of the formazans giving symmetrical six membered chelates ring structure XXXVIII.



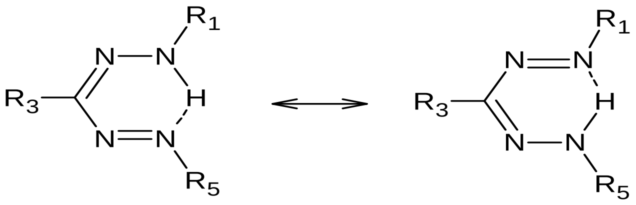
XXXVIII

Structure of Formazans

The structure of formazans was rather complex. The tautomerism of formazans is first described by Pechmann and Runge[14-15] but their results were inconclusive.

In 1941 Hunter and Roberts[22] conclusively established for several pairs of formazans that the individual in each pair was identical, although previously they were described as tautomeric.

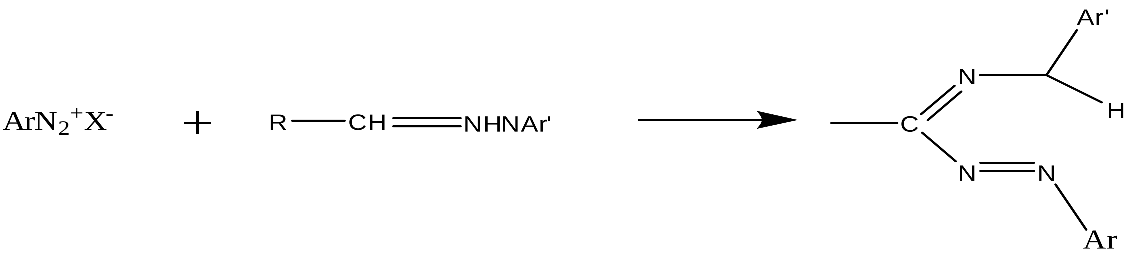
They proposed the existence of internally co-ordinated hydrogen bond structure that existed in two mesomeric forms (XXXIX and XL).



XXXIX **XL**

The product obtained is identical whether the reaction is carried out by any of the following methods.

(i) The condensation of diazonium salt $ArN_2^+X^-$ with phenylhydrazone Ar'NHN=CHR (scheme - VI)



Scheme - VI

(ii) Reaction of diazonium salt $Ar'N_2^+X^-$ with phenylhydrazoneArNHN=CHR (scheme - VII)

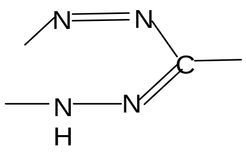
Scheme – VII

The mesomeric forms of 1,5-diphenylformazans are thus indistinguishable. Nineham[28] in summarizing the early literature on this question, cited evidence which enabled him to conclude that.

"When all three substituents in a molecule are alike only one formazan can be synthesized. When two of the three groups are same, only two isomers can be prepared, one with the odd group attached to the carbon, the other with the odd group attached to the nitrogen. When all three substituents are different, three isomers can be prepared"

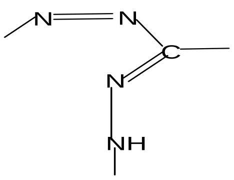
Most of the spectroscopic data till 1970 supported the above viewpoint. Schiele et al.,[78] however, maintained that in certain cases the formazan is more truly represented by a hybrid involving the chelate structures as well. Pechmann[79-81] proposed that the formazans exhibit tautomerism of the type exhibited by amino-azo compounds and amidines in which the mobile hydrogen atom is attached to nitrogen atoms in turn. But Lapworth[17] did not find substantial proof for such a tautomerism in the case of some optically active formazans. A number of reports based on UV-visible, IR, ^{1}HNMR studies of formazans confirm the tautomeric view of formazans.[82-121] A number of studies have been made on the tautomerism, stereoisomerism and state of hydrogen bond in formazans.[122-143] The relation between the structure and color of formazans have also been studied[144,145] and several attempts have been made to explain the intense color of formazans based upon quantum mechanical calculations on π-electron system.[146-151]

Hausser et al.[123-125] showed that some formazans could be changed from red to yellow forms upon exposure to visible light. Formazan can, in principle, adopt any one of sixteen possible geometric isomers due to isomerization about double bonds. However, a formazan allows the existence of four possible structures owing to steric hindrance. The four geometric isomers arise due to the presence of two double bonds (C=N, syn-anti and N=N, cis-trans). The orientation of groups around C=N bond is described using syn/anti nomenclature while that arising due to orientation around N=N assigned cis/trans nomenclature (XLI a-d).



Cis-syn

a



Cis-anti

b

Trans-syn

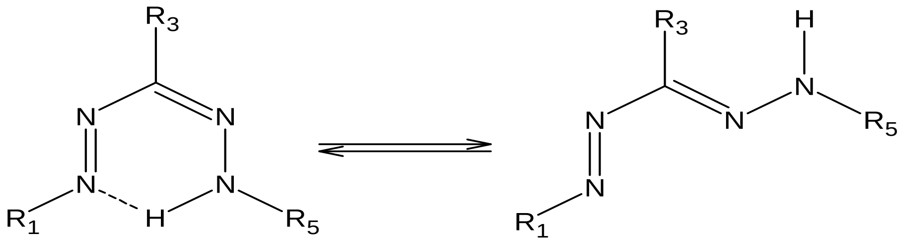
c

Trans-anti

d

XLI

It is obvious from the structure that cis-syn and trans-syn possess chelate structure due to hydrogen bondig whereas cis-anti and trans-anti donot show chelate structure owing to position of N-H. Trans-syn form is the most favorable chelate structure since it has minimum steric hindrance. The different colors of the formazans are due to their different stereoisomers.[152-153] Formazan molecules involving hydrogen bond are red (XLII) while those which are not involved in hydrogen bond are yellow (XLIII).



Red formazan chelate form

XLII

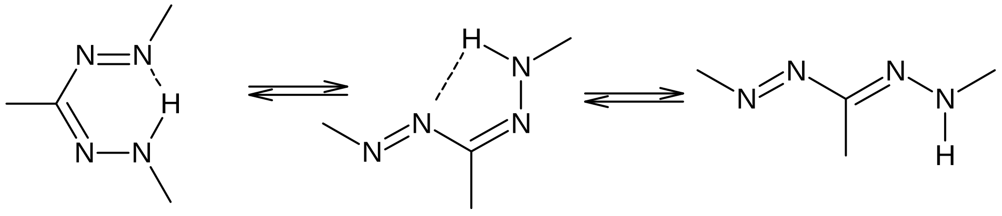
Yellow formazan open form

XLIII

The structure of a formazan chain is influenced significantly by the substituent R in the meso position phenyl and tertiary butyl groups promote the fixation of the chelate form. Alkyl substituents weaken the hydrogen bridge thus leading to the opening of chelate ring, while hydrogen stabilizes the anti, s-trans structure. In the solid state, formazans crystallize as red or orange/yellow solids, with the syn, s-cis or syn, s-trans configurations if red and anti, s-trans if yellow/orange.

Formazan molecule as a whole gives rise to a highly conjugated system. The presence of two multiple bonds in the formazan chain and the N-5 atom with a lone pair electron lead to the overall conjugated system.

Sigiekin et al.[154] has designated the configuration of formazan in terms of E and Z instead of cis, trans or syn, anti.

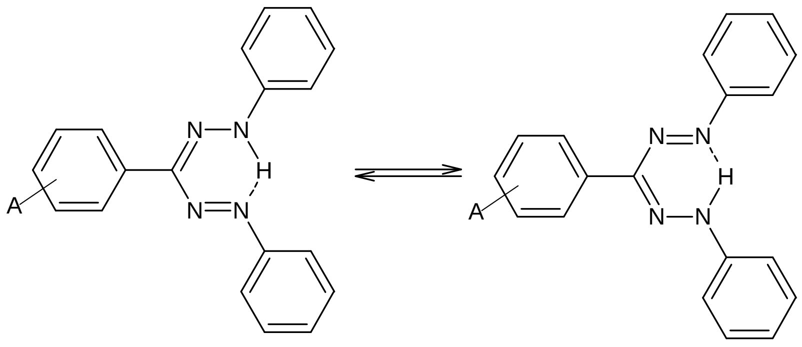


EZZ **EEZ** **EEE**

Scheme – VIII

X-ray diffraction studies of a large series of formazans revealed these configurational combinations in the azohydrazone chain of the crystal EZZ, EEZ and EEE (scheme - VIII). These configurations refer to the bond sequence N1-N2, N2-C3, and C3-N4.

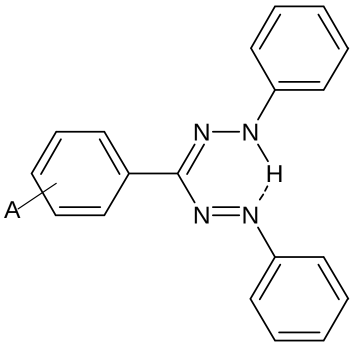
Triphenylformazans exist exclusively as pseudo 6-membered rings in solution and solid state. However, other substituents with relatively small 3-substituents have been observed to adopt different structures. Buemi et al.[155] (1998) investigated formazans and 3-nitroformazan at ab-initio level to explore the various possibilities of intramolecular hydrogen bonding formation. They concluded from their studies that trans-syn-s-cis (TSSC), also called the yellow form was strongly stabilized by a (N-H---N) hydrogen bridge in both the compounds (scheme - IX). The hydrogen bridge results in the formation of a hexa atomic chelate ring, with the possibility of a proton transfer process.



Scheme - IX

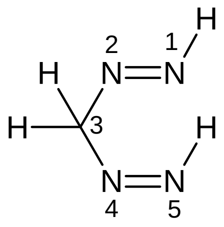
Hydrogen bond Formation and Chelating Property

Tezcan and Ozbek[74] showed that NH hydrogen is involved in hydrogen bond formation upon the electron pair on azo-nitrogen that causes chelation and tautomerism (XLIV).

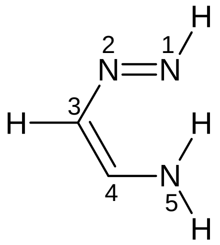


XLIV

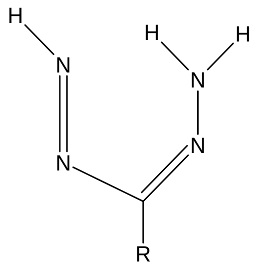
The chelated molecule possess element of symmetry. Comparison of the tautomeric forms of formazan molecule reveals that the tautomer (XLV) is more stable than (XLVI). This is attributed to the loss of conjugation, molecular planarity and hydrogen bonding. The electronic structures of the most favored TSSC (Trans-syn-s-cis) (XLVII), TSST (Trans-syn-s-trans) (XLVIII) and TAST (Trans-anti-s-trans) (XLIX) conformations of the formazans have been compared with the corresponding forms of 1, 5-diphenylformazans.

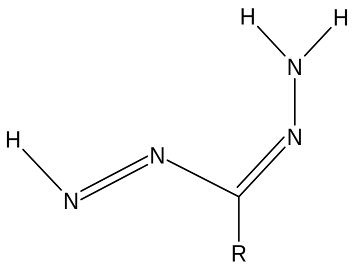


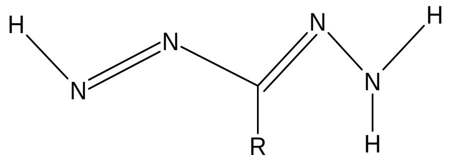
XLV



XLVI







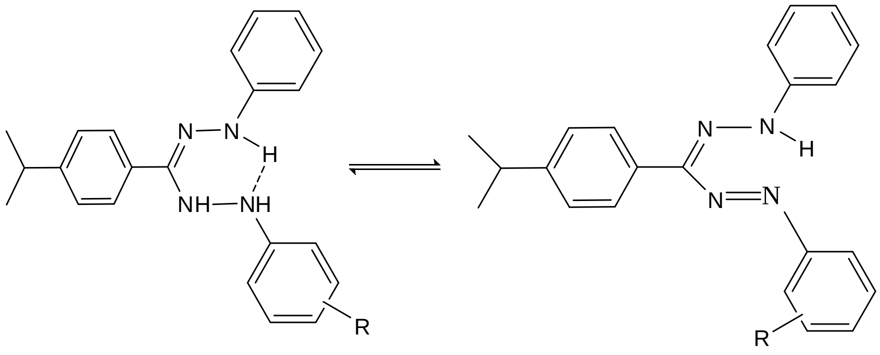
XLVII **XLVIII** **XLIX**

The stability of formazan in low acid solutions can be explained by the influence of substituents R_1, R_2 and R_2’. The electro-optical molecular parameters were substantiated at the level of E_{LUMO} values which prove that the ground electronic state is more stabilized than the excited state. Filip et al.[156-157] reported that the presence of substituents resulted in considerable increase in the dipole moment and electron charge density when compared to the formazan structure that have $(R_1 = R_2 = R_2' = H)$.

Spectral Properties

The characterization of formazans and tetrazolium salts has been done on the basis of UV-visible, IR spectroscopy. However X-ray diffraction studies and NMR spectroscopy have found immense utility in structure elucidation of these compounds in recent years. The formazans are colored compounds and the substituents have marked effect on the UV-visible spectra of the compounds. UV-visible spectroscopy remains an important tool in structural elucidation of formazans.

The FTIR spectra of formazans contain some characteristic bands of the stretching vibrations of the N-H, C-H, C=N and N=N. The weak bands are observed at 3016-3024 cm^{-1} corresponding to N-H symmetric stretching mode. Some N-H stretching modes observed for different substituted formazans are (3000-3600cm^{-1})[158] and (2850-3120 cm^{-1}).[159] However, band shifts are observed with regard to the different substituent-formazan L or LI structure. The chelate ring with intramolecular hydrogen bond appears to be less stable in solution.[160] The C=N stretching band at 1551-1561 cm^{-1} shows non-chelate structure.[161] The shift of these bands to higher frequencies is attributed to the loss of resonance stabilization of the six-membered chelate ring due to the rupture of hydrogen bond.



Chelate Structure

L

Non-Chelated Structure

LI

The lower values of the N=N stretching band can also be explained on the basis of intramolecular hydrogen bond and chelate ring resonance. Tezcan[34] assigned N=N stretching absorption in the region 1330-1455cm^{-1} for some bis-substituted formzans. The N=N stretching band of the chelated form of triphenylformazan is located at 1357cm^{-1} while for non-chelate form it is located at 1418 cm^{-1}.[160] In addition, the lower value of absorption bands N-H (3011-3090 cm^{-1}), pointed towards chelate structure. Majority of formazans of this type are characterized by the lack of N-H absorption band. Chelate structures have a six membered conjugated system that p-electrons are delocalized. The stretching bands of C=N, N=N and N-H are observed at lower frequencies.

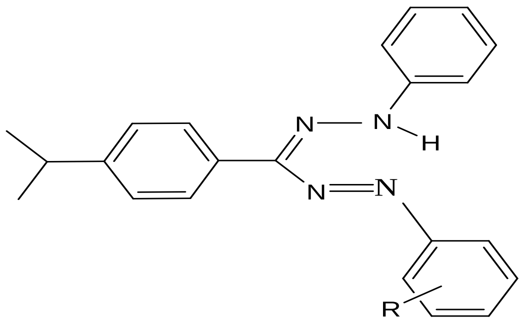
The aromatic nitro compounds have strong absorption due to asymmetric and symmetric stretching vibrations of NO_2 at '1485-1570 cm^{-1} and 1320-1370 cm^{-1}', respectively.[162]

The properties of the formazans have been mostly investigated by UV-visible spectroscopy and theoretical and experimental results have been reported.[163-165] Formazan peaks λ_{max} values are generally observed at 410-500nm and may be shifted to 550-600nm based upon the structure. These peaks are due to π-π* electronic transitions in formazan skeleton.[166] The electronic absorption spectra of the unsubstituted 1,3,5-triphenylformazan show one band at 482nm in visible region.[167] It is a characteristic of formazan structure due to π-π* transitions within the N=N group influenced by charge transfer within the whole molecule.

Besides the one in visible region, three more distinctive bands are visible in UV region.[168] The first band assigned to the phenyl moiety is observed in the wavelength range of 216-239nm. The second band in the range 240-285nm is attributed to the lower energy π-π* transition of the phenyl moiety. The third band within the 300-350nm range and the sharp peak is due to the□□□* transition within the hydrogen chelate ring formed by the azo and hydrazine group and tautomerization occurring within the ring.

With the recent advances in computer hardware and software, it has become feasible to correctly describe the physico-chemical properties of molecules using various computational techniques.[169] Density Functional Theory (DFT) has proved to be a powerful tool in molecular modeling in the recent years. It has greater accuracy in reproducing the experimental values in molecular geometry, vibrational frequency. NMR and UV-Visible spectra.[170-172] It has now become possible to calculate the physicochemical properties of the compounds using better exchange correlation function with more favorable computational costs.[173]

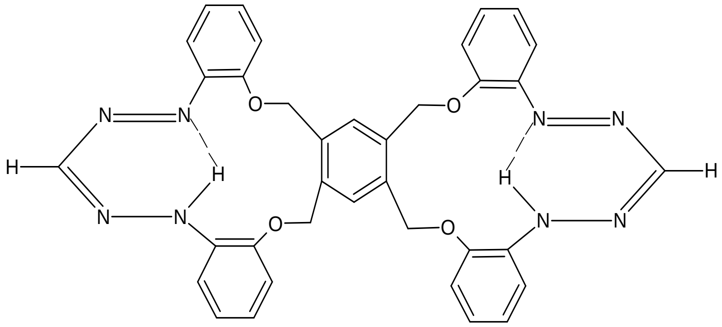
The physico-chemical properties of the various formazans i.e. 3-(*p*-iso-propylphenyl)-5-(*o,m* and *p*-nitrophenyl) (LII) have been studied using DFT calculations. The geometric structures, non-linear optical properties, electrostatic potential, frontier molecular orbital energies, natural bond orbitals, natural atomic charges, chemical stability and thermodynamic properties of these compounds were investigated which provide valuable insight into the molecular properties of formazans.[174]



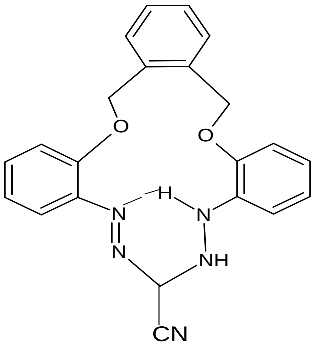
1. R= o-NO_2
2. R= m-NO_2
3. R= p-NO_2

LII

The N-H signal of formazan in NMR is indicative in evaluating the structure. N-H signal in the downfield region at δ12-15 exhibits intramolecular hydrogen bonding while upfield shifts of this signal at δ10 indicate weakening of intramolecular hydrogen bonding. The ^{1}H chemical shift of N-H was observed with the change in substituents. Abbas[51] examined N-H signals of macroscopic bisformazans in ^{1}HNMR of the proposed structures LIII and LIV. Compound LIII exhibited sharp N-H signal in the downfield region at δ15.70 which indicates the formation of intra-molecular hydrogen bonding which can be attributed to be the increased size of the macrocycles.



LIII



LIV

Umemoto[175] (1985) claimed that ditetrazolium salts are reduced to both mono and diformazans by one electron transfer through disprotionation reaction. It was also claimed that in polarography study of formazans, there were two irreversible diffusion controlled processes, each one with one electron transfer.

Abu Elenien[176] reported that formazans are oxidized in a single 2 electron transfer followed by a deprotonation reaction forming tetrazolium cation. In a study of the reduction of tetrazolium salts into formazans with superoxide ions, it is thought to be the cause of ageing and various diseases in human beings, one electron transfer at -0.20V (Ag/AgCl) and $1e^-$ $/1H^+$ transfer at -0.40V (Ag/AgCl).[177]

Applications of Formazans

Biological Applications of Formazans

Formazans, an important class of organic compounds have attracted the interest of many researchers particularly the pharmaceutical chemists, biologists and medical faternity as they are known to possess distinct and several pharmacological activities.[178,179] The biological importance of formazans was first recognised by Kuhn and Jerchel in 1941, their pharmacolgical activities are due to the presence of hydrazo-azo bonds in their molecules. Their pharmacological activity also depends on the nature of substituents present in the molecule at nitrogen atoms 1 and 5 and at the position 3 (meso position).

The relationship between the general structural formulas[178] of various formazans and the biological activity they possess are summarised in table 1.

Table 1: The General Structural Formulas of the various Formazans and their Biological Activities[178-179]

S.No.	General Structure	Their Screened Biological Activity
1	Ar-C=(NNHAr')-N=N-Ar	Antimicrobial Anti-inflammatory Antiviral Anticonvulsant Antioxidant Analgesic Antiparkinsonian
2.	Ar-C(=N-NHAr')-N=N-Het	Antimicrobial Antiviral Anticonvulsant Antiparkinsonian Antiproliferative
3.	Het-C)=N-NHAr')-N=N-Ar	Antiviral
4.	Ar-C(=NNH-R)-N=N-Ar	Antimicrobial Antiviral Antiinflammatory
5.	Ar-C(=NNH-R)-N=N-Ar	Antimicrobial Anti-inflammatory Antiparkinsonian Cardivascular
6.	Het-C(=N-NH-CO-Ar')-N=N-Ar	Antimicrobial
7.	Ar-C(=N-NH-CO-Het)-N=N-Ar	Antimicrobial Antitubercular Anti-oxidant
8.	Het-C(=N-NH-COAr')-N=N-Ar	Anti-inflammatory Antiviral
9.	Ar-C(=N-NH-CO-Het)-N=N-Ar	Antimicrobial Analgesic Anti-inflammatory Anthelmintic Anticancer Anti-HIV

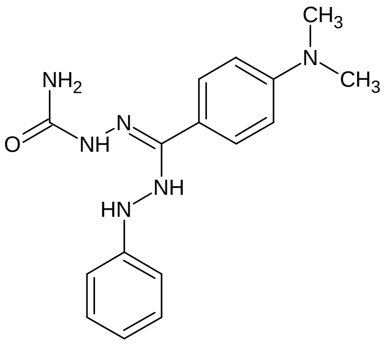
Various substituted formazans are known to possess. antifertility activity,[180] anti-inflammatory active,[181-188] antiviral activity,[189-194] anti-tubercular activity,[195-197] anticancer and anti HIV activities,198-202 anticonvulsant activity,[203-205] anthelmintic activity,[206-207] antiparkinsonian activity,[208-209] cardiovascular activity,[210] antiproliferative activity,[211] analgesic activity[212] as markers of cell vitality and antioxidant activity[212-227] and antimicrobial activities.[228-247]

The tetrazolium-formazan couple is a special redox system acting as a proton-acceptor or as an oxidant.[248] In 1941, Kuhn and Jerchel[21, 31] initiated their biological applications and

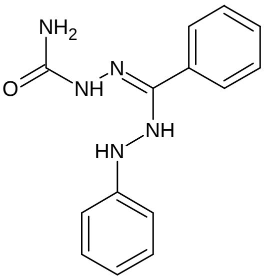
Reid[249] presented a documented survey of their significance in chemistry and biology. Formazan/tetrazolium system is described as the marker of vitality.[250-251]

Adsorption Behavior or Activities

The application of formazans based in their adsorption properties began on 2009 when Anand et al.[252] synthesized formazan of benzaldehyde (FB) and formazan of p-dimethylaminobenzaldehyde (FD) and investigated their corrosion inhibition for mild steel in 1.11N HCl by weight loss method (LIX and LX).



LV



LVI

It was concluded that FB and FD were efficient corrosion inhibitors in HCl solution medium due to the presence of hetero atom and unsaturated bond that results in effective adsorption process leading to formation of an insoluble protective surface film which suppresses the dissolution or eating away of metal. FD was a better inhibitor than FB attributed to the structure dependent electron donor property of the former. The quantum chemical calculations have been proved to be very useful for studying corrosion inhibition mechanism.[253-256]

DFT[257-258] studies have provided a very useful framework for developing new criterion for rationalizing, predicting and eventually understanding many aspects of chemical processes.[259-262]

Udhayakala et al.[263] studied the corrosion inhibition of following formazans.

1. 2-(phenyl(2-phenylhydrazinyl)methylene) hydrazine carboxamide (FB)
2. 2-((4-dimethylamino)phenyl)(2-phenylhydrazinyl)methylene)hydrazinecarboxamide (FD)

The inhibition efficiency of the formazan derivatives have been studied experimentally using weight loss method, potentiometric polarization and electrochemical impedance spectroscopic techniques. The results showed that FB was lesser efficient corrosion inhibitor than FD.[264] Parameters like E_{HOMO}, E_{LUMO}, energy gap (ΔE), dipole moment (μ), Global hardness (η), softness (S), the fraction of electrons transferred (ΔN) and total energy changed were calculated.

The local reactivity was analyzed by means of Fukui indices, since they indicate the reactive regions in the form of nucleophilic and electrophilic behavior of each atom in the molecule. An increase in E_{HOMO}, decrease in E_{LUMO} and decrease in energy gap led to an increase in inhibition efficiency. FD has higher inhibition efficiency due to highest E_{HOMO} and ΔN values.

Sanjeev et al.[265] studied the inhibition efficiencies of 3-substituted formazans of different concentrations for the corrosion of copper in 2N HCl at different temperatures. The formazan derivatives: 1-(p-anisyl)-3-(m-nitrophenyl)-5-phenylformazan (ANPF); 1-(p-tolyl)-3-(m-nitrophenyl)-5-phenylformazan(TNPF); amd 1-(p-cholorophenyl)-3-(m-nitrophenyl)-5-phenylformazan(CNPF) were tested for their possible use as corrosion inhibitors and order of their inhibition efficiency was found to be ANPF>TNPF>CNPF. Various isotherms were tested for the given compounds and the best of the isotherms (Frumkin) was applied to calculate the various thermodynamic parameters like Gibb's free energy of adsorption (ΔG_{ads}), Lateral interaction parameter (f), modified equilibrium binding constant (K), enthalpy of adsorption (ΔH_{ads}), and entropy of adsorption (ΔS_{ads}). The thermodynamic parameters were in compliance with the spontaneity of the process.

A modified electrode, based on electro-deposition of 5,5-(oxybis(4,1-phenylene)bis(3-(2-hydroxyphenyl)-1-phenylformazan onto pencil graphite electrode was investigated by Grocay et al.[266] for the determination of paracetamol.

Analytical Applications

The formazans form colored complexes with many metal ions, some of which are employed as important analytical reagents.[267-268] Owing to their high sensitivity toward many metals and organo metals, they find immense application in analytical chemistry. The complex forming activity and selectivity of formazans and properties of their complexes depend substantially on the nature of the substituents in the formazan ligand. The substitution by the acceptor (Cyano, Nitro) or complex forming (mercapto, hydroxyl and amino) groups via meso position facilitates complex formation. Additional complex forming groups in ortho position of the phenyl ring also affect complexation tendency. Aryl formazans containing sulpho groups and heteroatomic substituents are strongly recommended as prospective analytical reagents for metal ions.[269-270] Such substituted formazans react almost instantaneously with metal ion in organic solution even in cold.[271-288]

Formazan compounds containing heterocyclic groups such as pyridine, thiazole or oxazole ring have been found to be useful photometric reagents with high selectivity and sensitivity.[289] Formazans behave as very weak acids due to the presence of NH protons in the structure. Irving et al.[290] reported that the ionization of NH group is very difficult and expected pK_a value for 1, 3, 5-triphenylformazan is higher than 15. The nature of the substituents in the ortho position (halogen and alkyl groups) as well as the nature of substituent at meso-position affects the stability and acidity of formazans. Their tendencies to form different isomers affect their coordination ability and thus their extraction behavior. Distribution ratios determined for platinum group metals, gold and numerous base metals reveal the selective extractability of Pd(II) from dilute HCl. Grote et al.[291] determined the pK_a values of substituted formazans in mixtures of dioxane and water and concluded that the pK_a values of ortho substituted formazans were generally higher than 11.00. Ortho-iodoformazans is the most effective ligand for extraction of Pd as it forms 1:1 complex with the same whereas all other formazans coordinate as 1:2 chelates. Grote et al. proposed that the separation of Pd (II) from an excess of Pt(IV) can be successfully achieved by ortho-iodoformazan.

Lipunova et al.[292] studied the electrochemical behavior of some heterarylated formazans by introducing them into the bulk of carbon containing inks of thick-film screen printed electrodes for determining copper, lead, Cd and Zn.

Various substituted formazans have been employed an analytical reagents for the photochromic and extactional photometric determination of many metals, which form stable internal complex compounds with formazans.

Formazans have been used for the spectrophotometric determination of lithium, magnesium, aluminum, gallium, indium, thallium, germanium, lead, arsenic, scandium, titanium, vanadium, iron, cobalt, nickel, palladium, copper, silver, zinc, cadmium, mercury, zirconium, hafnium, niobium, yttrium and uranium.[293-301]

Ahmed et al.[302] have determined cerium (IV) using some triphenylformazan derivatives in the presence of cationic surfactant, cetyphyridimium bromide (CPB).

Solvatochromic behavior of 3-cyano Formazans

3-cyanoformazans have been reported to exhibit bathochromiuc shift (positive solvatochromism). The magnitudes of bathochromic shift increases with increase in solvent polarity. Multiple regression techniques have been employed by Sanjeev et al.[303] to evaluate Kamlet-Taft Coefficients. The contribution due to polarizability of the solvents supports the non-specific type of interactions.

Formazans as naked eye chemical sensor

3-cyano-1,5-diarylformazans have been reported to be the naked eye chemical sensor for the detection of the transition metal ions Cu^{2+} and Hg^{2+} by Sanjeev *et al.*[304] The compounds responded to Cu^{2+} even at 1equiuvalent of metal ion with the obvious color change from orange to violet.The detection limit for Cu^{2+} was found to be of order of 10^{-5} M.

CONCLUSION

The present review will pave the way for the future chemists to explore more efficient and synergestic synthetic routes for the synthesis of better funcionalized formazan molecules. These molecules can further revolutionize the new frontiers of formazan chemistry.

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