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Insights

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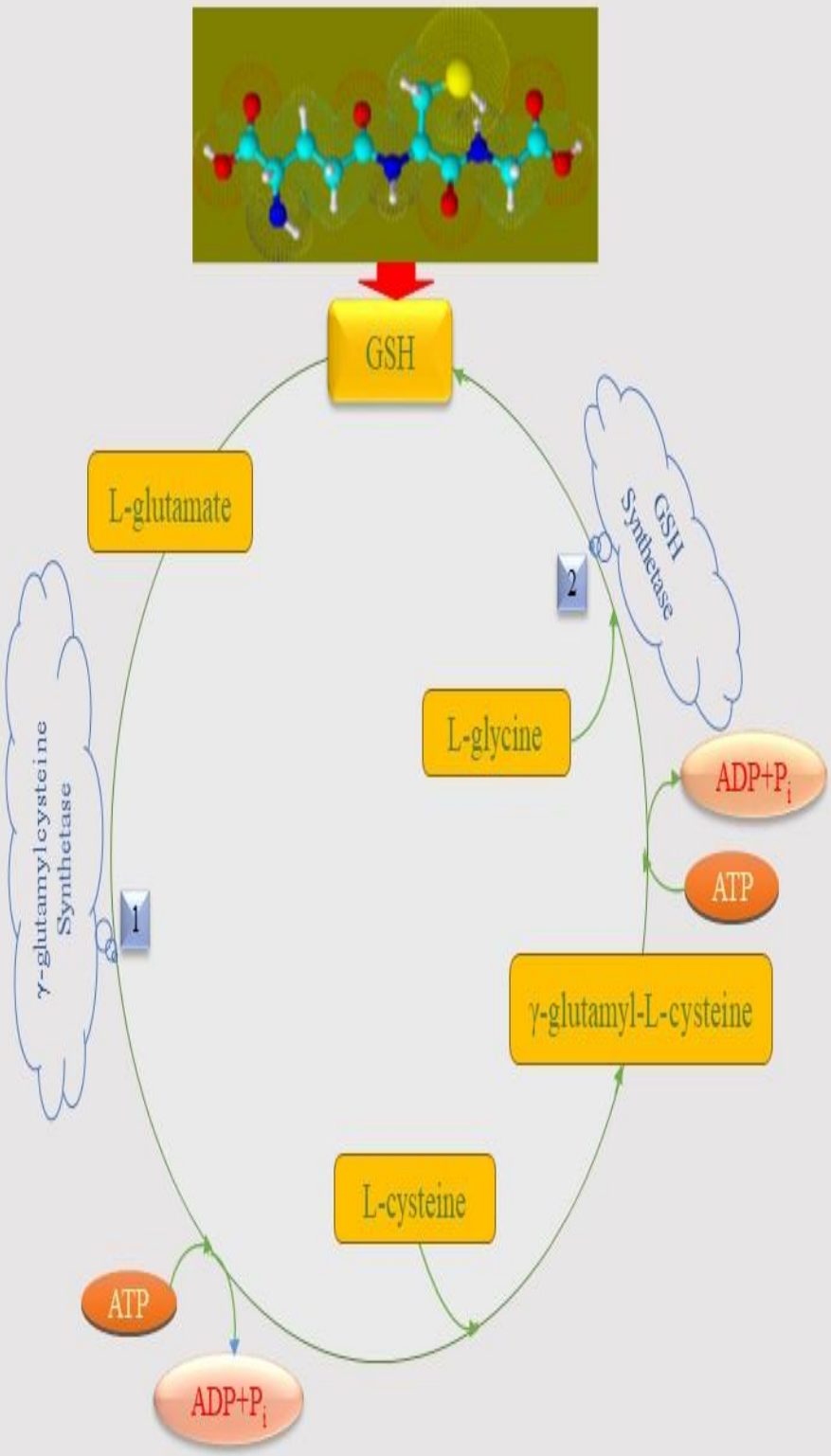

The Chemistry of Glutathione

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The Chemistry of Glutathione

Atef S. Iskander

Glutathione (GSH) is a pivotal endogenous antioxidant found in microorganisms. It is implicated in many vital functions, including defense against oxidative and electrophilic stress, redox homeostasis and protection against xenobiotics. The chemical reactivity of GSH is related to the thiol group of the cysteine residue. To understand how GSH is regulated and functionalized in the biological arena, it is of importance to shed light on the chemistry of thiols. This article focuses on the chemistry of thiols and the biochemistry of GSH as well as a cursory glance at some of the key functions of GSH in the cells.

Keywords: Glutathione, thiols in microorganisms, thiol-disulfide exchange, xenobiotics, oxidative modifications.

1. Introduction

Glutathione (GSH) is the most abundant non-protein thiol that found in all eukaryotic cells.[1] It is produced predominantly in the cytosol[2], and transported to mitochondria[3] and endoplasmic reticulum.[4] Throughout these subcellular organelles, glutathione exists mainly in the thiol-reduced form (GSH), which is then exchanged to the disulfide-oxidized form (GSSG) due to redox reactions. This ubiquitous intracellular peptide can undergo a wide array of physiological functions, including defense against oxidative and electrophilic stress, redox homeostasis, protection against xenobiotics, and modulation of cell proliferation. In fact, there is a high turnover of glutathione in the body, where the liver plays a key role in this dynamic flux. The chemical reactivity of GSH is related to the thiol group of the cysteine residue (the sulfur amino acid precursor). To understand the regulation and functions of GSH in biological arena, the chemistry of the thiol functionality must be taken into consideration. Along these lines, this article focuses on the synthesis and biochemistry of GSH as well as its functions in the cells.

2. Structure and biosynthesis

Historically, de Rey Pailhade discovered glutathione in ‘baker’s yeast’ in 1888, who called it “Substance hydrogènant le soufre” and later on, “philothione” (Greek for love and sulfur) owing to its spontaneous reaction with sulfur to afford hydrogen sulfide. In 1921, Frederick G. Hopkins rediscovered the compound and renamed “glutathione”, where its structure was elucidated in 1930s.[5]

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Glutathione (GSH) is a tripeptide (L-γ-glutamyl-L-cysteinyl-glycine) (Figure 1). The focal point of its reactivity is related to the thiol group of the cysteine residue, which can undergo a wide range of oxidative modifications in response to changes in the intracellular redox environment, and perform several physiological functions. Moreover, the thiol group of cysteine forms covalent cross-links that stabilize protein structure and functioning as a powerful nucleophile in many enzyme active sites.

The bond linking glutamate and cysteine of GSH is through the γ-carboxyl group of glutamate, instead of α-carboxyl group. Such atypical arrangement provides resistance to proteases and is hydrolyzed by γ-glutamyltranspeptidase (GGT), which exists on the surface of mammalian cells. This is the only enzyme able to split this bond and initiate breakdown of GSH to its constituent amino acids.[6] This low molecular weight thiol exists in various cells at low millimolar concentration ranges. In fact, the total protein thiol concentration in human cells is at least two times higher than GSH.[7] However, GSH plays an important role in sulfur metabolism.

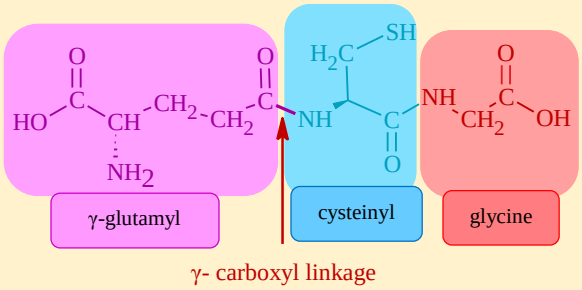

Figure 1. Structure of GSH. The N-terminal glutamate and cysteine are linked by γ-carboxyl group of glutamate.

GSH is synthesized from its constituent amino acids, glutamine which is converted to glutamate through normal metabolic pathways, sharing both of cysteine, and glycine. The intracellular synthesis of GSH is achieved in two enzymatic steps, each requiring hydrolysis of an ATP molecule (Figure 2).

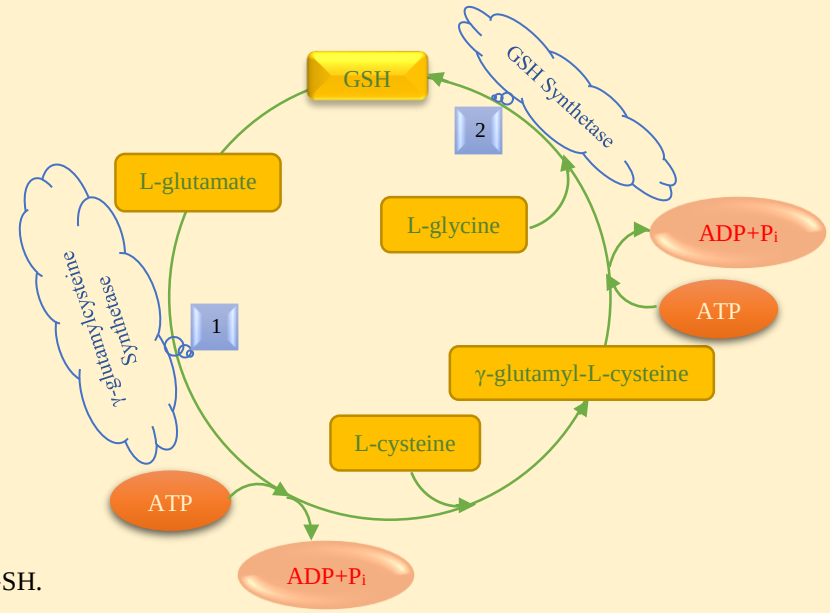

Figure 2. Biosynthesis of GSH.

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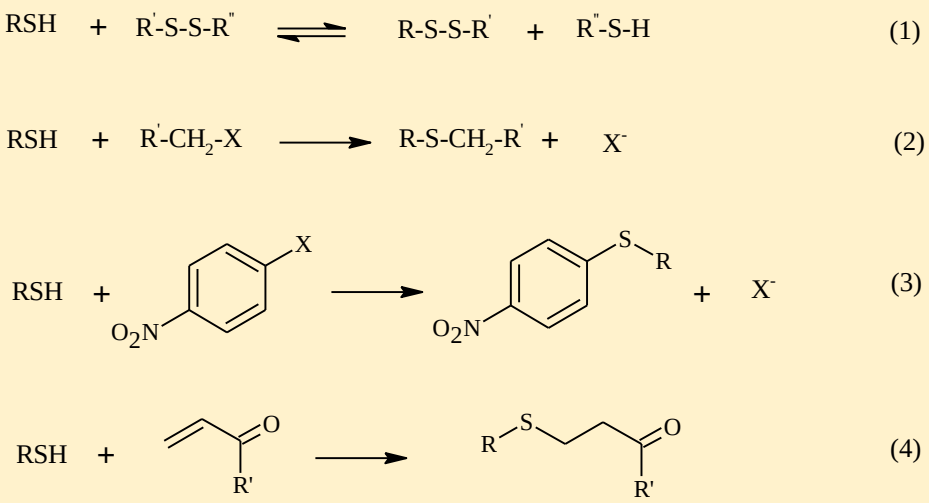
The first step of GSH biosynthesis is catalyzed by γ-glutamylcysteine synthetase (GCL) and considered as the rate limiting, which is required either Mg^{2+} or Mn^{2+}. While the second step is catalyzed by GSH synthetase (GS). GS deficiency in humans can lead to metabolic acidosis, hemolytic anemia and central nervous system damage as a result of the accumulation of γ-glutamylcysteine, which, in turn, is converted to 5-oxoproline.[8]

It is noteworthy to mention that *S*-adenosyl-L-methionine (AdoMet) is a precursor to the transsulfuration pathway, the metabolic pathway responsible for condensing homocysteine to form cystathionine, which is then converted to cysteine. Consequently, a decreasing in AdoMet leads to GSH depletion.

3. The chemistry of thiols

As the most abundant non-protein thiol in mammals, GSH plays an important role in sulfur metabolism. This is related to the presence of a thiol functional group. In a general sense, the thiol functional group is essential for reactivity of many enzymes such as thiol proteases, β-ketoacylthiolase, glyceraldehyde-3-phosphate dehydrogenase, and adenylate kinase.[9] Indeed, the thiol group can serve as an important site for many post-translational modifications.

Thiols are mild acids and the pK_a value of thiol residue in glutathione has been estimated to be 9.1[10]. However, the protein microenvironment can dramatically impact the pK_a value. Moreover, thiols are considered as a potent nucleophile under physiological conditions. For instance, thiol can react with disulfide to form a new disulfide and a thiol derived from the original disulfide (thiol-disulfide exchange) (Eq. 1). Furthermore, thiol reacts with alkyl halides (Eq. 2); and halonitrobenzen (Eq. 3) to give the corresponding thioethers. It also undergoes Michael addition reaction (Eq. 4).



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In biological landscape, thiol-disulfide exchange presents a cornerstone of action of many enzymes. The thiolate side chain of GSH is a stronger nucleophile and readily reacts with oxidants and electrophilic species. Such remarkable reactivity indicates that GSH can play an important biological role in catalysis. In fact, the formation of a strong covalent disulfide bond between two GSH residues or between a GSH residue and low-molecular-weight thiol involves the cleavage and formation of the S-S bond (bond energy *ca.* 60 kcal mol^{-1}). This may have a significant impact on the structure and function of the redox pairs of macro-molecule.[11] The reaction occurs reversibly at room temperature in water at physiological pH (*ca.* 7)[12], and its half-life is *ca.* 2 h for mM concentrations of thiol and disulfide in aqueous solution at pH 7. Thiol-disulfide exchange is an S_N2 reaction, where thiolate anion (RS^-) is the active nucleophile and a good leaving group because of its high polarizability and low degree of solvation. The reaction proceeds via a single transition state with little conformational distortion.[13] The geometry of the transition state has been estimated to be a trigonal bipyramidal configuration at the central sulfur with the nucleophile and leaving sulfurs in apical positions.[14]

Because protein disulfide generation requires thiolate anion (conjugated base of a thiol), the rate of reaction depends upon the pH and the extent of ionization of various thiols. For instance, thiolate anion can react with sulfenic acid (Eq. 5); sulfenyl halides (Eq. 6); sulfenyl thiocyanates (Eq. 7); thiosulfinate esters (Eq.8); and *S*-nitrosothiols (Eq. 9) to yield the corresponding disulfides.

$$R\text{-}S\text{-}OH + R'S^- \longrightarrow R\text{-}S\text{-}S\text{-}R' + OH^- \quad (5)$$

$$R\text{-}S\text{-}X + R'S^- \longrightarrow R\text{-}S\text{-}S\text{-}R' + X^- \quad (6)$$

$$R\text{-}S\text{-}S\text{-}CN + R'S^- \longrightarrow R\text{-}S\text{-}S\text{-}R' + SCN^- \quad (7)$$

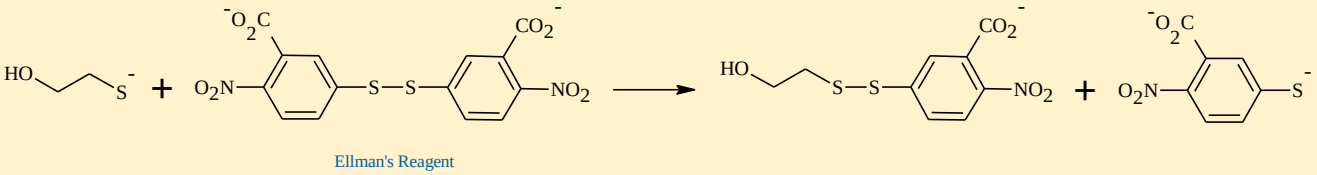
$$R\text{-}S\text{-}S(O)R_1 + R'S^- \longrightarrow R\text{-}S\text{-}S\text{-}R' + R_1SO^- \quad (8)$$

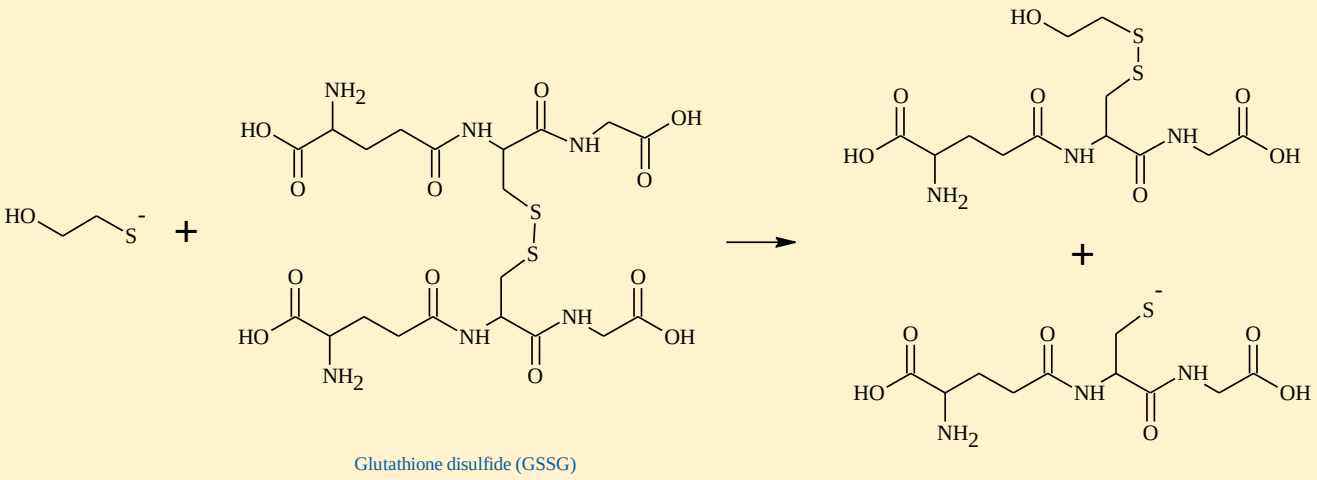
$$R\text{-}S\text{-}NO + R'S^- \longrightarrow R\text{-}S\text{-}S\text{-}R' + NO^- \quad (9)$$

As protein thiol-disulfide exchange reaction is one of the most important sulfur-based reactions in biology, which can regulate the structure and reactivity of proteins, the factors that influenced its rate include the pK_a of the thiolate anion; the leaving group thiol; nearby charged amino acid residues; and steric effects. In addition, the rate constant is affected by CSSC dihedral angle in the disulfide, which its optimum angle is estimated by *ca.* 90º.

As an example to demonstrate the influence of acidity of the substrate thiols on the rate constants of thiolate-disulfide exchange reactions is the utility of Ellman's reagent for the detection and monitor the quantity of protein free thiols. The reaction of mercaptoethanol with Ellman's disulfide, 5,5'-dithiobis(2-nitrobenzoic acid (DTNB), (k_{RS^-} = 1.5 x 10^7 $M^{-1}min^{-1}$)[15] is significantly faster than that of mercaptoethanol with glutathione disulfide (k_{RS^-} = 3.4 x 10^3 $M^{-1}min^{-1}$)[16] in water, the relevant values of pK_a are 4.5 for DTNB

and 8.7 for GSH (Scheme 1). The rate constant (k_{RS}^-) increases with increasing values of pK_a of the thiols because of the increasing nucleophilicity of the thiolate anions.





Scheme 1. Thiol-disulfide exchange reaction.

Thiolate-disulfide exchange reactions are faster in polar aprotic solvents, e.g., DMSO, DMF, than polar protic solvent, e.g., water, methanol. This may be explained by a smaller destabilization of the transition state than of the ground state thiolate, in going from polar protic solvents to polar aprotic solvents (Figure 3). On the other hand, the value of $\Delta S^{\#}$ for the reaction in polar protic and polar aprotic solvents is *ca.* -10 to -16 cal $K^{-1}mol^{-1}$.[17] Such decrease in entropy in the transition state relative to two particles in the ground state is partially compensated either by release of solvent molecules attached to the thiolate in the ground state,[17] or by a relatively loose transition state structure (with two weak, partial S…S bonds) or both.

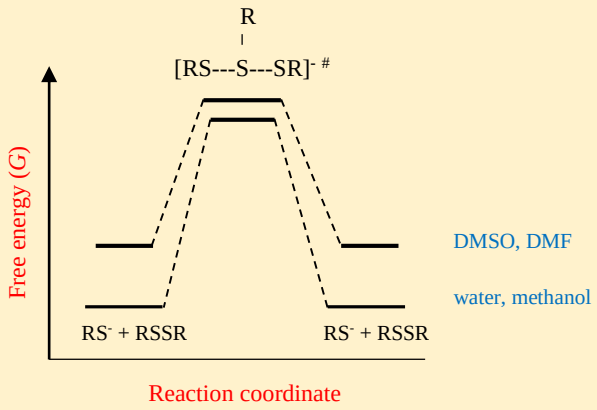


Figure 3. Hypothetical plot of free energy (*G*) vs. reaction coordinate for thiolate-disulfide exchange reaction in polar protic solvents (water, methanol) and in polar aprotic solvents (DMSO, DMF).

4. Functions of glutathione in the cell

GSH is a multifunctional compound that influences vital cellular processes, including detoxifying electrophilic xenobiotics; maintaining the thiol level of proteins; scavenging free radicals; regulating nitric oxide homeostasis; and other biological reactions. A cursory glance at some of the key functions of GSH is highlighted.

4.1. Protection against oxidative and electrophilic stress

The main function of GSH is to defend the cell against oxidative and electrophilic stress. GSH is a critical endogenous antioxidant, able to react at high rates with free radicals. For example, the neutralizing of reactive oxygen species (ROS) such as peroxides or free radicals, yields GSSG (Scheme 2). Hence, an increased GSSG/GSH ratio is indicative of oxidative stress.[18] Therefore, such a shift has major impacts on cellular signaling, thiol disulfide exchange reactions, and cell proliferation.[19] Reactive oxygen species are a family of molecules that produced in cells as consequence of aerobic life, and have been associated with physiological oxidative stress from mitochondrial respiration, and can lead to cell injury. They encompass a wide class of activated oxygen radicals, which can undergo further reaction with nitrogen or sulfur compounds to form reactive nitrogen (RNS) or sulfur (RSS) species.

GSH is also a substrate for glutathione peroxidases, a family of enzymes reducing hydrogen peroxide formed inevitably in aerobic cells, at the expense of oxidation of glutathione to dimeric glutathione disulfide (GSSG), which can be reduced back to GSH by the co-enzyme nicotinamide adenine dinucleotide phosphate oxidase (NADPH) in a reaction catalyzed by glutathione reductase (Scheme 3). The importance of this pathway is demonstrated by individuals suffering from an inborn deficiency of glucose 6-phosphate

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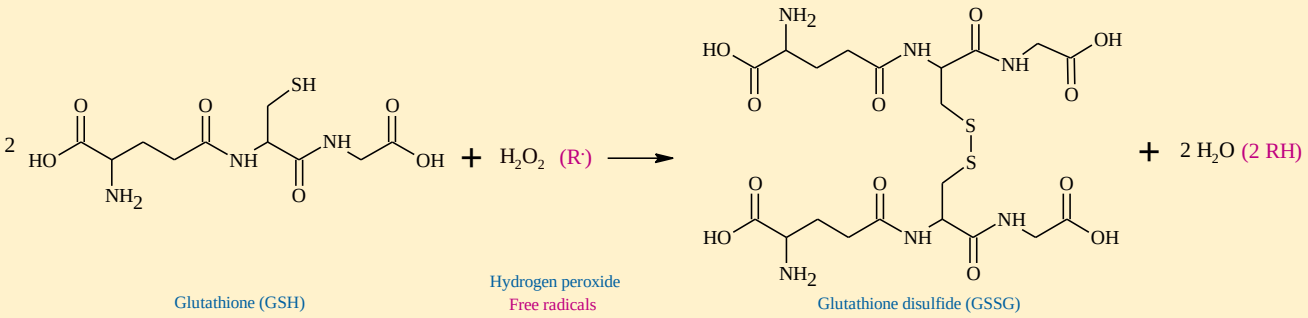
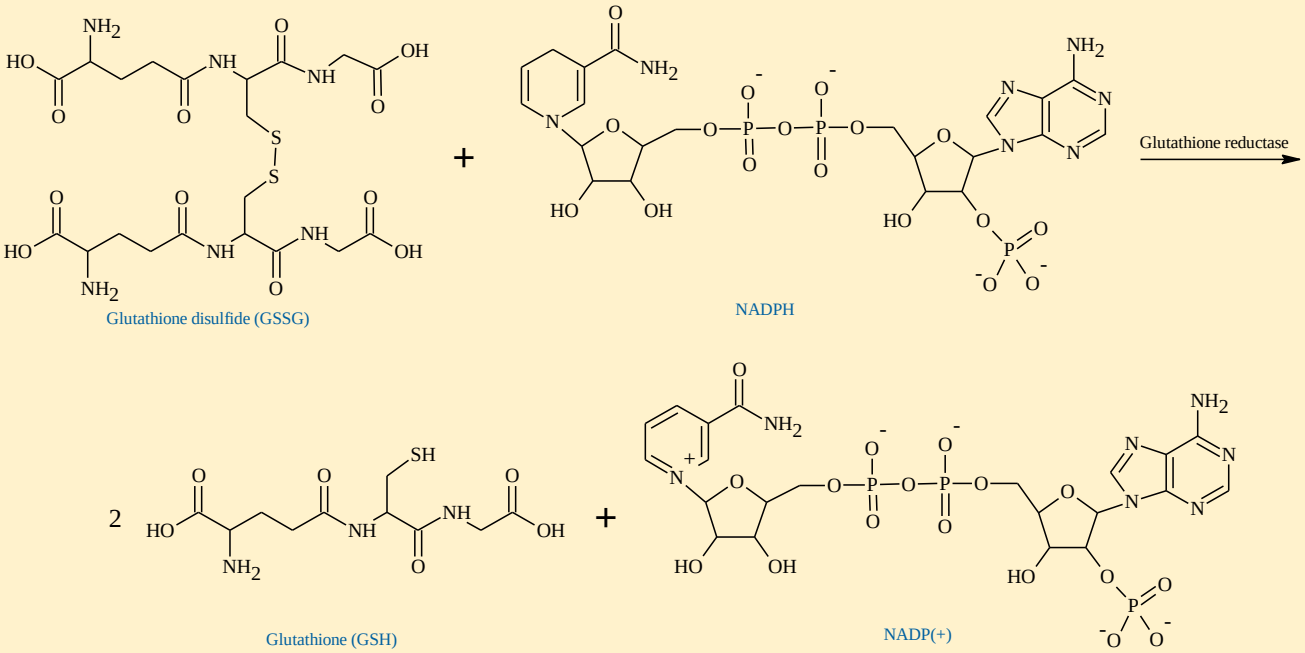
dehydrogenase. The inability to provide NADPH for reduction of GSSG leads to haemolytic episodes after ingesting certain drugs or fava beans rich in compounds generating H_2O_2 (a condition referred to as favism).



Scheme 2. The reduction of reactive oxygen species.



Scheme 3. The reduction of glutathione disulfide (GSSG) to glutathione (GSH) catalyzed by glutathione reductase.

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4.2. *Serving as a redox buffer*

GSH is the main redox buffer of the cell and is critical for maintenance of the redox homeostasis. A vast majority of cytosolic glutathione is in the reduced form, which is important for preventing the undesired oxidation of functional protein thiol groups. Such oxidation may lead to formation of mixed protein-glutathione disulfides, which their reduction may be a way for protecting protein thiols against further oxidation. The ratio of concentrations of reduced to oxidized glutathione (GSH/GSSG) is an important index of the physiological status of the cell. Its redox potential is low in rapidly growing cells, but increases sharply during cell differentiation as well as apoptosis.

4.3 *Detoxifying electrophilic xenobiotics*

A crucial function of GSH is the protection against reactive electrophilic xenobiotics. These compounds react with GSH in the absence of enzymes, however glutathione *S*-transferases (GSTs) extremely catalyze such reaction. The conjugates formed of potentially dangerous toxins are converted into less reactive and more hydrophilic compounds, which excreted from the cell. The cell's ability to survive tough conditions in different biological processes relies on the level of GSH. Both of exogenous and endogenously produced compounds undergo the same metabolic processes.

4.4 *Protection of vitamin B_{12} from depletion by xenobiotics*

Another important function of GSH is to protect vitamin B_{12} from depletion by xenobiotics such as those formed in mammalian metabolism of the industrial chemicals, e.g., styrene, chloroprene, and 1,3-butadien. It is well known that in microsomes, NADPH reduces the hydroxycob(III)alamin, a form of vitamin B_{12}, to cob(II)alamin and the supernucleophilic Cob(I)alamin [Cbl(I)], which are both highly reactive toward electrophilic xenobiotic compounds. The remarkable reactivity of Cbl(I) – one of the powerful nucleophiles known – is *ca.* 5 orders of magnitude more nucleophilic than thiols. However, the formation of glutathionyl-cobalamin (GS-Cbl) from the reaction of hydroxocob(III)alamin with GSH, blocks reactions of the cobalamins with metabolically formed epoxides, and protect vitamin B_{12} from destruction by xenobiotics.[20]

5. Conclusion

It is becoming clear that electrophilic xenobiotics can dramatically deplete the GSH pool, especially in liver. Several biochemical issues related to the thiol-disulfide exchange increase the challenge of studying the degree of stability imparted to the protein by the disulfide bond; the strain in the large-ring protein disulfides; the role and mode of the thiol-disulfide exchange in regulation of protein activity; and the design of drugs that can efficiently maintain and/or restore the GSH pool, would be important and valuable.

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Snapshots of some topics of interest of recent notable advances in chemistry

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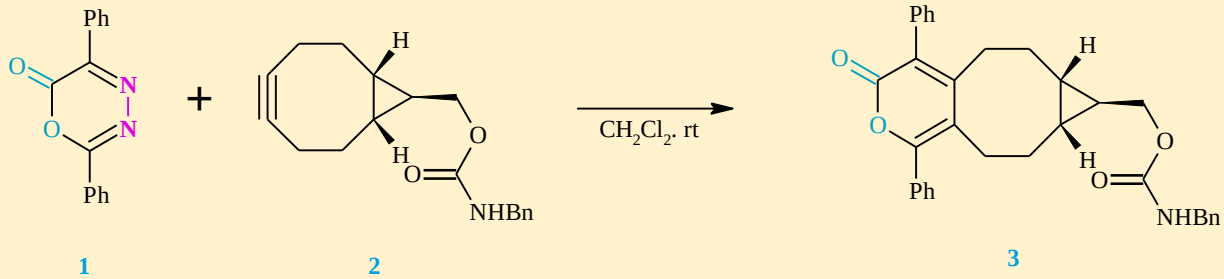
An Efficient Two-step Unsymmetrical Doubly-ring-fused Benzene Construction Procedure

A facile two-step method for the synthesis of partially reduced polyaromatics is described. The procedure is based on sequential reactions of oxadiazinones, as a cornerstone molecule, with cycloalkynes and arynes.

In the light of the potential importance of multiply ring-fused aromatic compounds in a wide range of disciplines and limited efficient synthetic methods, Hosoya and co-workers reported a modular synthetic pathway that employs oxadiazinones, as a cornerstone molecule, for the preparation of various unsymmetrical doubly-ring-fused benzene derivatives. Taking advantage of the electron-deficient dienes of oxadiazinones, their sequential Diels-Alder reactions with electron-rich dienophiles such as cycloalkynes and arynes afforded a wide range of partially reduced polyaromatics. The reaction proceeded with liberation of nitrogen and carbon dioxides.

The reaction of oxadiazinone **1** with bicyclo[6.1.0]nonyne (BCN) derivative **2** in dichloromethane at room temperature afforded pyrone **3** quantitatively (Scheme 1).



Scheme 1. Synthesis of cyclooctene-fused pyrones.

Based on the sequential benzene ring construction strategy, 9,10-di(2-thienyl)anthracene derivative **7** was obtained from oxadiazinone **4** via sequential reactions with 2-(trimethylsilyl)cyclohexen-1-yl triflate **5** and 4,5-dimethoxybenzyne **6** in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT) in THF at 60 ºC (Scheme 2).

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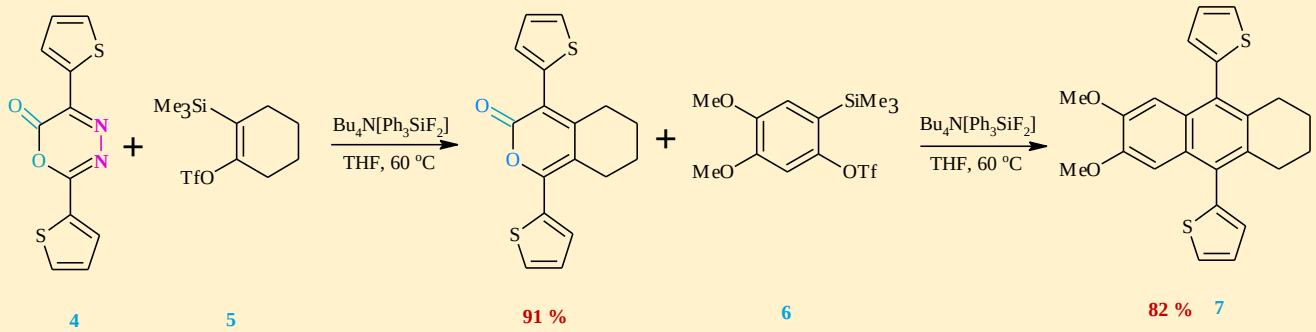
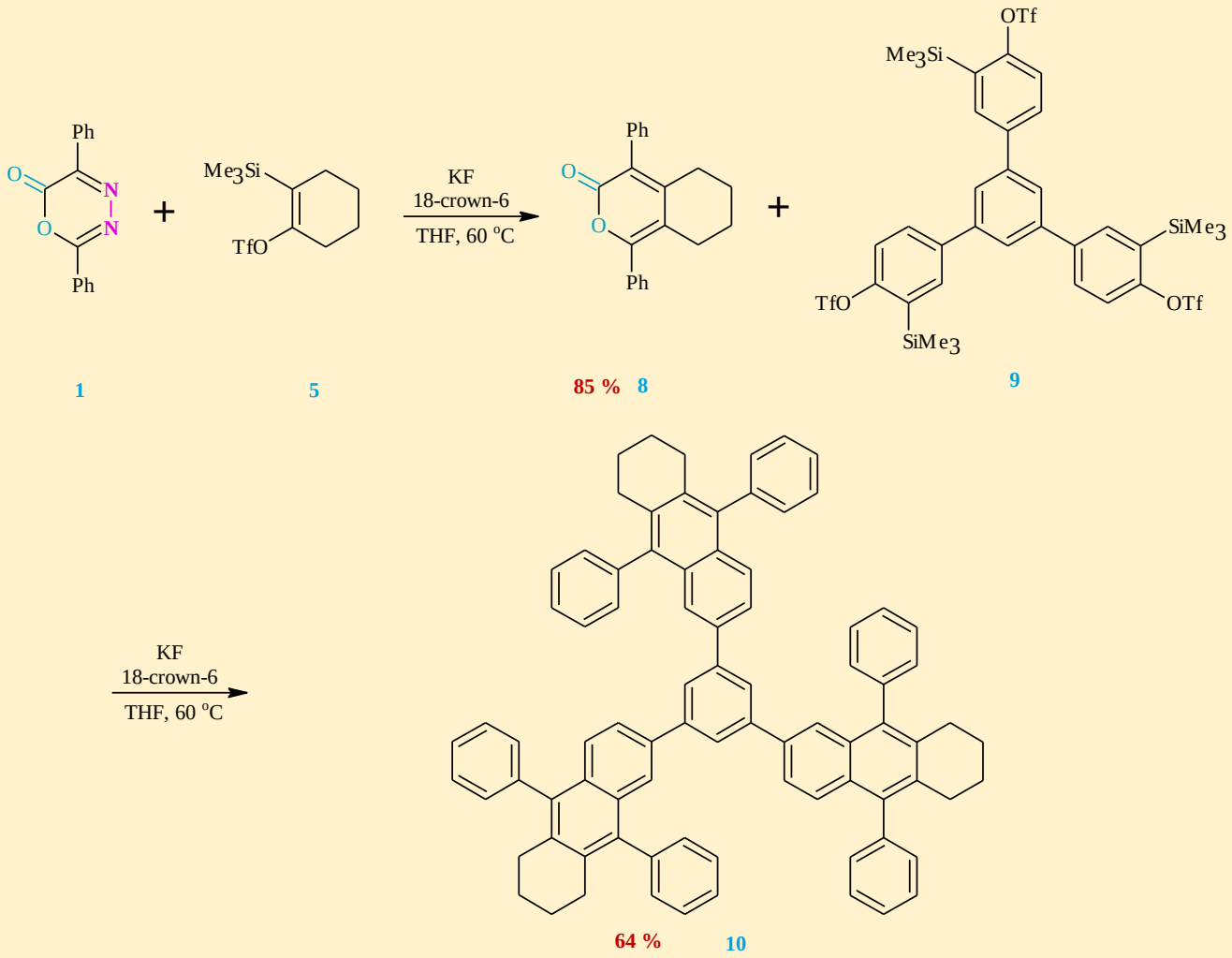


4 5 91 % 6 82 % 7

Scheme 2. Sequential benzene ring construction from **5**.

In addition, 1,2,3-tri(anthracenyl)benzene derivative **10** was obtained by treating a mixture of cyclohexene-fused pyrone **8** and aryne precursor **9** with potassium fluoride and 18-crown-6 (Scheme 3).

This procedure would be valuable for synthesis of partially reduced polyaromatics.



1 5 85 % 8 9

64 % 10

Scheme 3. Synthesis of tetrahydroanthracene **10**.

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T. Meguro, S. Chen, K. Kanemoto, S. Yoshida, T. Hosoya, *Chem. Lett.*, **2019**, *48*, 582-858.

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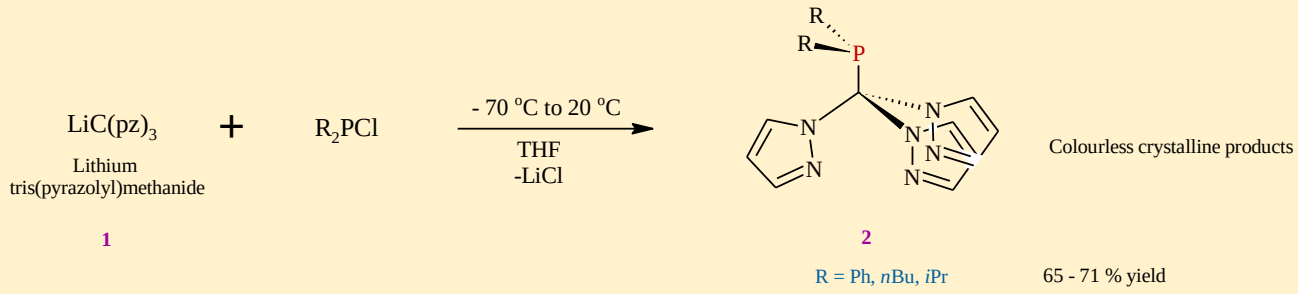
Third Generation Scorpionates

A novel class of phosphine-functionalized tris(pyrazolyl)methane ligands is described. This family of ligands is characterized by many different coordination modes for several transition metals. In addition, the synthesis of the first heterobimetallic complex of a tris(pyrazolyl)methyl phosphine containing the metals palladium and copper is presented.

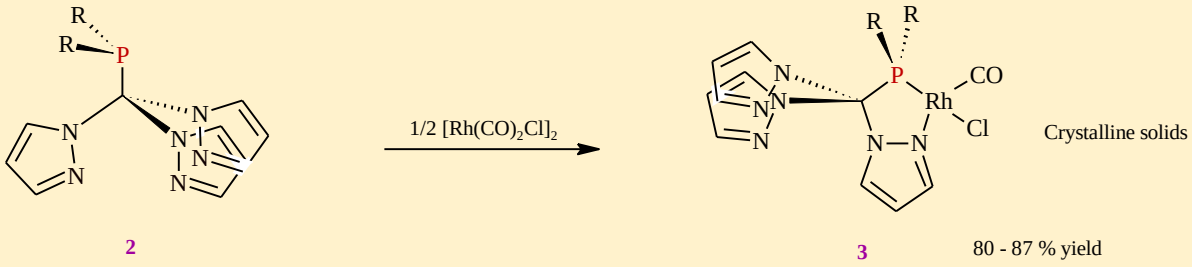
Scorpionate-type ligand is a class of molecules that contains tripodal ligand analogs to Trofimenko's model ligand, tris(pyrazol-1-yl)borate anions (Tp), with central atoms other than boron, such as carbon, nitrogen, silicon, and phosphorus. Like the pincer of scorpion, these tripodal ligands bind metal centers with nitrogen atoms from two pyrazole rings attached to the central atom, while the third pyrazole rings attached to the central atom rotates forward like a scorpion's tail to "sting" the metal; hence the name of scorpionates. Owing to the trigonal nature of these ligands, they preferably link to metal ions by occupying a trigonal face of a coordination polyhedron (*fac* binding), as a tetrahedron or as an octahedron, so that the T-shaped coordination mode (*mer* binding) is precluded.

In order to further increase the number of donor atoms in scorpionate-type ligand scaffolds alongside the previously developed anionic tris(pyrazolyl)methanide and -silanide ligands, more likely donor-containing entities can be introduced at the apical central atom or at 3-position of the pyrazolyl ring, which they can serve as non-coordinating back position. Such ligand systems are referred to as third generation scorpionates. Breher's team reported new phosphine-functionalized tris(pyrazolyl)methane ligands ($TpmPR_2$) as neutral, backbone-functionalized hybrid ligands featuring additional C_{apical}-bound PR_2 donor sets (Scheme 1).



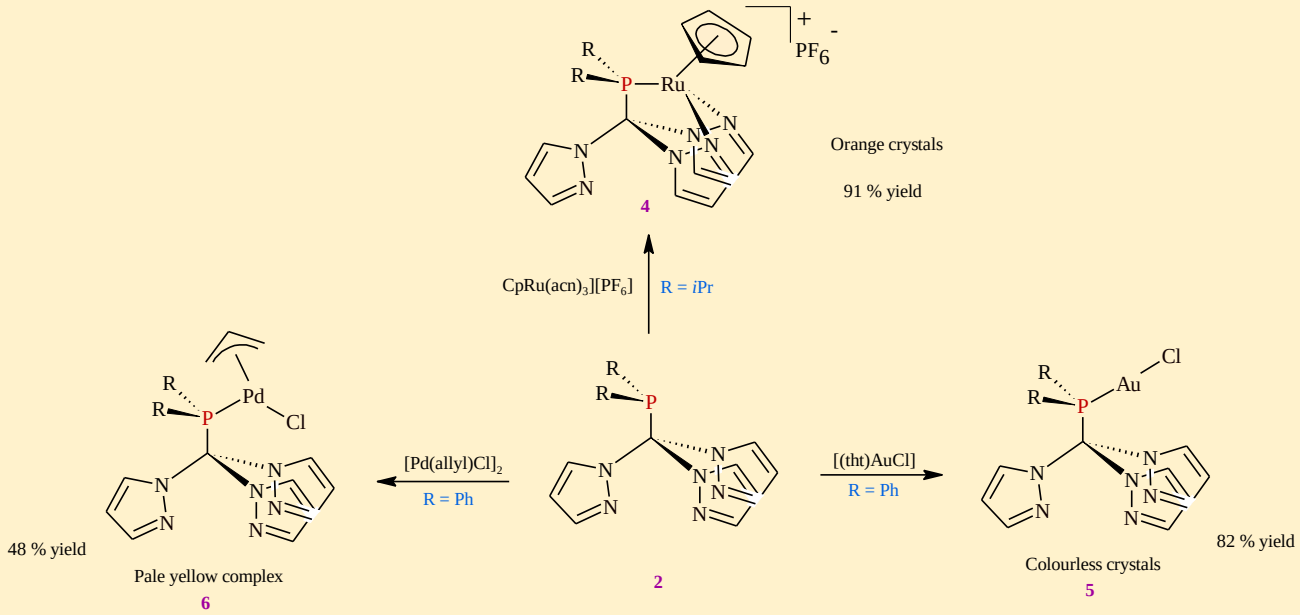
Scheme 1. Preparation of heteroscorpionate ligand.

The coordination behavior of these ligands (**2**) with the mononuclear rhodium carbonyl complexes $[Rh(CO)_2Cl_2]_2$ showed that these hybrid ligands either act as bi- or tridentate chelate providing complexes (**3**) bearing only one carbonyl group (Scheme 2).



Scheme 2. Synthesis of d-block metal complexes coordinating with tripodal ligands.

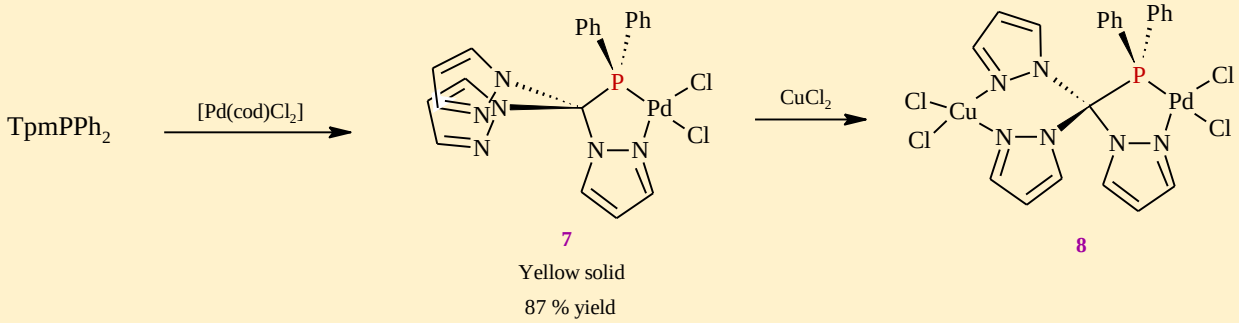
Furthermore, the investigation of coordination flexibility of these hybrid ligands was achieved through their reaction with $[CpRu(can)_3][PF_6]$ (can = acetonitrile), which revealed that these ligands are coordinated in a $\kappa^3 N,N',P$ fashion (**4**) (Scheme 3).



Scheme 3. Synthesis of transition metal complexes containing new hybrid ligand family.

In the reaction with [Au(tht)Cl] (tht = tetrahydrothiophene), the phosphorous donor atom served as 2-electron donor to the gold atom providing complex (**5**) (Scheme 3) due to the fact that Au(I) is a soft metal ion and prefers linear coordination. Whereas the reaction with $[Pd(allyl)Cl]_2$ showed that the phosphorous atom is acting as donor ligand while the pyrazolyl rings stay uncoordinated (**6**) (Scheme 3).

On the other hand, whereas various attempts to synthesis heterobimetallic complexes of 4-6 with other metal sources were unsuccessful, the reaction of $TpmPPh_2$ with $[Pd(cod)Cl_2]$ and $CuCl_2$ afforded the heterobimetallic complex (**8**) (Scheme 4)



Scheme 4. Synthesis of heterobimetallic complex.

This class of hybrid ligands is very flexible and paved the way for coordination with many transition metals as a result of their different coordination modes.

Review

H. E. Wagner, S. Hohnstein, M. G. Schußmann, L. A. Steppe, F. Breher, *Dalton Trans.*, **2019**, https://doi.org/10.1039/C9DT02057H.

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Insights

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Influence of Anions on Bipolaron Formation in Ionic-liquid-gated Transistors

An investigation of the type of carrier (polaron and bipolaron) generated in PBTTT-C16 ionic-liquid-gated transistors fabricated with two different polymers was achieved. The results revealed that the anions of these polymers impacted negatively the formation of bipolaron, and hence, the performance of transistors.

In ionic or highly polar crystals, the coulomb interaction between a conduction electron and the lattice ions results in a strong electron-phonon coupling. In this case, even with no real phonons present, the electron is always surrounded by a cloud of virtual phonons. The cloud of virtual phonons corresponds physically to the electron pulling nearby positive ions toward it and pushing nearby negative ions away. The electron and its virtual phonons, taken together, can be treated as a new composite particle, called a polaron. The hole polaron is defined analogously. Polarons are the proper way to describe electrons and holes within any conducting materials in highly polar or ionic solids.

On the other hand, if two electrons (or two holes) repel by the coulomb interaction, they can have a net attractive force, as a result of the attraction of each to the lattice distortion induced by the other. Thus, a bound state of two electron polarons (or two hole polarons) is called a bipolaron. A polaron has +e (or –e) and ½ spin, whereas bipolaron has +2e (or -2e) and no spin.

When a conjugated polymer is doped with electron acceptors, positive polarons are first formed, then upon further doping, positive bipolarons are formed. The critical doping level at which the transition from polarons to bipolarons takes place, depends on the conjugated nature of the polymer.

Enokida and Furukawa investigated the influence of anions, TFSI **2** and FAP **3** (Figure 1), on the critical doping level and the mobilities of positive bipolarons generated in ionic-liquid-gated transistor (ILGT) fabricated with poly(2,5-bis(3-hexadecyl thiophen-2-yl)thieno [3,2-b]thiophen) (PBTTT-C16) **1** (Figure 1) and ionic liquids, 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)-imide [EMIM][TFSI] **2** or 1-ethyl-3-methylimidazolium tri(pentafluoroethyl)trifluorophosphate [EMIM][FAP] **3** (Figure 1).

This design is characterized by achieving a high doping level, due to the wide electrochemical window of the ionic liquid, as well as measuring the doping-level dependence of the carrier mobility by using ILGT configuration. The device structure of an ILGT is shown in Figure 2. Properties of the type of carrier was measured through a combination of Raman spectroscopy and electrochemical measurements.

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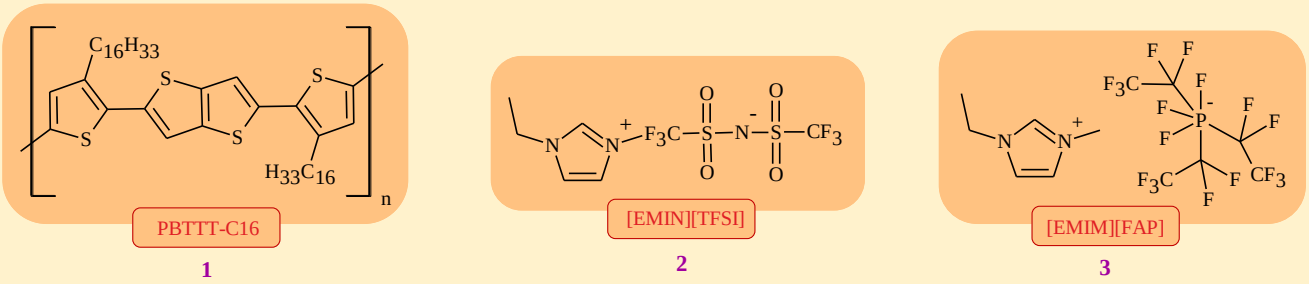

Figure 1. These ionic liquids were used as gate dielectric in the fabricated of ionic-liquid-gated transistor (ILGT).

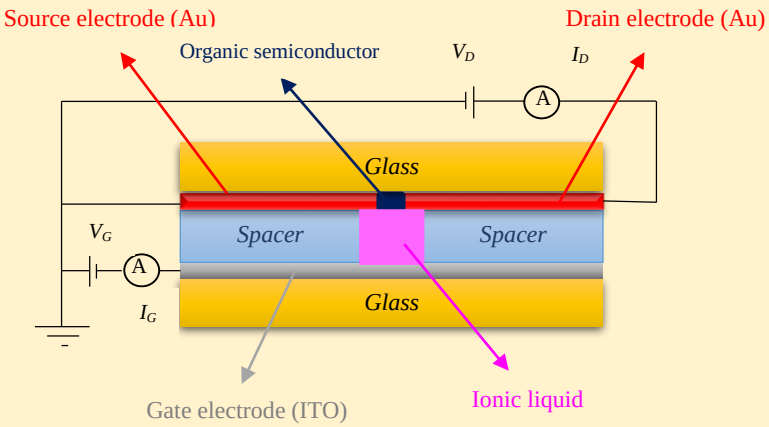

Figure 2. The device structure of an ILGT. Source and drain electrodes: made by depositing Ni (5 nm) and successively Au (45 nm); Gate electrode (ITO): indium-tin-oxide (ITO)-coated glass substrate; Spacer: Naflon® (polytetrafluoroethylene).

The outcome of their studies reveals that: (i) with increasing the doping level, positive polarons were first formed, followed by the generation of bipolarons; (ii) the critical doping level of the polaron-to-bipolaron transition was 4.5 and 12 mol% / π electron in one repeating unit for employed samples with [EMIM][TFSI} and [EMIM][FAP], respectively; (iii) the large dopant anion $[FAP]^-$ prevent the bipolaron formation even at a high doping level.

Therefore, the carrier type generated can be controlled by choosing the proper anion in an ionic liquid, which, in turn, can lead to improve the performance of transistors.

Review

I. Enokide, Y. Furukawa, *Chem. Lett.*, **2019**, *48*, 498-501.

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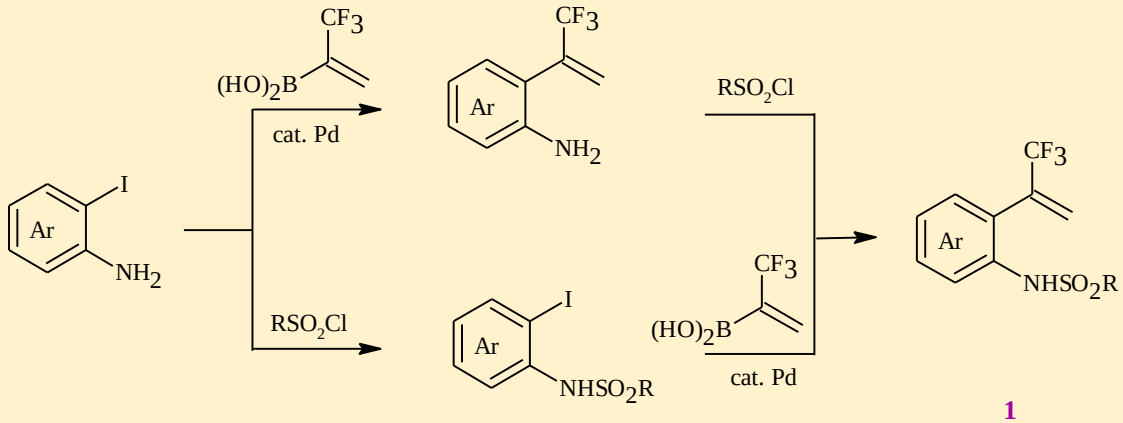
Synthesis of 3-(trifluoromethyl)indoles *via* Radical 5-*endo-trig* Cyclization

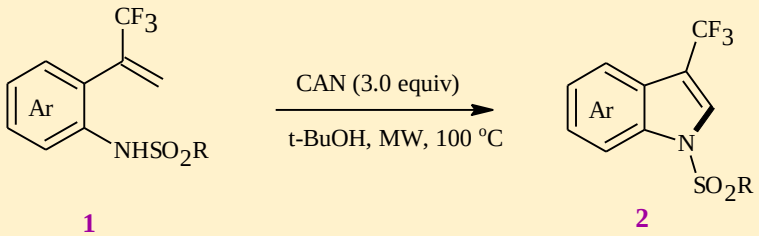
Cerium (IV) ammonium nitrate mediated the synthesis of 3-(trifluoromethyl)indoles from *o*-sulfonamido-α-(trifluoromethyl)styrenes *via* oxidative cyclization. The reaction is assisted by microwave irradiation in *tert*-butyl alcohol.

This snapshot highlights the reported preparation of 3-(trifluoromethyl)indoles from α-(trifluoromethyl)styrenes bearing a sulfonamide group in the *o*-position. The cyclization precursor, *o*-sulfonamide-α-(trifluoromethyl)styrene **1**, is prepared through two steps: (1) palladium-catalyzed coupling of 2-iodoanaline with 1-(trifluoromethyl)vinyl boronic acid, which is generated from 2-bromo-3,3,3-trifluoropropene; and (2) *N*-sulfonylation with sulfonyl chlorides, and vice versa (Scheme 1).



Scheme 1. Synthesis of *o*-sulfonamide-α-(trifluoromethyl)styrenes.

The oxidative cyclization of **1** was accomplished through the addition of cerium (IV) ammonium nitrate (CAN) in *tert*-butyl alcohol at 100 °C under microwave irradiation to afford indole **2** in high yield (Scheme 2).



Scheme 2. Synthesis of 3-(trifluoromethyl)indoles.

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The mechanistic study reveals that the reaction proceeded *via* 5-*endo-trig* cyclization of intermediary aminyl radical species.

Review

T. Fujita, K. Ide, T. C. Jankins, T. Najima, J. Ichikawa, *Asian. J. Org. Chem.*, **2019**, *8*, 637-640.