s-Tetrazines as Building Blocks for New Functional Molecules and Molecular Materials

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Contents

1. Introduction

s-Tetrazines are long ago discovered molecules, whose first report dates back to the end of the 19th century.[1] The first synthesis was reported by Pinner, who reacted equimolar quantities of hydrazine and benzonitrile and, after easy oxidation, isolated a red compound to which he assigned (rightfully by the way) the formula for 3,6-diphenyl-*s*-tetrazine from elemental analysis (Scheme 1). Pinner prepared several other *s*-tetrazines in the same way, but did not go into many further investigations on their properties.

Over the years, there have been relatively very few groups that turned their interest toward the *s*-tetrazine chemistry.[2] Actually, until now only three main purposes triggered some research in the field: (1) Preparation of tailored molecules and their implication in inverse demand Diels−Alder cycloaddition reactions to make new pyridazines.[3] After the first observation by Carboni and Linsey in 1959[4] of the ability of *s*-tetrazines do undergo cycloaddition, this application has becomed the most developed to date, with large contributions from the groups of Sauer and Boger. It has been particularly employed successfully in the synthesis of numerous natural products. Recently, new nanocomposites materials have been obtained by reaction of *s*-tetrazines with C$_{60}$[5] or carbon nanotubes.[6] Another group also used this reaction for fast bioconjugation.[7] (2) High nitrogen content molecules for explosive materials,[8] with as the main realization the dihydrazino-*s*-tetrazine and the bis(tetrazolylamino)-*s*-tetrazine. (3) Preparation of dipyridyl-*s*-tetrazines and related molecules for coordination chemistry.[9] *s*-Tetrazines and their *n*-hydro (di, tetra, or hexa) derivatives have also been claimed to have a potential for biological activity,[10] and some of them were recently tested for their antitumor activity with some success.[11]

We do not plan to review extensively here the first field, because it is not directly linked to material or molecular building blocks chemistry, and also an excellent general recent review[2] gives a large place to this area. However, we will recall some works on energetic materials because they often contain very useful information for materials and physical chemistry applications. We will also only mention a few results related to coordination chemistry because a recent detailed review on the domain already exists, which covers most aspects of tetrazines used as ligands for metals.[9] Therefore, we will focus more on the latest research on the original optical and electrochemical properties of *s*-tetrazines, as well as their incorporation into polymers and their potential in supramolecular chemistry.

Despite these intense fields of research, there are maybe no more than 300 publications describing *s*-tetrazine syntheses over the whole past century, including many scattered works where people happened to prepare tetrazines occasionally without real interest in the field. This situation is quite surprising, because some physicochemical characteristics of *s*-tetrazines, such as fluorescence, were recognized a long time ago and studied in a rather limited context, but quite intensely. Indeed, the photophysical properties of the generic H,H-*s*-tetrazine and dimethyl-*s*-tetrazine have been the subject of rather complete studies in rather specific conditions such as gas-phase spectroscopy,[12] crystals,[13] supersonic jets,[14] and spectrophysics (hole burning)[15] of highly diluted compounds. Despite this promising start, the interest of physicochemists dropped in the early 1980s, and almost only research on explosives and later on coordination chemistry remained somewhat active. One notable exception is found in the work of Neugebauer, who studied the cation and anion radicals[16] and photophysics[17] of various simple and more elaborated *s*-tetrazines.[18] This is all the more surprising given the extraordinary burst of research in the new field of functional molecular materials (tailored conducting polymers, OLEDs, photovoltaic devices, etc.), which has seen in the past two decades almost all aromatic buiding blocks employed with various successes to the fabrication of new molecular assemblies and functional devices.

Altogether, the tetrazine building block has enormous advantages and some drawbacks. Among the advantages are,

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Gilles Clavier was born in Villeneuve sur Lot (Southwest of France). He graduated from the University of Bordeaux 1 in 1994 and received his M.Sc. from Ecole Polytechnique in 1996. In 1994 he received an ERASMUS grant and worked for 6 months in the laboratory of Professor Stoddart in Birmingham (U.K.). He joined the team of Professor Bouas-Laurent in Bordeaux in 1995 and received his Ph.D. in 1999 for research on the synthesis and gel-forming abilities of dialkoxyarenes and structural study of their gels. He then joined the group of Professor Vince Rotello at the University of Massachusetts at Amherst, where he worked on the syntheses and study of supramolecular plug and play polymers for two years. In 2001, he was recruited as Chargé de Recherche at the French CNRS and joined the Ecole Normale Supérieure de Cachan to work with Professor Audebert. His research interests include the design, synthesis, and study of new fluorescent and multichromophoric organic molecules with special properties and their nanoformulation. He is the author of about 40 research papers.

Pierre Audebert was born in Périgord (homeland of foie gras and black truffles), France, in 1959. He defended his Ph.D. on halogenated and functionalized polypyrroles at CENG (Grenoble, with Dr. G. Bidan) in 1987, before becoming a CNRS scientist in the Laboratoire d'Electrochimie Moléculaire (Université de Paris 6, under the supervision of Drs. C. P. Andrieux and J. M. Savéant). He moved into a professor position first at the Université de Franche Comté in 1993 and then again in 1998 at the PPSM laboratory at the Ecole Normale Supérieure de Cachan (near Paris), where he still leads a team. His research interests encompass conducting polymers and conjugated organics, molecular electrochemistry, sol–gel chemistry and related nanoparticles, and NLO and electrofluorochromic materials and devices. He is the author of about 150 research papers, 3 book chapters, and 1 electrochemistry teaching book.

first, the fact that the tetrazine is the electron-poorest aromatic system of the classical C, H, O, N, S chemistry,[19] since the higher homologue pentazine and of course hexazine have been recognized to be unstable, at least at room temperature.[20] This makes the tetrazine ring a strong electron attractor, comparable approximately to tetranitrobenzene, with therefore obvious applications in the NLO field for example. In addition, tetrazines can be reversibly reduced to their radical anion, and some are fluorescent, which opens the way to

Scheme 1. Original Pinner Synthesis of Dihydro-*s*-tetrazines
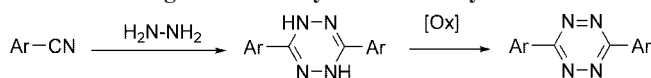
many applications in the field of addressable sensors or display for example.

So what are the possible reasons for this banishment? First, certainly some fear, first because of the (often usurpated) reputation of instability. From the scarity and dispersion of the synthetic works, besides a small number of widely used molecules such as dipyridyl-*s*-tetrazines, tetrazines give the impression of being rather exotic and unstable molecules that would decompose just out of the freezer compartment. We will see that this is quite wrong in many occurrences. Second, the research on explosives probably refrained many chemists who feared to see their glassware occasionally exploding; we will see in the following that this is also an unreasonnable fear, although in rare occasions, a few synthetic steps may require some carefulness. It should be added that the precious synthon dichloro-*s*-tetrazine, which has already been recognized as indispensable to the preparation of many tetrazines, was not readily accessible from the only formerly published synthesis,[21] which contained several tricky steps, including the last one involving the use of liquid chlorine.
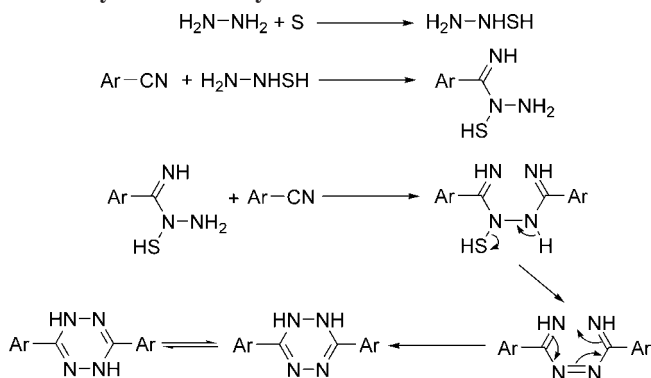
This sad situation changed thanks to the beautiful work of Michael Hiskey and David Chavez et al., who found a remarkable synthesis of 3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-*s*-tetrazine.[22] The same group also described a relatively easy preparation of dichloro-*s*-tetrazine from the former bis(dimethylpyrazolyl)-*s*-tetrazine.[23] Hiskey and Chavez had therefore paved the way toward the entrance of the tetrazines on the molecular materials scene.

2. Synthesis of Tetrazines

Despite the fact that the main aim of this review is to describe the physicochemical properties of *s*-tetrazines, it might be useful to recall the main synthetic paths for their preparation and to introduce some of the recent contributions to this field.

There is no direct synthesis of the *s*-tetrazine ring. It is always obtained by oxidation of its 1,2- or 1,4-dihydro (or even in very few cases its tetrahydro) counterpart, which can be obtained by various methods. Five main different ones are reported,[24] but the long-known Pinner synthesis and a modified version[25] remain the most employed. The Pinner synthesis involves the reaction of hydrazine with a nitrile (Scheme 1). The dihydrotetrazine is always obtained, and it has to be further oxidized into the fully aromatic tetrazine. The mechanism of the original Pinner synthesis is not known, but we have proposed a reasonable one for the improved synthesis involving sulfur addition along with the hydrazine (Scheme 2).[26]

This synthetic route is effective for most of the aromatic tetrazines where the nitrile is not sterically crowded (Figure 1), but does not work, or does work in a very low yield, for aliphatic ones.[2,27] No clear explanation has been proposed for this observation. Yields can be improved by using a pressure tube at higher temperature. This not only allows the use of low boiling point solvents such as dichloromethane at high temperature, but also offers the possibility to reduce the amount of reactants using a small sealed tube. In the case of aliphatic derivatives, the nitrile can be replaced by an aldehyde to give the hexahydro-*s*-tetrazine, which can be
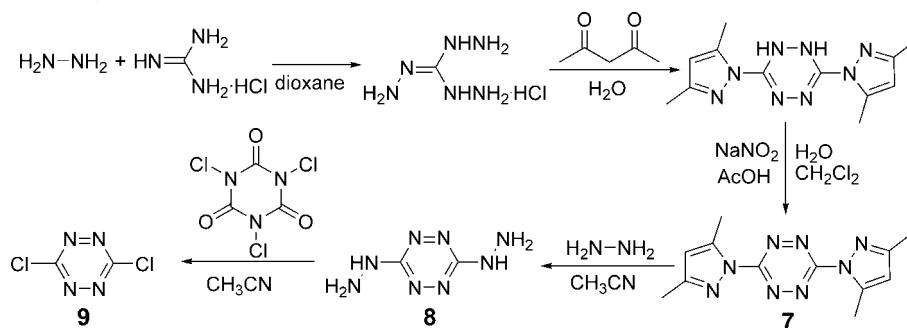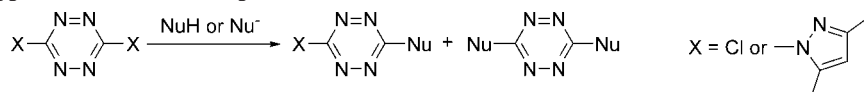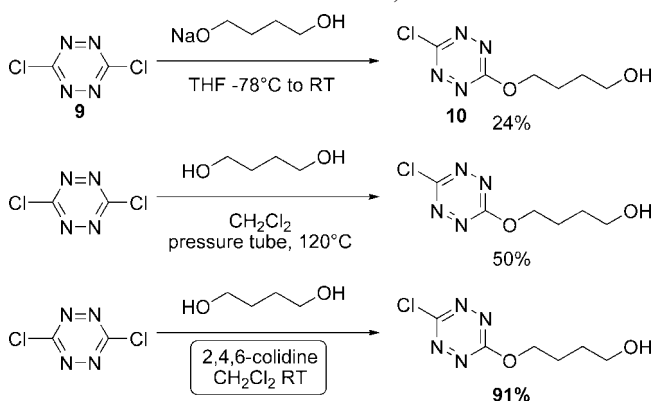
Scheme 2. Proposed Mechanism for the Sulfur-Assisted Pinner Synthesis of Dihydro-*s*-tetrazines

Scheme 5. Study of the S$_N$Ar Reaction Conditions for the Monosubstitution of 9 with Butane-1,4-diol

oxidized to the tetrazine in two steps albeit in an overall modest yield.[11a,28] Indeed, aliphatic tetrazines are highly volatile, can easily sublimate (some at atmospheric pressure and room temperature), and are difficult to isolate.

Besides the formation of the tetrazine ring that leads to symmetrical tetrazines, a very important route toward functional tetrazines relies on their functionalization through nucleophilic aromatic substitution (S$_N$Ar), starting from an adequate precursor. For this purpose, bis(thiomethyl)-*s*-tetrazine was initially (and sometimes still is) the starting compound of choice because of its relatively easy synthesis.[29] However, recently, Hiskey et al. introduced an easy and quasi-quantitative procedure for the production of the 3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-*s*-tetrazine[22] and, maybe more importantly, its subsequent conversion to 3,6-dichloro-*s*-tetrazine in two steps[23] with an overall yield of ca. 80%
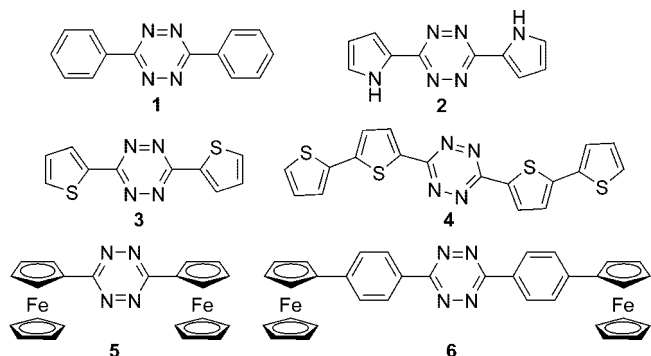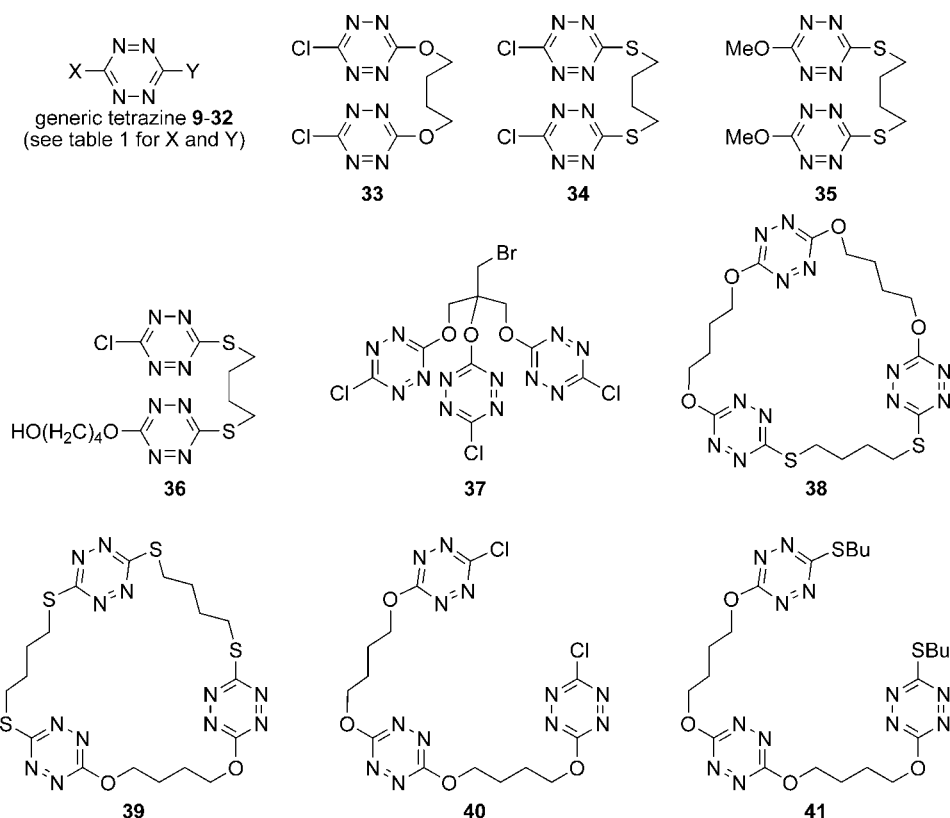

Figure 1. Examples of symmetrical aromatic *s*-tetrazines obtained by the modified Pinner synthesis.

and no tedious purification during the process (a very short chromatography is however required if very pure dichlorotetrazine is needed). Recently more convenient reaction conditions for the last step were proposed by Harrity et al., who replaced chlorine gas by the less dangerous trichloroisocyanuric acid.[30] We also contributed to this synthetic scheme by substituting the nitrous gas used in the oxidation step of the dihydrotetrazine with sodium nitrite (Scheme 3).

Dichlorotetrazine and on some occasions dipyrazolyltetrazine are remarkably versatile starting synthons for the preparation of a huge number of tetrazines simply using nucleophilic displacement of the chlorine (respectively the pyrazolyl groups) by various nucleophiles including alcohols, thiols, and amines as the most representative (Scheme 4). Monosubstitution usually occurs very readily at room temperature,[31] while disubstitution may require more forcing conditions, such as the use of ionic nucleophiles in the case of alcohols.

To obtain some of our target molecules, we have been interested in optimizing the reaction conditions for the mono- and disubstitution of dichlorotetrazine with alcohols.[32] Several sets of conditions have been tested (Scheme 5). Alcoholates proved to be too reactive as a lot of degradation takes place and the desired products are obtained only in moderate yields (25% average). We also tried to use the alcohol directly in a pressure tube, and the reaction yield was improved (50% average). Bases were also tested. Inorganic ones such as potassium bicarbonate did not improve the outcome of the reaction, nor did the hindered amine base DBU, but 2,4,6-collidine allowed us a break-

Scheme 3. Synthesis of the 3,6-Dichloro-*s*-tetrazine

Scheme 4. General Approach for the Nucleophilic Subsitution of *s*-Tetrazine

Figure 2. Examples of s-tetrazines prepared by S_NAr.

through in getting high conversions (up to 90%) to the monosubstituted derivative.

Disubstitution with the same alcohol can be effected in good yield when using a combination of the two most effective methods (2,4,6-collidine and pressure tube). Unsymmetrical tetrazines can also be prepared from the monoether, but an alcoholate must be used in this case, with, again, a moderate success (25% average). We and others[2] have prepared many tetrazines in this way. Some examples are reported below (Figure 2 and Table 1).

Although most heteroatomic nucleophiles can be used in this transformation, it is important to note that most carbanions (alkyl or aryl) do not undergo the S_NAr reaction but instead undergo azaphilic addition to yield 1,4-dihydro-s-tetrazine.[33] The only successful cases of S_NAr reported were with potassium cyanide[34] or malonates.[35] However, we recently found out that it is possible to obtain the product of substitution with lithium alkynes from 3-chloro-6-pyrrolidin-1-yl-s-tetrazine in moderate yield (Scheme 6).[36]

This reaction works with acetylenes substituted with electron-donating aromatics (benzene or thiophene) (Table 2), but when substituents with electron-withdrawing groups were used, no reaction took place.

Cross-coupling reactions of aromatics catalyzed with palladium are a very powerful synthetic tool for C−C bond formation. This type of chemistry was only very recently adapted to the tetrazine series and in limited cases. This is probably due to the fact that the tetrazine ring can act as a ligand[9] for metals and deactivate their catalytic activity or the tetrazine can be reduced by metals followed by decomposition of the ring.[37] It was also demonstrated that the tetrazine ring must be deactivated with one donating substituent to be able to undergo cross-coupling reactions. Indeed, if s-tetrazines **7**, **9**, and **11** are used, they decompose, but if one amino substituent (diethylamine, pyrrolydine, or

Table 1. Substituents Introduced on the Generic s-Tetrazines 9−32

| compd	substituent X	substituent Y
9	Cl	Cl
10	Cl	O(CH$_2$)$_4$OH
11	Cl	OMe
12	Cl	naphthalen-1-yloxy
13	Cl	pyrrolidin-1-yl
14	Cl	2,3-diphenylaziridin-1-yl
15	Cl	borneol
16	Cl	9H-fluoren-9-ylmethoxy
17	Cl	paracyclophan-4-ylmethoxy
18	Cl	adamantan-2-yloxy
19	Cl	adamantan-1-ylmethoxy
20	Cl	pentachlorophenoxy
21	Cl	N-phtalimidyl
22	OMe	OMe
23	OMe	O(CH$_2$)$_4$OH
24	O(CH$_2$)$_4$OH	O(CH$_2$)$_4$OH
25	adamantan-1-ylmethoxy	adamantan-1-ylmethoxy
26	OMe	SMe
27	SMe	SMe
28	S-n-butyl	S-n-butyl
29	pyrrolidin-1-yl	pyrrolidin-1-yl
30	3,5-dimethyl-1H-pyrazol-1-yl	OMe
31	3,5-dimethyl-1H-pyrazol-1-yl	pyrrol-1-yl
32	pyrrol-1-yl	pyrrol-1-yl

Scheme 6. S_NAr with an Akynyl Anion[a]
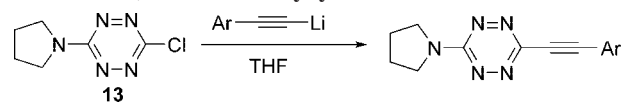
[a] See Table 2 for Ar and the corresponding yields.

morpholine) is introduced, both chlorine (Sonogashira or Negishi)[38] or thiomethyl (Suzuki or Stille)[39] can be replaced by an aromatic or heteroaromatic ring (Scheme 7).
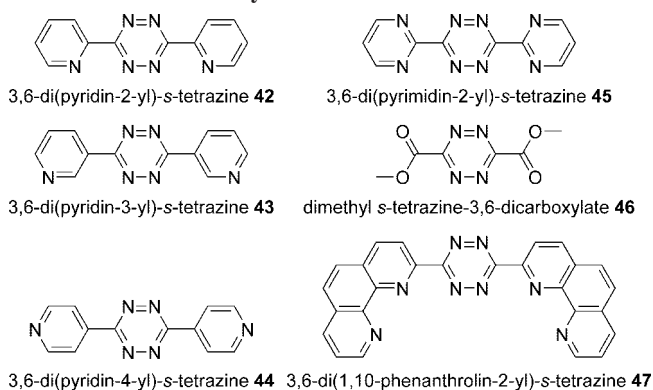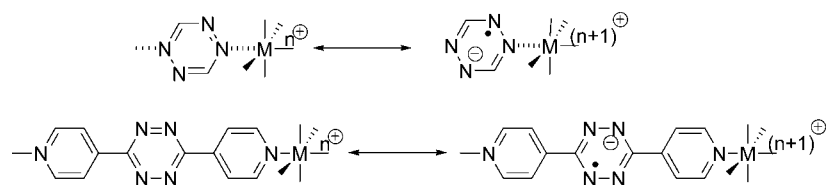
Table 2. Reaction Yields for the S$_N$Ar of Tetrazine 13 with Lithium Arylalkynes

Ar				
Yield (%)	39	26	0	0

Scheme 7. Examples of Cross-Coupling Reaction with *s*-Tetrazine Derivatives
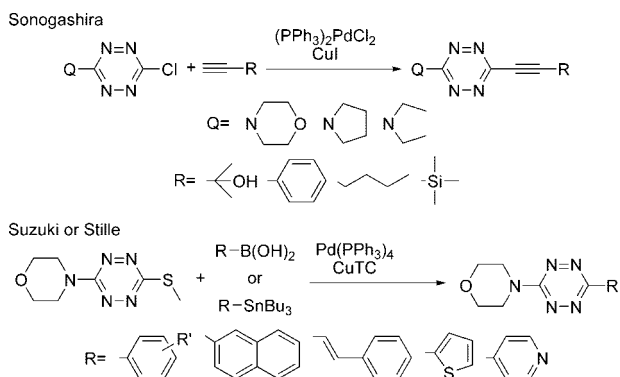
3. Molecular Materials from the Coordination Chemistry of Tetrazines

Coordination chemistry is difficult starting from tetrazines only, because the tetrazine nitrogen atoms usually only serve as ancillary ligands. In fact, their basicity, and therefore their coordination ability, is low. The basicity of *s*-tetrazine was never determined, but it is weaker than that of triazine. Indeed, extrapolating the pK diminution coming along with the replacement of a C by a N atom in six-membered heterocycles, the pK_a of *s*-tetrazine can be estimated to be on the order of -6 (-1.7 for *s*-triazine).[40] Therefore, almost all the coordination compounds including tetrazines have been made from the well-known pyridyltetrazines, especially the dipyrimidin-2-yl-*s*-tetrazine, the esters of *s*-tetrazine 3,6-

Scheme 8. *s*-Tetrazine Derivatives Commonly Used in Coordination Chemistry

3,6-di(pyridin-2-yl)-*s*-tetrazine **42**   3,6-di(pyrimidin-2-yl)-*s*-tetrazine **45**

3,6-di(pyridin-3-yl)-*s*-tetrazine **43**   dimethyl *s*-tetrazine-3,6-dicarboxylate **46**

3,6-di(pyridin-4-yl)-*s*-tetrazine **44**   3,6-di(1,10-phenanthrolin-2-yl)-*s*-tetrazine **47**

Scheme 10. One Example of a Tetrazine Coordination Polymer with Ruthenium^a
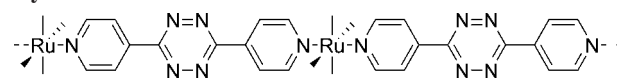
^{a} Adapted from ref 43c.

dicarboxylic acid, bis(3,5-dimethylpyrazol-1-yl)-*s*-tetrazine, and the recently described bis(1,10-phenanthrolin-2-yl)-*s*-tetrazine[41] (Scheme 8).

However, some coordination polymers, based on ruthenium and iron phthalocyanines[42] and either tetrazine or dimethyltetrazine, have been described. A recent review[9] has described in detail the coordination chemistry of all these compounds, while giving an exhaustive list of all the complexes that were prepared from the above ligands, and we will only present here a specific example related to molecular materials without entering into any further details.

One of the most specific characteristics of this tetrazine-based coordination chemistry is the ability, demonstrated by Hanack et al., to produce easily 1-D conducting polymers, two examples of which are given below.[43] This is due to the excellent electron affinity of the tetrazine, which allows charge transfer, in a way close to that of a conducting polymer. Actually resonance formulas exist between, on one hand, the lower redox states of the metal and the tetrazine rings and, on the other hand, the higher redox states of the metal and the tetrazine anion radical (Scheme 9).

The tetrazine ring therefore provides the electronic connection between the metal centers. In addition, all these complexes have a very nice electrochemistry, often featuring several reversible reduction waves. Scheme 10 provides an example of a 1-D polymer from a tetrazine ligand. Conductivities up to ca. 0.1 S·cm^{-1} were reported for these polymers, which fit quite well in the range of that of standard polypyrrole.

4. Physical Chemistry of Tetrazines

4.1. Electrochemistry of Tetrazines

The easy reduction of tetrazines (compared to other polyazines) was reported by Stone et al. as soon as 1963.[44] Subsequently their electrochemical reversibility was mentioned several times.[45] Notably, a paper by Neugebauer et al. gathers newly recorded along with ancient data from his group and former works.[16c] It should be mentioned that this interesting and relatively complete work reports a measurement on the very interesting compound difluoro-*s*-tetrazine, the synthesis of which was never subsequently reported. The anion radicals of various tetrazines have also been studied by ESR spectroscopy.[16a,46]

In our hands, all tetrazines substituted by heteroatoms[47,48] and aromatics[26] can be reversibly reduced in organic solvents, because of their electron-deficient character, accepting one electron to give an anion radical, very stable in the absence

Scheme 9. Scheme of the Low-Energy Electron Exchange within a Tetrazine Linear Coordination Polymer in Two Slightly Different Cases

of acids (Figure 3). The differences in $E_{1/2}$ values for the reversible reduction to the corresponding anion radicals reflect the electronic influence of the substituents and give good linear correlations with $[\sigma]$ constants according to the Hammett equation. Table 3 gathers the data of Neugebauer along with ours.

Most of the tetrazine derivatives can accept a second electron, despite the fact that this process is not electrochemically reversible in standard conditions. However, interestingly, this latter process is chemically reversible (with the exception of diclorotetrazine), as demonstrated by the cyclic voltammogram in Figure 4. Despite the fact that the second electron transfer does not give a stable dianion (which is probably very basic and reacts with traces of water or protic impurities), a stable species is formed which is sluggishly reoxidized into the original anion radical, which is completely restored. It is probable that the reduced species formed is the known dihydrotetrazine, or more likely its monoanion.

This particular property could open the way for tetrazines to be selected as active material in organic batteries. Actually, for example, the quite stable dimethoxytetrazine (**22**) is able to store two electrons for a molar mass of 118 g·mol^{-1}, which corresponds to a theoretical capacity of 227 (A h)·kg^{-1} if used as a battery active material. Although we never
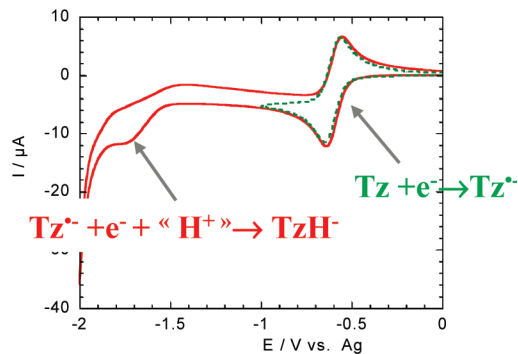
Figure 4. Cyclic voltammograms of **4** showing the first and second reductions.

observed the dianion formation, it is likely that this species would be observable working in strictly anhydrous conditions in a completely nonacidic solvent (e.g., THF), in a drybox for example.

The anion radicals of all tetrazines are completely stable in the absence of proton donors. This is true even for the dichlorotetrazine, and here again the tetrazine behavior differs from that of the other six members' aromatic heterocycles bearing halogen atoms. Effectively, in most cases a halide ion is expelled, which leads to the production of a neutral
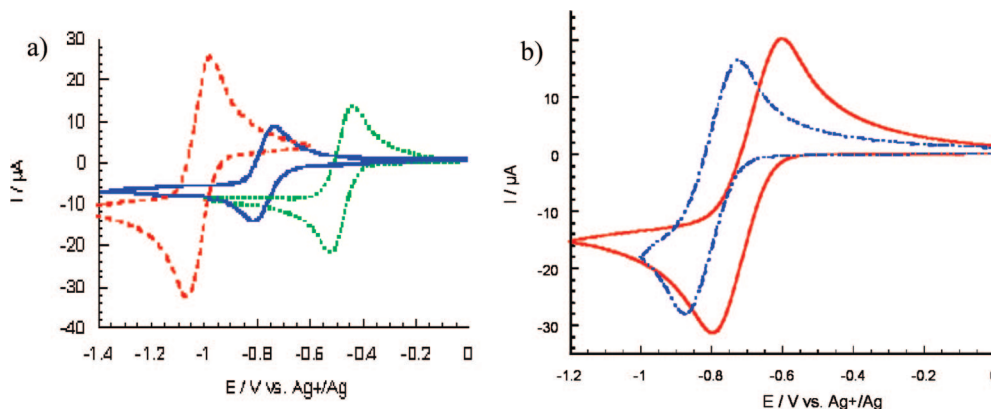

Figure 3. (a) Cyclic voltammograms of (a) **9** (green), **11** (blue), and **22** (red). Reprinted with permission from ref 47a. Copyright 2005 Wiley-VCH. (b) Cyclic voltammograms of **4** (blue) and **32** (red). Adapted from ref 26. Copyright 2004 Royal Society of Chemistry.

Table 3. Half-Wave Reduction Potential (V vs Fc/Fc$^+$) of s-Tetrazines in Dichloromethane^a

compd	$E°$ from our work (refs 26, 32, 36, 47, and 48)	$E°$ from lit. data (ref 16c and references therein)	compd	$E°$ from our work (refs 26, 32, 36, 47, and 48)	$E°$ from lit. data (ref 16c and references therein)
1		−1.21	**25**	−1.13	
2	−1.31		**26**	−1.23	
3	−1.24		**27**	−1.20	−1.03
4	−1.25		**29**	−1.73	−1.60
5	−1.28		**30**	−0.89	
6	−1.32		**31**	−0.97	
7	−0.96		**32**	−1.07	
9	−0.68	−0.56	**33**	−0.99	
11	−0.99		**34**	−0.90	
12	−0.97		**37**	−0.94	
13	−1.35		**38**	−1.24	
14	−1.04		**39**	−1.21	
15	−0.74		s-tetrazine		−1.16
16	−0.75		difluorotetrazine		−0.56
17	−0.82		dicyanotetrazine		−0.31
18	−0.79		bis(methylamino)tetrazine		−1.51
19	−0.85		bis(dimethylamino)tetrazine		−1.55
20	−0.54		dimethyltetrazine		−1.32
21	−0.51		bis(aziridyl)tetrazine		−1.25
22	−1.25	−1.13	bis(azetidyl)tetrazine		−1.47

^{a} Except for the literature results, where acetonitrile was used. Fc/Fc$^+$ was estimated to be +0.09 V vs Ag/Ag$^+$.
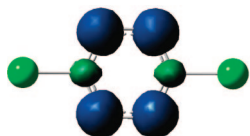
Figure 5. Spin density (isodensity at 0.004 au) calculated (B3LYP/6-31+g(d)) for the anion radical of dichloro-*s*-tetrazine (**9**).
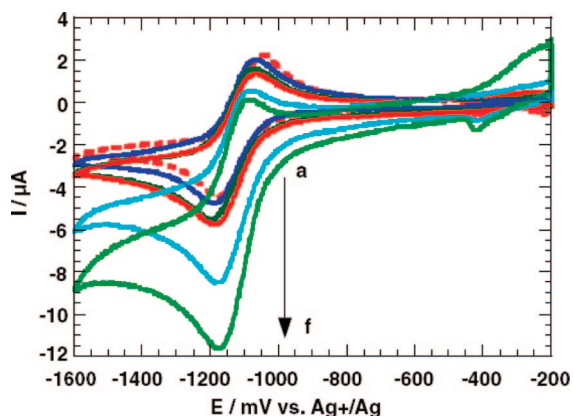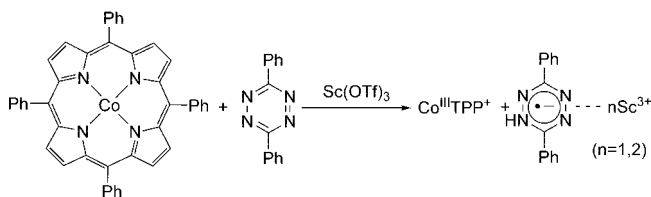

Figure 6. Cyclic voltammograms of the reduction of **24** (ca. 2 mmol·L^{-1}) in dichloromethane (+TBAP) after addition of increasing amounts of resorcinol (dissolved in acetonitrile): (a) 0 equiv (dashed line), (b) 0.5 equiv, (c) 1 equiv, (d) 1.5 equiv, (e) 3.5 equiv, (f) 4.5 equiv. Currents are corrected for dilution effects.

Scheme 11. Reduction of Diphenyl-*s*-tetrazine Promoted by Scandium Ion
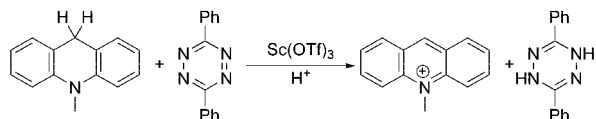
radical which in course can undergo several reaction pathways.[49] This splitting of the anion radical never occurs with tetrazines, because of the remarkable electron-poor character of the ring and the stabilization of the radical anion charge on all four nitrogen atoms as evidenced by the calculated spin density of the radical anion (Figure 5).

However, in the presence of an even weaker proton donor, the anion radical can be protonated and the electrochemical

reversibility is lost (Figure 6). The loss of reversibility depends both on the acidity of the proton donor and on its amount.[47b]

In the case of phenols, this is a progressive process which requires up to about 10 equiv of acid to be complete. In principle, such reactivity could be exploited for sensing weak acids or phenols provided that the tetrazines are included in accessible modified electrodes or polymer membranes.

The kinetics of the one-electron reduction has been studied with different chloroalkoxy- and dialkoxy-*s*-tetrazines bearing substituents with various steric hindrances, namely, derivatives **11**, **19**, and **25**.[48] However, no influence of the bulkiness of the alkyl group could be observed on the rate constants.

Recently, Kukuzumi et al. studied the reduction of 3,6-diphenyl-*s*-tetrazine (**1**) promoted by scandium ion[50] in an effort to produce a mimic of NADH (Scheme 11). They chose the tetrazine ring as an acceptor because of the stability of its anion, which, contrary to other organic acceptors, does not react with species present in the medium. It was shown that in deaerated solution and in the presence of a 10-methyl-9,10-dihydroacridine the tetrazine is reduced to the dihydrotetrazine by a two-electron/two-proton transfer process. If cobalt complexed with tetraphenylporphyrin is used instead of acridine, only a one-electron reduction is observed and a stable complex between the tetrazine's anion radical and the scandium cation is formed.

## 4.2. Photophysical Properties of Simple Tetrazines

Tetrazines are compounds having a deep color ranging from purple to orange to red (Figure 7) because of a weak n−π* transition located in the visible (Figure 8).

The position of the absorption band corresponding to this transition is weakly influenced by the nature of the substituents (Figure 8) and was shown not to be solvatochromic.[51] Its maximum can be found between 510 and 530 nm (Table 4). The molar extinction coefficient associated with this transition is low (ca. 1000 L·mol^{-1}·cm^{-1}). A second intense band appears in the UV region. It is a π−π* transition whose position is strongly dependent on the substituents, and as described for the reduction potential, it correlates linearly with their electron-donating or -withdrawing character.

A large number of tetrazines are fluorescent. This observation is quite intriguing as most monocyclic azines either are phosphorescent or do not emit light. *s*-Tetrazine and dimethyl-*s*-tetrazine have been reported to fluoresce for a long time.[52] Unfortunately, these two compounds are photochemically unstable: their quantum yields of decomposition have been determined to be 0.99 and 0.5, respectively,[53] yielding
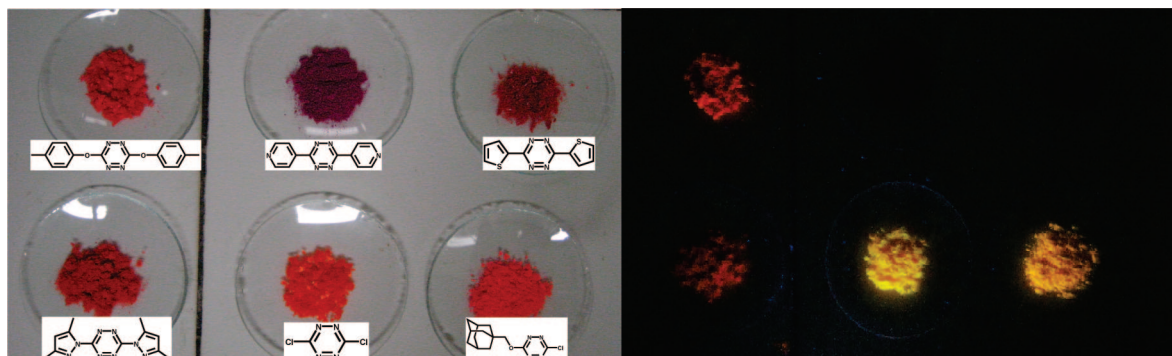
Figure 7. Left: photograph under ambient light of selected tetrazines with their corresponding formulas. Right: same samples irradiated at 354 nm showing the variability of the fluorescence of the tetrazines according to their substituents' nature.
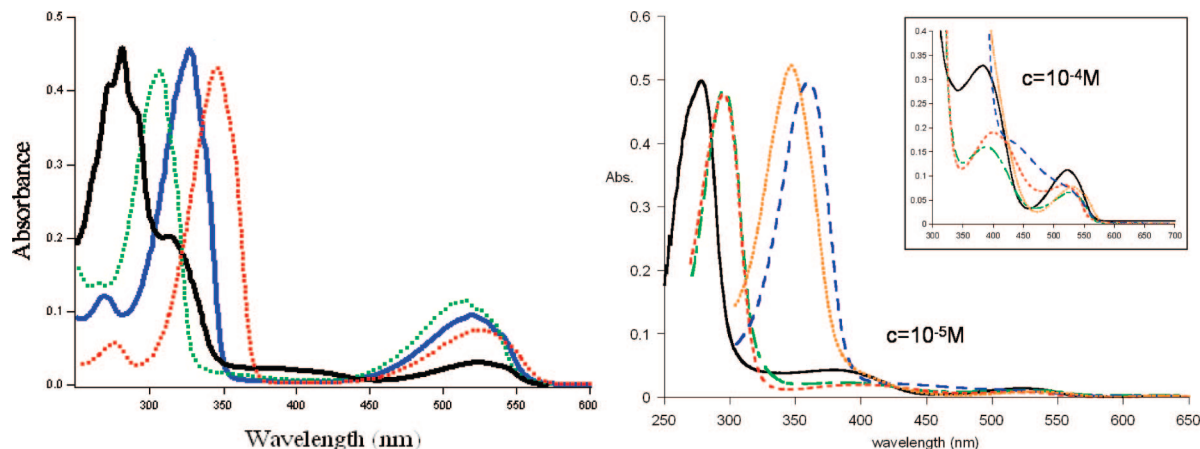
Figure 8. Left: absorption spectra of compounds **9** (green), **11** (blue), **22** (red), and **33** (black) in dichloromethane. Reprinted from ref 47a. Copyright 2005 Wiley-VCH. Right: UV−vis absorption spectra of compounds **2** (blue), **3** (orange), **7** (black), **31** (green), and **32** (red) in dichloromethane. Adapted from ref 26. Copyright 2004 Royal Society of Chemistry.

Table 4. Absorption and Fluorescence Maxima of Tetrazines Recorded in Dichloromethane

tetrazine	UV−vis absorption			fluorescence		
	λ_1^{abs}	λ_2^{abs}	λ_3^{abs}	$\lambda^{em\ a}$	$\phi_f^{\ b}$	τ^c (ns)
1	544	295		602		<0.5
7	524	383	278			
9	515	307		551, 567	0.14	58
11	520	327	269	567	0.38	160
12	523		281	567	0.004	120, 6
13	514	436				
14	522	365	259	576	0.045	
15	522	334		563	0.4	
16	519	328		563	0.08	
17	521	326		564	0.04	
19	522	330		567	0.4	
20	518			566	0.09	
21	518	311		546	0.006	
22	524	345	275	575	0.11	49
23	526	347		572	0.10	59
24	528	348		575	0.09	
25	530	351		579	0.07	
26	528	394				
27	528	422	287			
28	528	428	290	590	9×10^{-4}	$\langle 1.17 \rangle^d$
29	525	496	274			
30	529	367		578		
33	521	328	270	572	0.36	144
34	522	391	273	576	0.025	12.8, 6.3
35	529	396	258	580	5×10^{-3}	7.1, 1.93
36	524	394	263	577	5×10^{-3}	$\langle 5.39 \rangle^d$
37	518	323	269	565	0.29	150
38	528	397, 349	257	585	6×10^{-3}	
39	529	403	288	585	2×10^{-3}	
40	522	330	269	570	0.126	59
41	528.5	398, 348	259	575	6×10^{-3}	10
s-tetrazine	542	320	252	575	6×10^{-4}	1.5

$^a \lambda^{ex} = \lambda_1^{abs}$. $^b \phi_f \pm 8\%$. $^c \tau \pm 2\%$. ^{d} Average of a multiexponential decline.
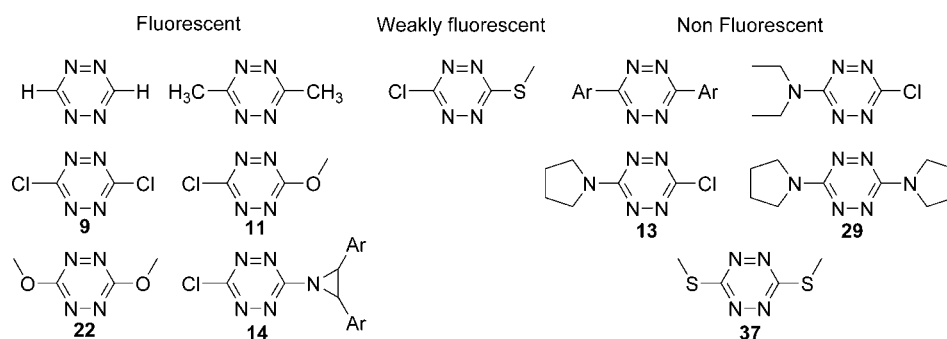
nitrogen and cyanuric acid or acetonitrile, respectively. Fortunately, increasing the size of the substituents makes the ring photochemically stable. Introduction of one benzene ring increases the photostability by an estimated factor of 30, and diphenyl-*s*-tetrazine is stable upon light irradiation. However, its singlet-excited-state lifetime is short (τ_s < 500 ps). Nevertheless, *s*-tetrazine and dimethyl-*s*-tetrazine have been extensively studied in the gas phase because they are easily sublimated. However, very few systematic studies on the fluorescence of other tetrazines have been published.[17,54] It should be noted as well that, following some early controversy,[55] it is now established that the direct photoexcitation of tetrazines does not afford the triplet state and that phosphorescence is observed under particular conditions.[17,56]

In our hands, we noticed that some tetrazines substituted by heteroatoms were highly fluorescent. Others were not or were very dimly emissive (Figures 7 and 9), just like those directly linked to aromatics. We then decided to investigate more deeply the origin of the fluorescence and to search for some general rules to understand the substituent−fluorescence relationship.

The fluorescence spectra of tetrazines are large and not structured in dichloromethane (Figure 10).[32] The position of the maximum of emission ranges between 550 and 590 nm. The quantum yields are very dependent on the nature of the substituents. The highest one was found for 3-chloro-6-methoxy-*s*-tetrazine, while those of the symmetric equivalents (dichloro- or dimethoxytetrazines) are nearly 4 times lower. Similarly to electrochemistry, the solution fluorescence of the tetrazines did not appear affected by the substituent
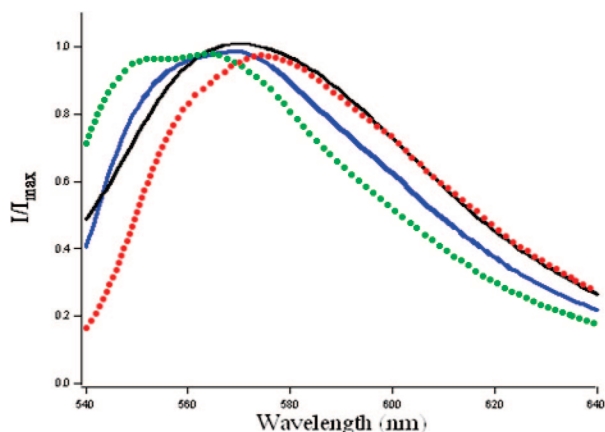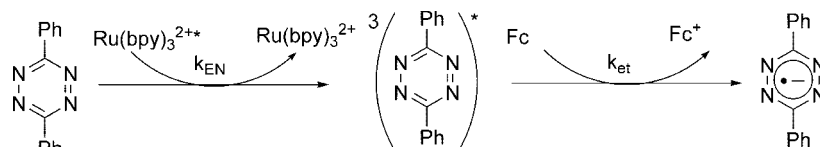

Figure 9. Qualitative photophysical properties of substituted tetrazines (note that the 3-chloro-6-(methylthio)-*s*-tetrazine was not prepared but the observation was made on compound **34**).

Figure 10. Fluorescence emission spectra of compounds **9** (green), **11** (blue), **22** (red), and **33** (black) in dichloromethane (λ^{ex} = 495 nm).

Table 5. Oxidation Potentials (E_{ox}) of Various Electron Donors and Rate Constants (k_{et}) of Photoinduced Electron Transfer from Various Electron Donors to ^{3}PhTz* in Deaerated Acetonitrile at 298 K
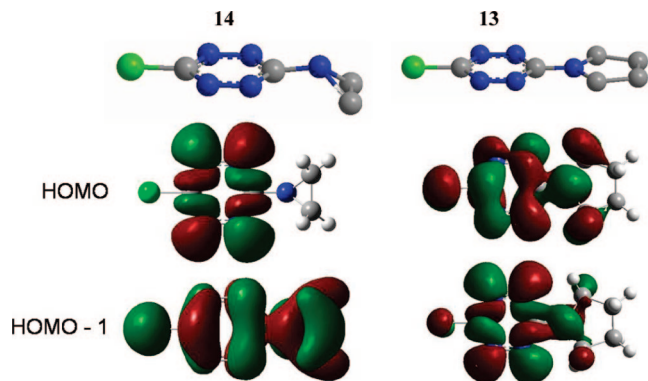
electron donor	E_{ox} (V vs SCE)	k_{et} (mol^{-1}·L·s^{-1})
decamethylferrocene	−0.08	1.2×10^{10}
dimethylferrocene	0.26	9.5×10^{9}
ferrocene	0.37	7.6×10^{9}
N-benzyl-1,4-dihydronicotinamide	0.57	3.6×10^{9}
4-methyl-*N*,*N*-dimethylaniline	0.69	1.5×10^{9}
N,*N*-dimethylaniline	0.78	6.4×10^{8}
4-bromo-*N*,*N*-dimethylaniline	0.92	1.3×10^{8}
1,2,4-trimethoxybenzene	1.12	6.3×10^{6}
1,4-dimethoxybenzene	1.34	1.5×10^{5}

acceptor (as determined by its E_{ox}°), the faster the quenching. It is possible to analyze further and to draw a Rehm−Weller plot which is the logarithm of the quenching rate constants as a function of the redox potentials of the quencher (Figure 11, right). Such a straight plot shows clearly that the quenching occurs through electron transfer and therefore that it is the oxidizing character of the tetrazine excited state which is responsible for the quenching.

The oxidizing ability of the triplet state of diphenyl-*s*-tetrazine (**1**) has also been studied by Yuasa et al. (Figure 12).[58] The triplet state was generated by photosensitization with Ru(bpy)$_3^{2+}$. Its lifetime (τ_T = 28.4 μs) and excited-state reduction potential (E_{red}^* ≈ 1.09 V vs SCE) are improved compared to those of Ru(bpy)$_3^{2+}$. The quenching of the triplet state was observed with various electron donors (Table 5) and explained by an outer-sphere electron transfer process.

4.3. Computational Chemistry on Tetrazines

To understand the photophysical properties of *s*-tetrazine derivatives, systematic quantum chemical studies have been conducted.[32] It has been found that in many cases the HOMO of the tetrazines is made of the nonbonding n electrons of the nitrogen atoms. However, a π orbital lies frequently very close to this n orbital, and according to the substituent nature,

size.[48] Because of the particular nature of the transition responsible for the fluorescence, it has a very long lifetime, typically in the 10−160 ns range in solution (Table 4). The molecules with the highest quantum yields of fluorescence also present the longest lifetimes.

Besides the long lifetimes, tetrazines' fluorescence has another very interesting peculiarity. We have already underlined that the tetrazines have a strong electron-deficient character. While this is true for the fundamental state, this is even more pronounced for the first excited state, which therefore has a relatively strong oxidizing power. Indeed, when the Rehm−Weller equations[57] are applied, an average increase of 2.25 V of the reduction potential is found. This value does not vary much because of the tiny fluctuations of the absorption and emission bands among the various tetrazines. Consequently, fluorescence can be quenched by various electron donors. The left curve in Figure 11 represents the Stern−Volmer plots for fluorescence quenching of tetrazine. It is clear that the stronger the electron
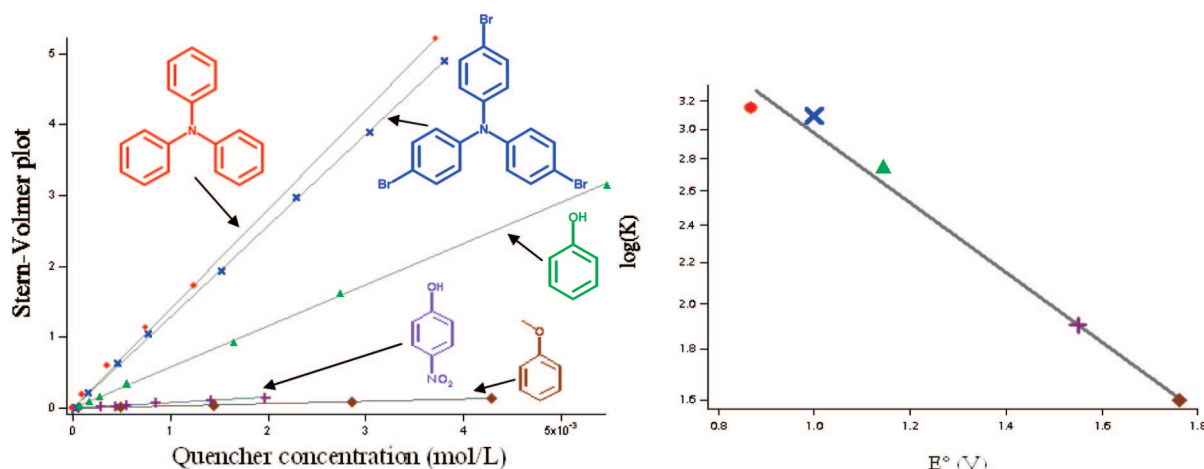
Figure 11. Left: Stern−Volmer plots for compound **33** as functions of quencher concentrations for the various quenchers. Right: correlation between the logarithm of the Stern−Volmer constant and the standard potential (vs SCE) of the various quenchers. Adapted from ref 47a. Copyright 2005 Wiley-VCH.

Figure 12. Generation of the triplet state of diphenyl-*s*-tetrazine (**1**) and its subsequent quenching by electron transfer from ferrocene.

Figure 13. Calculated structures of the HOMO and HOMO − 1 of compounds **13** and **14**.

their order can be reverted; that is, the π orbital one becomes the HOMO of the molecule. This is perfectly visible in Figure 13, which shows the HOMO and the HOMO − 1 obtained by DFT calculations in the two antagonist cases of the pyrrolidine and the aziridine substituents. In one case the HOMO orbital has an n nature, with the electron density on the tetrazine ring nitrogen atoms, while in the other case it has a π nature, with a strong participation of the substituted nitrogen atom lone pairs. This unusual situation has tremendous consequences on the spectroscopic characteristics of the tetrazines, and more particularly the fluorescence, as the first one displays good emission properties while the second does not emit light (Table 4, molecules **14** and **13**, respectively).

This inversion of orbitals was already proposed in an earlier report by Gleiter et al.,[16c] who measured and attributed the photoelectron spectroscopy of s-tetrazines. Neugebauer et al. also studied the radical cations of s-tetrazines and observed that, depending on the substituents, the radical was delocalized only on the central ring (n-type s-tetrazines) or on the overall molecule (π-type s-tetrazines). On the contrary, even though a lot of calculations[59] (semiempirical, HF, or

DFT) have already been conducted on s-tetrazine and its derivatives, these trends have never been highlighted by the authors before, except in one case[60] where Thulstrup et al. rationalized linear dichroism and magnetic circular dichroism spectroscopy results of symmetrically substituted tetrazines with semiempirical calculations (INDO/S).

s-Tetrazine derivatives that we had actually prepared and some others previously reported in the literature have been systematically calculated by the DFT method (B3LYP/6-31*G(d)), and the plot of the four most important orbitals related to fluorescence processes, that is, the HOMO, the HOMO − 1, the LUMO, and the LUMO + 1, revealed a correlation between the ordering of the orbitals and the fluorescence property (Figure 14).[32]

From a close examination, it is clear that the π orbital becomes the HOMO as soon as some mixing between the π orbitals of an electron-rich-enough substituent and the tetrazine ring is possible. This is the case when a nitrogen atom is present, because of the mixing of its nonbonding lone pair. However, when the substituent on the tetrazine is a poor electron donor (e.g., halogens or oxygen) or has no delocalizable electrons, the opposite situation happens and the n orbital becomes the HOMO. This is the case of aliphatic carbons and silicon, but also phosphorus and aziridine, which despite their lone pair, have a twisted arrangement which forbids orbital mixing. An intermediate case is the case of sulfur substituents, where both n and π orbitals lie roughly at the same energy.

The major consequence of this particular situation is the existence, or not, of appreciable fluorescence, which is one of the most interesting properties of tetrazines. Actually, the analysis of the fluorescence of the various tetrazines that we prepared is fully described by the theoretical predictions. Only the tetrazines substituted by strongly electronegative atoms are fluorescent, while the others are not fluorescent (or are very weakly fluorescent). This approach could be very useful to predict the photophysical behavior of new tetrazines. For example, introduction of silicon or phosphorus
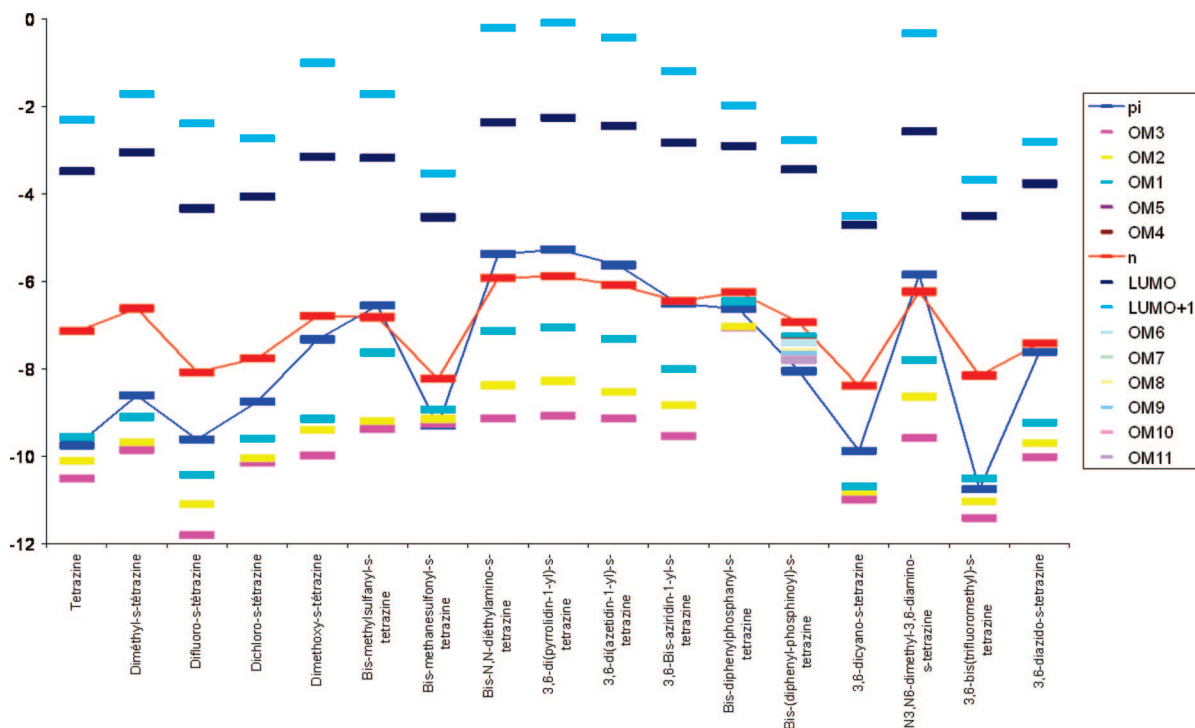
Figure 14. Orbital energies of symmetric s-tetrazines with heteroatomic substituents.
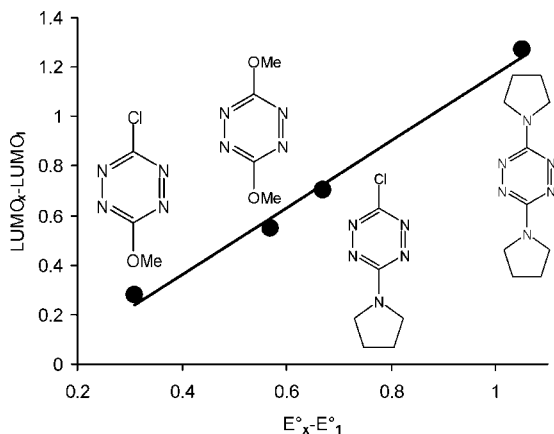
Figure 15. Correlation between the differences of the LUMO energies of *s*-tetrazines **11**, **13**, **22**, and **29** relative to **9** and the differences of their standard potentials ($R^2 = 0.9904$).

substituents should lead to fluorescent compounds, but the first ones are still unknown and two examples of the second have been reported[61] but not studied in this respect.

The calculations also allow a good estimation of the relative position of the reduction potentials of the tetrazines. Indeed, it is directly linked to the relative LUMO position, as could be expected (Figure 15).

5. Applications of Tetrazines

5.1. Energetic Materials from Tetrazines

One of the very first, and however continuing, applications of *s*-tetrazines has been energetic materials and related materials (propellants, fire retardants, etc.). This is more than worthwhile signaling, because this area has triggered many of the most beautiful synthetic works on this family. There are several tetrazine derivatives that display particularly interesting properties for explosives or pyrotechnics (Figure 16): dihydrazino-*s*-tetrazine (**8**) and its derived compound diazido-*s*-tetrazine (**48**), bis(tetrazolylamino)-*s*-tetrazine (**49**), bis(nitroguanyl)-*s*-tetrazine (**50**) and its salts, 6,6′-diamino-3,3′-azobis-*s*-tetrazine (DAAT; **51**) and derived oxides, and above all the famous LAX-112 high explosive 2,6-diamino-*s*-tetrazine 1,4-dioxide (**52**).

Dihydrazino-*s*-tetrazine (**8**) was first prepared in 1963,[62] but a considerably improved synthesis by Hiskey and Chavez appeared in the late 1990s.[23a] This compound easily expels nitrogen during the combustion and has a very fast burning rate; however, it has to be mixed with an oxidant (and a dying agent) to make a good pyrotechnic material. Chavez
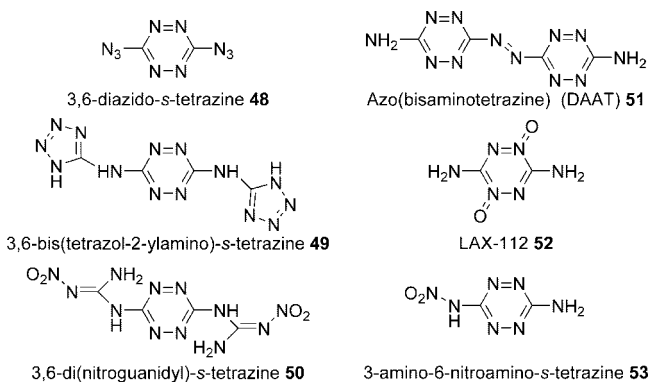
Figure 16. High nitrogen content *s*-tetrazine derivatives for energetic material applications.

et al. have also shown that dihydrazino-*s*-tetrazine could be in specific conditions converted to diazido-*s*-tetrazine (**48**). Unfortunately, this compound is only weakly stable and explodes very easily. However, its decomposition in controlled conditions can generate nanoparticles of carbon or carbon nitrides, which are very difficult to obtain otherwise.[63]

Like many previously described tetrazines, bis(tetrazolylamino)-*s*-tetrazine (**49**) and bis(nitroguanyl)-*s*-tetrazine (**50**) are obtained by nucleophilic displacement of pyrazoles from *s*-tetrazine **7**.[8a] Bis(tetrazolylamino)-*s*-tetrazine has some interesting properties to be used as a propellant, but is sensitive to sparks.[63,64] Its properties have been investigated by several groups. A special feature is the remarkable acidity of bis(nitroguanyl)-*s*-tetrazine, which allows the formation of the bisguanidinium salt, which has a very high heat formation of 1255 kJ·mol^{-1}. DAAT (**51**) and derived oxides were also prepared by Hiskey and Chavez. DAAT exhibits a very high density. Also, the hardly separable DAAT oxide mixture that is obtained by reaction with hydrogen peroxide in the presence of trifluoroacetic anhydride can be processed as such and used as an excellent propellant in association with a binder. The same group has also discovered 3,6-diamino-*s*-tetrazine 1,4-dioxide (**52**), the LAX-112 high explosive, and recently new potentially promising molecules, the silver and guanidinium salts of 3-amino-(6-nitroamino)-*s*-tetrazine (**53**), again taking advantage of the acidity of the proton borne by the nitroamino group (Figure 16).[64,65]

5.2. NLO-phores with Tetrazine

The tetrazine ring being a strong electron acceptor, there is a potential for the preparation of active molecules for nonlinear optics. The tetrazine moiety can either serve as the attractor for a classical dipolar push−pull molecule or more interestingly contribute to the formation of a linear octupole, as proposed by Zyss et al. some years ago.[66] In addition, the tetrazine ring can be the attractive center of purely symmetrical quadrupolar molecules, with enhanced third-order γ values. Scheme 12 details these features.

Again the potentially wide panel of possibilities comes into evidence, despite the fact that no example of dipoles nor octupoles including tetrazines has yet been published. However, the demonstration of the third-order NLO activity of quadrupolar tetrazines **3**, **5**, and **6** with ferrocenyl or thienyl substituents displaying a high charge transfer in the fundamental state was recently published by us.[67] Unfortunately, the third-order susceptibility γ values recorded (Table 6) were a little bit disappointing; however it is the first example of NLO-active molecules including tetrazines and will probably be followed by several others. A possible explanation for the average γ values could also be that the ferrocene is not a strong enough donor.

5.3. Active Polymers Including Tetrazines

Because of all the reasons exposed in the previous paragraphs, it is very desirable to include tetrazines in structured polymers or build supermolecules from tetrazines. One of the most obvious applications was to prepare n-dopable conducting polymers including tetrazines in the main chain. The target molecules (Figure 17) were evident, and their synthesis was straightforward through a standard or modified Pinner synthesis.

All these molecules with $n = 1$ were prepared, along with bis(bithienyl-2-yl)tetrazine (**4**), the only tetrazine bearing a

Scheme 12. General Schemes of NLO-Active Molecules Including a Tetrazine Ring and Examples of Target Molecules
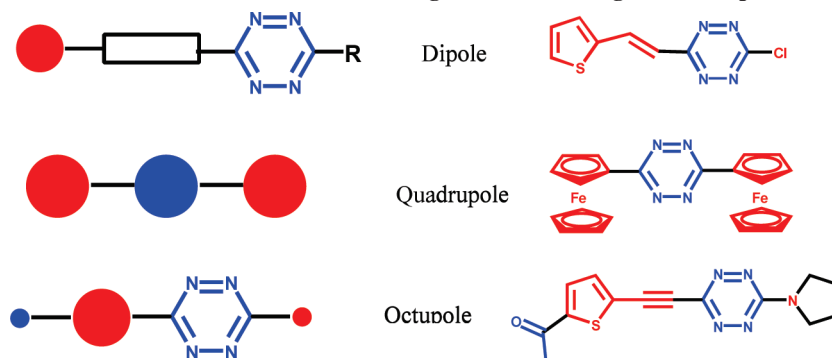
Table 6. Third-Order Nonlinear Susceptibilities γ of Ferrocenyl- and Thienyl-s-Tetrazines Recorded in Dichloromethane

compd	concn (mol·L^{-1})	γ_{micro} (10^{34} esu)
5	7.8×10^{-3}	0.9 ± 0.35
	8.9×10^{-3}	0.8 ± 0.07
6	1.5×10^{-2}	0.85 ± 0.3
	1.1×10^{-2}	0.76 ± 0.1
3	1.1×10^{-2}	2.5 ± 0.1

heterocyclic dimer published up to now.[68] Actually, the first molecule of the family was the dipyrrol-2-yl-s-tetrazine prepared first by Soloducha et al.[69] and shortly after by us. However, this molecule does not polymerize, which probably did not encourage further investigations. It was discovered later that this was a general feature for all tetrazines bearing a single heterocycle. The reasons for this peculiarity are quite unclear. It was believed in the beginning that the tetrazine nitrogen atoms could deprotonate the cation radical, but this explanation does not hold with the other heterocycles, especially EDOT.[70] The electron-withdrawing character of the tetrazine also cannot be considered as the only criterion, because, for example, difluoropyrrole does polymerize,[71] as well as (trifluoromethyl)thiophene.

Therefore, it was necessary to attach more than one heterocycle to the tetrazine ring, which was achieved a few years ago with the preparation of bis(bithienyl-2-yl)-s-tetrazine (**4**).[68] This compound can be readily polymerized into a nice red-colored polymer (Figure 18), which is electroactive in both the anodic and the cathodic regions.

Electrochemical studies have shown that, if in the anodic region the polymer behaves exactly like a conventional polythiophene (with a slight potential shift), on the other hand in the cathodic region it behaves like a pending group polymer, because the cathodic peak currents were found to vary with the square root of the scan rate. Therefore, conducting polymers containing tetrazines in the main chain cannot be considered "stricto sensu" as n-dopable, because the charge appears to be rather localized on the tetrazine ring, with the charge transfer occurring by hopping between redox centers instead of real conduction. A future challenge would be to realize conducting polymers incorporating fluorescent tetrazines. Work is in progress in this direction.
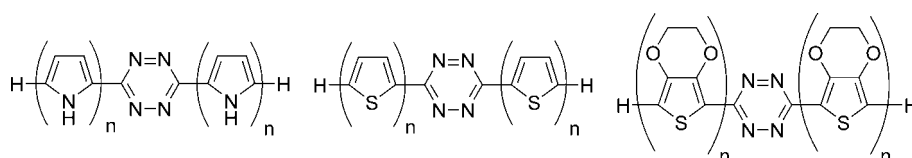
5.4. Supermolecular Tetrazines and Supramolecular Applications

Another challenge is the preparation of specific supermolecules including several tetrazines as functional moieties. By arrangement of several tetrazine units around the same structural block, one could in principle enhance the sensitivity of the tetrazine response. We have reported recently the preparation of new cyclophanes **38** and **39** made of three tetrazine rings linked by alkyl spacers between them (Figure 2).[47b,72] Unfortunately, these molecules were weakly fluorescent, but their redox behavior was found to be very sensitive to alcohols with a 3-fold symmetry such as 1,3,5-benzenetrimethanol.

Cyclodextrins are particularly attractive molecules because of their ability to include selectively hydrophobic molecules in their cage. Besides this, they have hydroxyl groups which can be used for many types of functionalization. Since dichloro-s-tetrazine readily reacts with a relatively accessible hydroxyl function in the presence of 2,4,6-collidine, it was attractive to prepare new functionalized cyclodextrins with substituted tetrazine moieties (Scheme 13).[73] In addition, the relatively rigid cyclodextrin core leaves little flexibility to the tetrazine motion and therefore is likely to enhance the
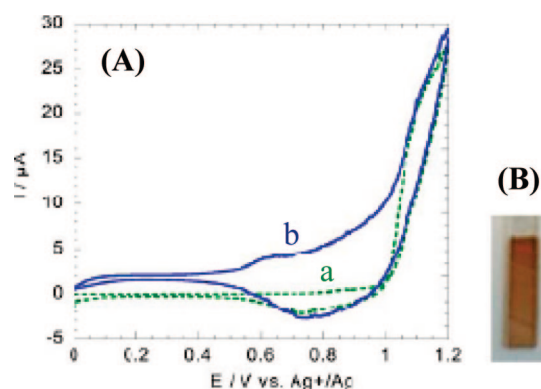
Figure 18. (A) Accumulative cyclic voltammogram for the electropolymerization of bis(bithienyl-2-yl)-s-tetrazine (**4**) on platinum in dichloromethane (ca. 5 mmol·L^{-1}): (a) first cycle, (b) tenth cycle. Scan rate: 0.1 V·s^{-1}. (B) Picture of a film of the polymer deposited onto an ITO glass electrode (about 10^{-2} C·cm^{-2}).

Figure 17. Electropolymerizable tetrazine-based precursors of conducting polymers.

**Scheme 13. Synthesis of Tetrazine-Substituted Cyclodextrins**
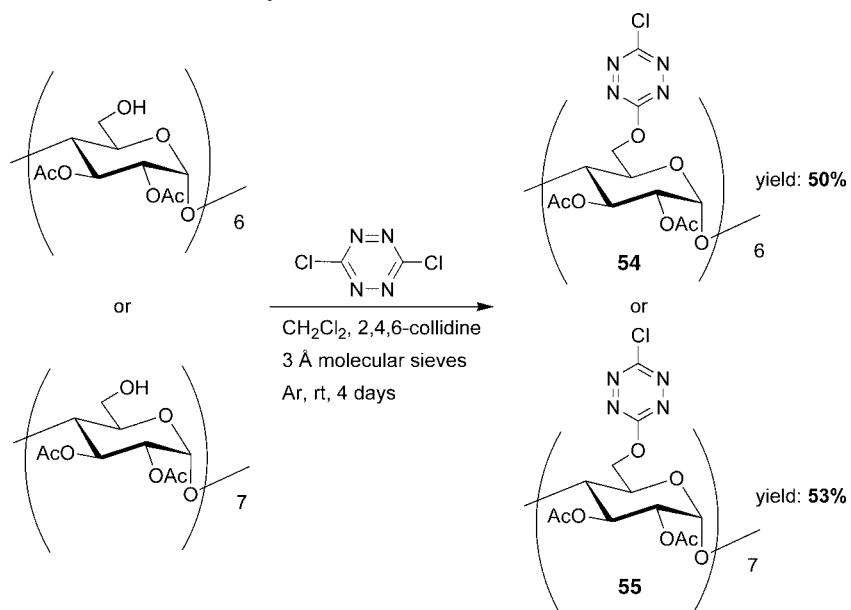
energy and/or electron transfer between the tetrazine centers and a given host molecule.

The two functionalized cyclodextrins show different types of quenching depending on the solvent nature which dictate the location of the quencher inside or outside the cyclodextrin cavity. In the case of dichloromethane (a nonpolar solvent), only dynamic quenching is observed with TTF (Figure 19, left). Indeed, the fluorescence lifetime of the tetrazine is reduced, but the intensity remains constant. Contrariwise, in methanol (a more polar solvent) static quenching is observed at first (Figure 19, right) as can be deduced from the decrease by a factor 3 of the fluorescence intensity when 1 equiv of TTF is added while the fluorescence lifetime remains constant. Addition of more quencher leads to more fluorescence decrease but in a dynamic regime (constant intensity, reduced lifetime). This discrepancy

between the two solvents comes from the fact that up to 1 equiv of the aromatic donor lies in the hydrophobic cavities of the cyclodextrin in methanol while it is always distributed throughout the solution in dichloromethane.

Supramolecular applications of *s*-tetrazine are still scarce. It has recently been postulated, on the basis of ab initio calculations, that they could be used as binding units for the molecular recognition of anions.[74] Calculations showed that the formation of a complex between *s*-tetrazine and fluoride (Figure 20) should be energetically favorable (calculated complexation energy $E = -18.75 \text{ kcal} \cdot \text{mol}^{-1}$) and would be mainly governed by electrostatic and polarization energies. Conversely, complexation with chloride or bromide would be less favorable ($E \approx -10.5 \text{ kcal} \cdot \text{mol}^{-1}$), and in principle, the halogen anions could be discriminated.
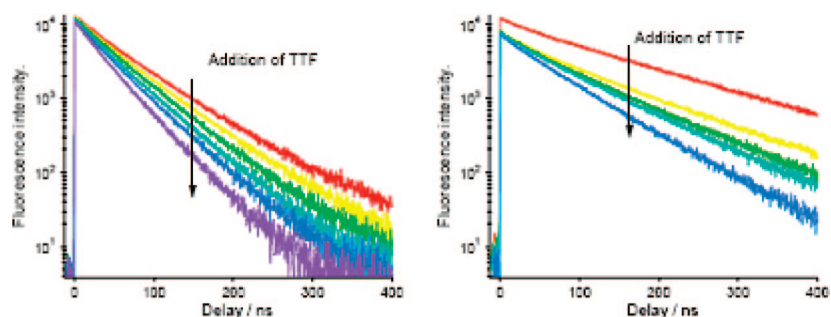

Figure 19. Variation of fluorescence lifetime decay curves upon quenching of *β*-cyclodextrin **48** fluorescence with TTF in dichloromethane (left) and methanol (right).
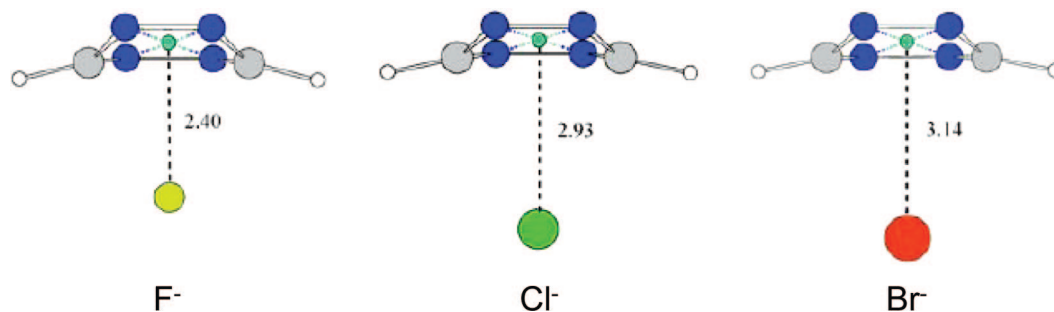
Figure 20. MP2-optimized geometries of *s*-tetrazine complexes with fluoride, chloride, and bromide. Distances are in angstroms, and the ring centroid is represented by a dummy atom.

Scheme 14. Principle of the Redox-Controlled On/Off Switching of the Tetrazine−Thiourea Complexation (Left) and Thermodynamic Cycles Used To Quantify the Redox-Modulated Binding between Hydrogen-Bound Complexes of Tetrazine and Thiourea[a]
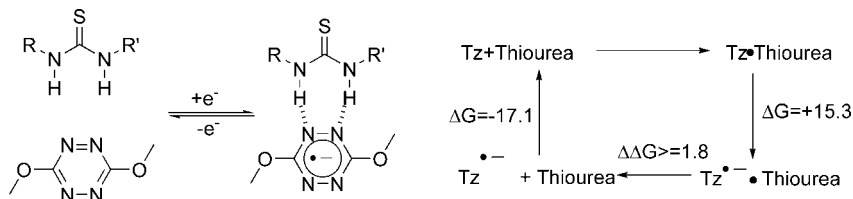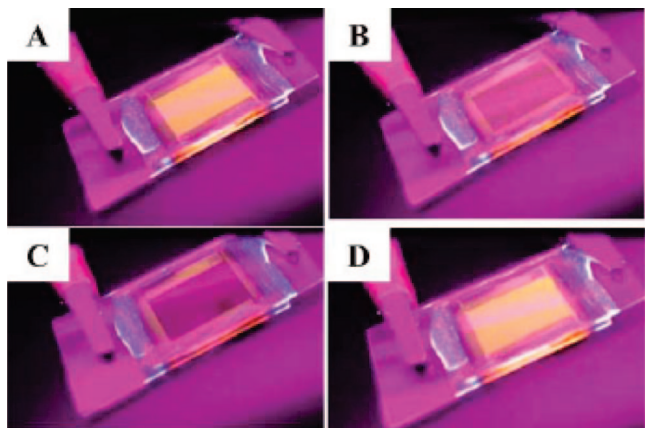

[a] Energies in kilocalories per mole.

The use of this so-called anion−π interaction was demonstrated by Dunbar et al.,[75] who could control the supramolecular arrangement of metallic complexes of dipyrid-2′-yl-s-tetrazine (**42**) through the interaction with the counteranion. Indeed, upon complexation of the tetrazine with various first-row transition metals (Ni, Zn, Mn, Fe, Cu) cyclic products are formed in which the structure (square or pentagon) depends on the counteranion used and its interaction with the tetrazine ring. More recently, this group extended this approach with silver as a metal to form polymeric chains, propellers, or grids.[76]

Synthetic host−guest systems that respond to external stimuli provide supramolecular building blocks for applications in sensors, molecular electronics, and tunable solid-state materials. Molecular recognition coupled with electrochemistry generates synthetic host−guest systems whose binding strength is modulated by the capacity of the host to readily accept or donate electrons. s-Tetrazine derivatives were tested as potential candidates for redox modulation via two-point hydrogen bonding (Scheme 14).[77] The reduction of the tetrazine derivatives affords an electrochemical "on/off" switch where the addition of an electron turns "on" the hydrogen bonding between tetrazine and thiourea and the reoxidation of the tetrazine breaks apart the complex.

5.5. Control of the Fluorescence of Tetrazine by Its Redox State

A particularly attractive issue with tetrazine is the modulation of the fluorescence with the redox state of the tetrazine. This has been recently achieved by incorporating chloromethoxytetrazine (**11**) and a polymeric electrolyte into a sandwich cell.[78] It has been demonstrated, as shown in Figure 21, that the fluorescence of the tetrazine can be reversibly modulated according to its redox state: the device is highly fluorescent when the tetrazine is in its neutral state, and very low emission was detected upon its reduction. This type of passive fluorescent displays (essentially different from active LEDs) could find some use in the production of large-sized fluorescent tunable panels, for example for decoration purposes.

Since this first demonstration of the efficiency of the electrochemical switching of fluorescence with the help of a centimeter-sized transparent electrochemical two-electrode cell, some questions on the mechanism have however arisen. The main point was to ascertain whether the fluorescence extinction came solely from the conversion of the tetrazine to its anion radical or whether there was an additional contribution from mutual quenching between the excited state of the tetrazine and the already formed anion radical through photoinduced electron transfer. We performed more conclusive experiments using a localized laser beam in the electrode diffusion layer[79] and very recently a TIRF setup.[80] In the TIRF experiments, the fluorescence excitation occurs via the evanescent wave arising out of multiple internal reflections inside a waveguide through the working electrode which consists of a very thin (≈∼30 nm) platinum semitransparent layer.

The conclusion of these studies, through lifetimes analysis, was that the quenching by the anion radical took place when its concentration was important enough. However, complete extinction of the tetrazines could be achieved deep within the electrode diffusion layer, and in this case almost complete extinction of the fluorescence was observed, thus confirming the nonfluorescent (or very weakly fluorescent) character of the anion radical.

6. Conclusion

Throughout this review we have shown that tetrazines display a panel of rare and useful characteristics that make them usable for several types of applications in various domains, far beyond their traditional use in explosives and flame-retardant technology. They have a rich and varied physical chemistry, especially in the case where their unusual fluorescence is observed.

We emphasize more particularly the starting field of research, which is the study of the interplay of redox chemistry and fluorescence. This is a complete new area of research, and for which tetrazines are almost ideal candidates. Also of particular interest is the use of tetrazines for energy storage. These molecules can be considered in fact as being at the frontier between organic and inorganic (traditional "mineral") chemistry. Indeed, they can accommodate up to two electrons in a very small volume. They stand, together with compounds such as cyclohexanehexone or squaric acid,

Figure 21. On and off switching by electrochemistry of a fluorescent panel display: (A) initial 0 V, (B) −1 V, (C) −2 V, (D) +1 V.

as a family of organic compounds binding standard inorganic materials such as metal oxides, chalcogenides, or nitrides, which can store efficiently one to two electrons per species, but which are heavy due to the metal molecular weight, and the traditional organic compounds (e.g., conducting polymers), which benefit from the low weight of the first-row atoms, but can only store one to two electrons on three to four rings. Pioneering work is also being initiated in this direction. Therefore, it is likely that applications of tetrazines will certainly find many extensions in the near future and that their interesting chemistry will continue to develop at a fast pace.

7. References

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