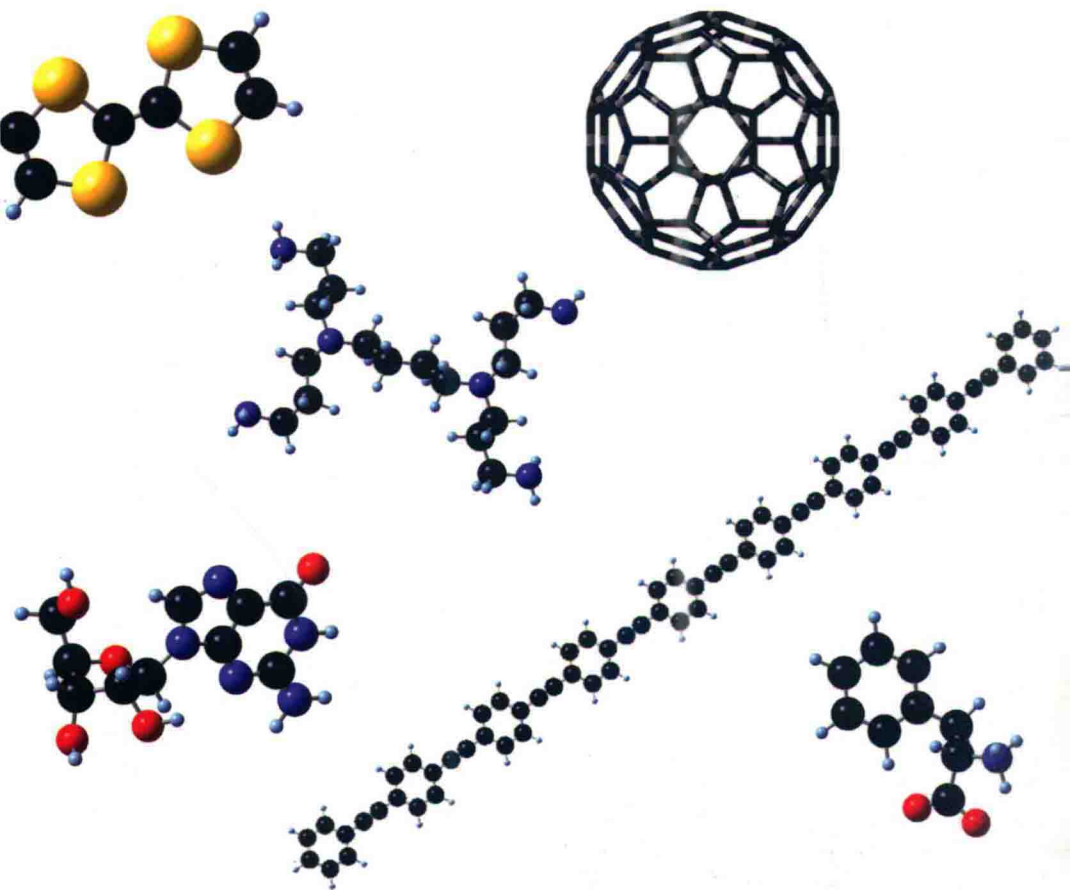


Organic Synthesis and Molecular Engineering

Edited by
Mogens Brøndsted Nielsen



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ORGANIC SYNTHESIS AND MOLECULAR ENGINEERING

Edited by

MOGENS BRØNSTED NIELSEN

Department of Chemistry
University of Copenhagen
Copenhagen, Denmark



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I would also like to thank valuable feedback from students who have read some parts of the book, in particular, the students who have followed my course in supramolecular chemistry. With its wide coverage, it is indeed my hope that this book will be useful as a textbook for courses in organic, supramolecular, and macromolecular chemistry.

M.B.N.

CONTRIBUTORS

MUTLU BATTAL, Department of Chemistry, University of Miami, Coral Gables, FL

SOPHIE R. BEEREN, Carlsberg Laboratory, Copenhagen V, Denmark

MIKAEL BOLS, Department of Chemistry, University of Copenhagen, Copenhagen Ø, Denmark

DAVIDE BONIFAZI, Department of Chemistry, University of Namur, rue de Bruxelles, Namur, Belgium

MARIANO L. BOSSI, INQUIMAE, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Buenos Aires, Argentina

MARTINA CACCIARINI, Department of Chemistry, University of Florence, Sesto Fiorentino, Italy

DAVID CANEVET, Laboratoire MOLTECH-Anjou, UMR CNRS 6200 UFR Sciences, Université d'Angers, Angers, France

JØRN BOLSTAD CHRISTENSEN, Department of Chemistry, University of Copenhagen, Copenhagen Ø, Denmark

JANET CUSIDO, Department of Chemistry, University of Miami, Coral Gables, FL

ERHAN DENIZ, Department of Chemistry, University of Miami, Coral Gables, FL

SÉBASTIEN GOEB, Laboratoire MOLTECH-Anjou, UMR CNRS 6200 UFR Sciences, Université d'Angers, Angers, France

HELENA GRENNBERG, Department of Chemistry – BMC, Uppsala Universitet, Uppsala, Sweden

KARSTEN JENNUM, Department of Chemistry, University of Copenhagen, Copenhagen Ø, Denmark

JAN O. JEPPESEN, Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Odense M, Denmark

KARINA R. LARSEN, Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Odense M, Denmark

KASPER LINCKE, Department of Chemistry, University of Copenhagen, Copenhagen Ø, Denmark

TOMAS MARANGONI, Department of Chemistry, University of Namur, rue de Bruxelles, Namur, Belgium

MORTEN MELDAL, Department of Chemistry, University of Copenhagen, Copenhagen Ø, Denmark

KASPER MOTH-POULSEN, Department of Chemical and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden

KENT A. NIELSEN, Department of Physics, Chemistry and Pharmacy, University of Southern Denmark, Odense M, Denmark

MOGENS BRØNDSTED NIELSEN, Department of Chemistry, University of Copenhagen, Copenhagen Ø, Denmark

CHRISTIAN MARCUS PEDERSEN, Department of Chemistry, University of Copenhagen, Copenhagen Ø, Denmark

MARCO PETRIELLA, INQUIMAE, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Buenos Aires, Argentina

MICHAEL PITTELKOW, Department of Chemistry, University of Copenhagen, Copenhagen Ø, Denmark

BRIAN RASMUSSEN, Department of Chemistry, University of Copenhagen, Copenhagen Ø, Denmark

FRANÇOIS M. RAYMO, Department of Chemistry, University of Miami, Coral Gables, FL

MARC SALLÉ, Laboratoire MOLTECH-Anjou, UMR CNRS 6200 UFR Sciences, Université d'Angers, Angers, France

JONATHAN L. SESSLER, Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX

ANNE SØRENSEN, Department of Chemistry, University of Copenhagen, Copenhagen Ø, Denmark

SALVATORE SORTINO, Department of Drug Sciences, University of Catania, Catania, Italy

MASSIMILIANO TOMASULO, Department of Chemistry, University of Miami, Coral Gables, FL

IBRAHIM YILDIZ, Department of Chemistry, University of Miami, Coral Gables, FL

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CHAPTER 1

INTRODUCTION

MOGENS BRØNDSTED NIELSEN

Molecular engineering is an interdisciplinary research field, where design, synthesis, and manipulation of molecules and molecular assemblies are used to create advanced functions. Molecular engineering is an inherent part of nanotechnology and often involves manipulation of molecules at the nanoscale. The synthesis of organic molecules is usually the first experimental step to take whether the overall aim is to develop a nanomachine or molecular motor, a memory device, or an artificial enzyme that can catalyze specific transformations. Organic synthesis is therefore an integral part of this book, and several chapters have a special emphasis on synthetic protocols. With respect to the molecular and supramolecular function, the field of molecular engineering is relevant to a broad range of disciplines, from materials science, molecular electronics, environmental chemistry, chemical biology to pharmaceutical science. Some important targets are molecule-based computers (faster and smaller than silicon-based ones), intelligent drug delivery systems, organic molecules that are as efficient as enzymes for performing catalytic reactions but structurally much simpler (by being much smaller), peptide engineering of new catalysts, molecular sensors, materials for optical data storage, new electrically conducting materials, and new energy-storage materials. This book attempts to cover broadly these fields via chapters of which some are very general and some more specific. The chosen topics described in the chapters present a selection of important scientific contributions that have been made. Many other important contributions could have been covered in a book with such a broad title, but at least I hope that the reader will get an impression of the rich possibilities that exist to create molecules and supramolecular systems with unique properties and functions from those examples covered in this book.

The book is organized as follows. Chapter 2 gives an overview of useful molecular building blocks, covering, for example, different chromophores, redox-active molecules, photoswitches, peptide building blocks, macrocyclic receptors, and examples of how they can be integrated in advanced systems with specific functions. Some of these units are particularly useful in the design of molecular electronics components, which is the

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focus of Chapter 3. According to *Moore's law* [1], the number of components on integrated circuits doubles approximately every 2 years. Nobel Laureate Richard P. Feynman stated in his famous talk in 1959 at an American Physical Society meeting at Caltech that "There is plenty of room at the bottom," which can be considered the start of nanotechnology and the idea of using a "bottom-up" manufacturing technique by self-assembly of suitable molecules. Thus, development of molecules as components for molecular electronics may provide a way to extend Moore's law beyond the limits of small-scale conventional silicon-integrated circuits. Carbon allotropes are also successfully exploited in this field as well as in organic photovoltaics, and production and functionalization of carbon nanotubes and graphene (single sheets of graphite) are covered in Chapter 4. For achieving functional devices and nanomachines, self-assembly of the molecular components in a desired manner is crucial. Chapter 5 describes how hydrogen bonding interactions can be employed for obtaining self-organizing nanostructures. By rational design of the structural parameters of the single molecular modules and by a strict control of the solvent and temperature conditions, it is possible to produce supramolecular polymeric materials possessing different geometrical structures such as nanofibers, two-dimensional organic networks, vesicles, or toroids.

Exploitation of solar energy is the focus of Chapter 6 and in particular how to store energy in chemical bonds by light-induced isomerization reactions. As described in this chapter, some of several challenges are to harvest light at the right wavelengths and to release the stored energy as heat in an efficient way when needed. Photoswitchable compounds are also central to Chapter 7, which describes strategies to switch fluorescence of photochromic oxazines. Such photoswitchable fluorophores have potential for the visualization of biological samples with subdiffraction resolution.

Supramolecular chemists have, over the last decades, developed a wide variety of macrocyclic receptors for binding of ionic or neutral guests. Specific efforts have focused on transducing the host-guest recognition process in a redox event, targeting sensors, smart materials, or devices for molecular electronics. Such redox-responsive systems are the focus of Chapter 8. The subsequent chapter shows how a chemosensor for nitroaromatic explosives, based on color changes, is designed, improved by systematic variation of the chemical structure, and how this molecule can be integrated into different solid-state devices.

Development of artificial receptors for substrates in water is particularly challenging, but central for engineering of biomimetic systems. In Chapter 10, the focus is recognition of carbohydrates in water and the different techniques used to evaluate this process. Carbohydrates are involved in the metabolic pathways of living organisms and play a crucial function in the first step of cell-cell, cell-virus and cell-bacteria interactions. Chapter 11 describes the development and synthesis of artificial enzymes based on cyclic oligosaccharide receptors, so-called cyclodextrins, which can bind substrates in a hydrophobic cavity and catalyze their conversion to specific products via suitably located catalytically active groups. The subsequent chapter covers another class of catalysts, organozymes, based on rationally designed peptides. Peptide-based catalysts that display some of the qualities of enzyme conversions have been developed in an approach partly based on the application of combinatorial methods. While natural enzymes have evolved to be efficient and selective through millions of years, combinatorial evolution in the laboratory can be performed rapidly within a few years. Catalysis and/or transport can also occur inside so-called dendrimers, which are classes of highly branched "tree-shaped" nanosized molecules. Exploitation of these molecules in biology and nanomedicine and the synthetic strategies to achieve them are covered

in Chapter 13. Chapter 14 describes how reversible formation of host molecules can be used to identify the most suitable receptors for substrates in water, a field which is termed dynamic combinatorial chemistry. In this approach, the most suitable molecule is selected—"survival of the fittest" at the molecular level.

REFERENCE

- [1] Moore, G. E. (1965). Cramming more components onto integrated circuits. *Electronics*, 38, 114–117.

CHAPTER 2

ORGANIC BUILDING BLOCKS FOR MOLECULAR ENGINEERING

KASPER LINCKE and MOGENS BRØNDSTED NIELSEN

2.1 MOLECULAR FUNCTION

Organic engineering of advanced molecules and supramolecular assemblies requires a variety of molecular modules with specific functions and properties, as shown schematically in Figure 2.1. Redox activity is an example of an important function, which allows charging of the organic molecule, either by removal or by donation of electrons. π -Conjugated molecules are often redox active and are usually also conveniently used as wires for electron transport (conductance). We also need building blocks that can absorb and emit light at specific wavelengths (chromophores and fluorophores) or that can undergo light or thermally induced structural changes (photo/thermoswitches) to form molecules with new properties. We need structural motifs that allow complexation of specific guest molecules or ions in various media via noncovalent interactions. Such molecular hosts may concomitantly act as catalysts for the chemical conversion of the guest molecules, substrates, into new products, thereby mimicking enzymes, or they could act as carriers for transporting the guest molecules from one phase to another, for example, through a cell membrane. Host–guest complexation may also alter properties such as fluorescence, which can be employed in the design of molecular sensors. Other important molecular properties include Brønsted and Lewis acidity and basicity, chirality, dipole moment, magnetic properties, nonlinear optical (NLO) and two-photon absorption properties, liquid crystallinity, solubility in polar (in particular, water) or nonpolar solvents, and not least, chemical stability and photostability.

Altered properties of the functional unit by virtue of interactions with its surroundings should also be taken into account. For example, chromophores can exhibit solvatochromism and hence exhibit different absorption maxima in different solvents. Absorption tuning is particularly important for the action of many proteins, such as opsin proteins present in the eye. These proteins are involved in the process of vision. The entire visible region is covered by three different cone pigment cells, each containing photoactive transmembrane proteins. While the chromophore is identical in these

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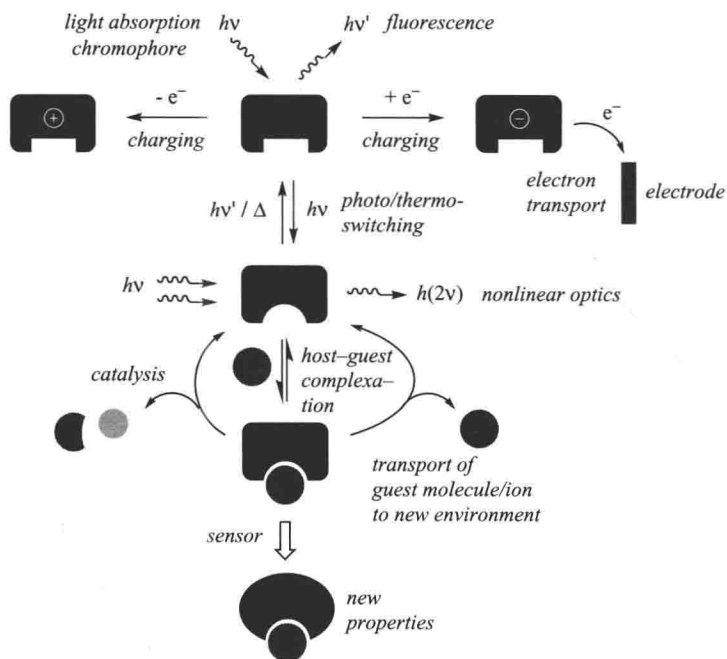


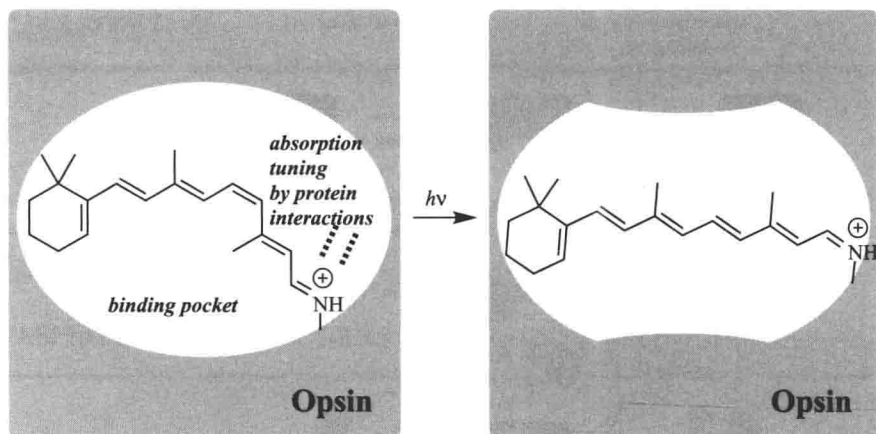
Figure 2.1. Schematic overview of different molecular functions.

proteins, namely, a protonated retinal Schiff base linked to a specific lysine residue, the protein-binding pockets differ slightly in the three types of cones. By subtle protein–chromophore interactions, one protein tunes the chromophore absorption maximum to blue, one to green, and one to red light [1–3]. As shown in Scheme 2.1, the absorption of light induces a *cis* to *trans* isomerization of a double bond in retinal; this is the primary event in visual excitation and alters the geometry of the retinal in the protein-binding pocket, which triggers a cascade of processes [1]. Along the same line, the green fluorescent protein (GFP), which absorbs blue light and emits green light, provides a rigid environment for its chromophore (a 4-hydroxybenzylideneimidazolinone, Figure 2.2), which is only very weakly fluorescent in solution, but inside the binding pocket, fluorescence is turned on. On account of its fluorescent properties, GFP is widely used as a marker protein in molecular and cell biology [4–6].

Systems can be cleverly engineered that couple together individual functions, such as light absorption, energy transfer, and electron transfer, which is of importance when constructing, for example, photovoltaic cells or artificial photosynthesis systems. A selection of specific molecular building blocks will be provided in this chapter, and a few advanced systems will be discussed. Some reaction types useful in synthesis will also be presented, of which several will be encountered in the following chapters.

2.2 REDOX-ACTIVE UNITS

Organic molecules with alternating single and double or triple bonds, that is, π -conjugated molecules, are as mentioned earlier, often redox active and can either



Scheme 2.1. Schematic illustration of the protonated retinal Schiff base in the opsin-binding pocket. The absorption maximum of the chromophore is tuned by protein interactions. Absorption of light is followed by a *cis-trans* isomerization of the chromophore, which leads to geometrical changes of the protein.

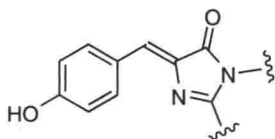
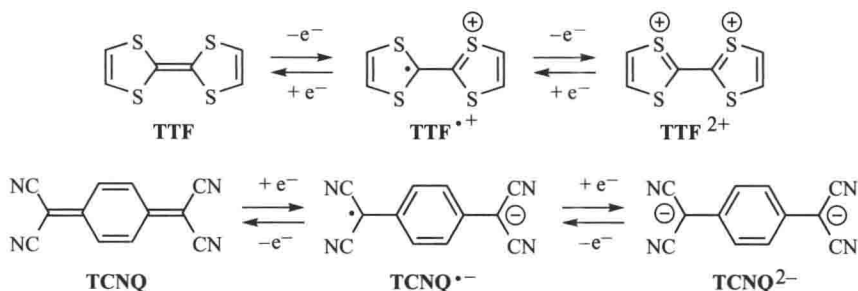


Figure 2.2. The GFP chromophore. It is covalently linked at two positions (indicated by wavy lines) to the protein and is present either as neutral phenol or as phenolate.

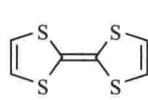


Scheme 2.2. Reversible oxidations of tetrathiafulvalene (TTF) and reversible reductions of tetracyano-*p*-quinodimethane (TCNQ).

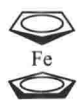
donate or receive electrons resulting in stable cations or anions. Such redox-active organic molecules are particularly useful in supramolecular and materials chemistry. For example, the first conducting organic metals were based on a charge-transfer salt between tetrathiafulvalene (TTF) and tetracyano-*p*-quinodimethane (TCNQ) [7, 8]. TTF is a so-called Weitz-type redox system (end groups are cyclic π -systems that exhibit aromatic character in the oxidized form), which is oxidized in two one-electron steps to generate two aromatic 1,3-dithiolium rings (Scheme 2.2) [9]. TCNQ is instead a

Wurster-type redox system (end groups located outside a cyclic π -system that exhibits aromatic character in the reduced form), which, like *N,N,N',N'*-tetramethyl-*p*-phenylenediamine (Wurster's blue), is aromatic in its reduced form (Scheme 2.2). Its acceptor strength can be further enhanced by functionalization with electron-withdrawing fluoro substituents. Buckminsterfullerene (C_{60}) can undergo up to six reversible one-electron reductions in solution [10], but usually three to four reductions are observed depending on the solvent [11]. C_{60} and its derivatives are widely explored as electron-acceptor moieties for photovoltaic devices such as solar cells [12]. Large carbon-rich acetylenic scaffolds have also achieved recognition as good electron acceptors [13, 14]. The expanded [6]radialene shown in Figure 2.3 presents one such example [15]; interestingly, its perethynylated core comprises a total of 60 carbon atoms. Figure 2.3 shows a variety of other electron-donor and acceptor molecules, including ferrocene

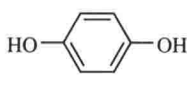
Electron donors



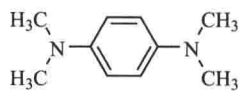
TTF



Fe

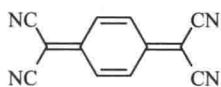


Hydroquinone

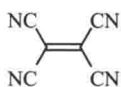


Wurster's blue

Electron acceptors



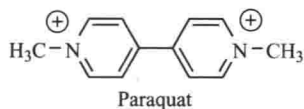
TCNQ



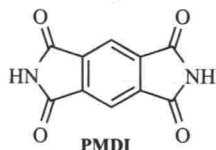
TCNE



Benzoquinone



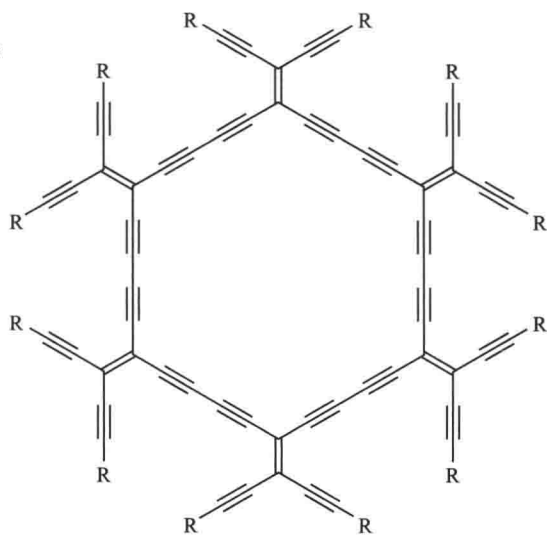
Paraquat



PMDI



Buckminsterfullerene, C_{60}



Expanded [6]radialene: $C_{60}R_{12}$

Figure 2.3. Redox-active organic electron donors and acceptors.

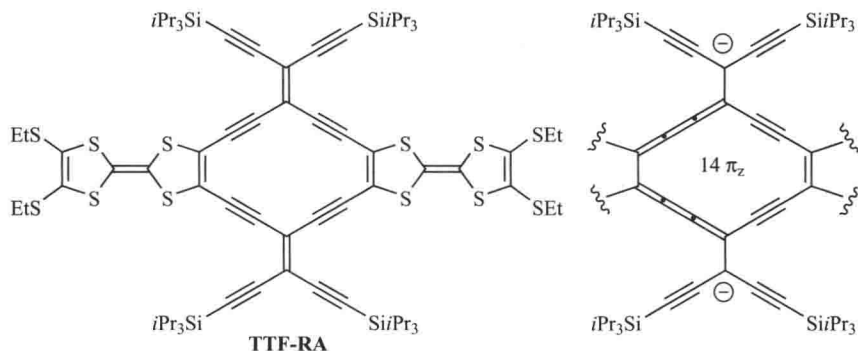


Figure 2.4. TTF-Radiaannulene (TTF-RA), a combined Weitz–Wurster-type redox system. Upon two-electron reduction, the central core formally becomes 14 π -aromatic.

(Fc), hydroquinone/benzoquinone, tetracyanoethylene (TCNE), paraquat, and pyromellitic diimide (PMDI).

Fusing together redox-active systems can result in molecules with multiple redox states furnished by either oxidation or reduction. For example, a so-called expanded radiannulene core (containing both endo- and exocyclic double bonds) was recently fused together with two TTF units to afford a molecule (TTF-radiaannulene [TTF-RA], Figure 2.4), which was found to reversibly exist in six redox states: -2 , -1 , 0 , $+1$, $+2$, $+4$ [16]. The cyclic core of the dianion contains 14 π -electrons, and it thereby satisfies the Hückel $4n + 2$ aromaticity rule for planar cycles with $n = 3$ (in general, n should be zero or a positive integer). The TTF-RA molecule can accordingly be considered as a Wurster-type redox system (the cyclic core) combined with Weitz-type redox systems (the TTFs). Thus, it formally gains aromaticity by either reduction or oxidation. The resonance formula drawn for the dianionic core in Figure 2.4 resembles an annulene structure. Annulenes are completely conjugated monocyclic hydrocarbons with endocyclic double bonds, of which the simplest are cyclobutadiene, benzene, and cyclooctatetraene. Instead, radialenes are alicyclic organic compounds with exocyclic double bonds, of which trimethylenecyclopropane is the simplest. By fusing together two perethynylated radiannulenes in a bicyclic structure as shown in Figure 2.5 [17], a particularly strong electron acceptor is obtained, even stronger than C_{60} . Thus, this compound shows a first reduction at -0.83 V versus Fc^+/Fc (in THF + $0.1\text{ M Bu}_4\text{NPF}_6$), while that of C_{60} is at -1.02 V under comparable conditions. Such large two-dimensional, carbon-rich scaffolds, resembling all-carbon graphene sheets, are particularly interesting in the quest for optoelectronic and conducting materials.

2.2.1 Case Study: TTF Building Blocks

TTF has, in particular, found use as a redox-active building block. Its successful incorporation into macromolecular and supramolecular systems takes advantage of ready access to useful building blocks, which can be converted into nucleophiles by treatment with suitable bases, as shown in Scheme 2.3. Direct lithiation can be accomplished with lithium diisopropylamide (LDA), and the resulting lithiated species can be treated with, for example, 1,2-diiodoethane to provide an iodo-substituted TTF for further