ing the properties of these synapses, their interactions with each other and with the resident voltage-dependent membrane currents, rest on a bed of untested inferences and assumptions. In the near term, computer models should help us to see further into these hard-to-reach places, and the rapid evolution of imaging technologies could plug the dendritic recording gap in the next few years (*7*–*9*). Methods are also needed that permit selective activation of many synaptic sites, not just one or two, under flexible experimental control. Here again, technological advances, such as multisite laser uncaging of glutamate and other neurotransmitters, will free experimentalists to test hypotheses they would like to test, rather than those they are able to test. The elegant work of Williams and Stuart has moved us one step closer to that exciting day when our neurons finally lay bare the secrets of their internal lives.

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PERSPECTIVES: RADICAL CHEMISTRY

From Reactive Intermediates to Stable Compounds

Curt Wentrup

More than 100 years ago, Gomberg prepared the first stable free radical, triphenylmethyl, **1** (see the figure) (*1*, *2*). Carbon-based free radicals are trivalent compounds with one unpaired (nonbonding or "free") electron that usually renders them highly reactive and short-lived. Triphenylmethyl is stable because the free electron is delocalized and the radical center is shielded from reaction by the three phenyl groups, which are arranged in a propellerlike fashion.

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Since this pioneering work, numerous free radicals, both fleeting intermediates and stable compounds, have been prepared (*3*). However, when it comes to di- or higher radicals, which contain more than one nonbonding electron, stability decreases drastically. The most stable localized singlet (*4*) diradical known to date, **2**, has a lifetime of microseconds at room temperature (*5*). On page 1880 of this issue, Scheschkewitz *et al.* (*6*) report the synthesis of a diradical, **3**, that is stable indefinitely at room temperature. The work may open the door to new types of molecular magnetism and conductivity.

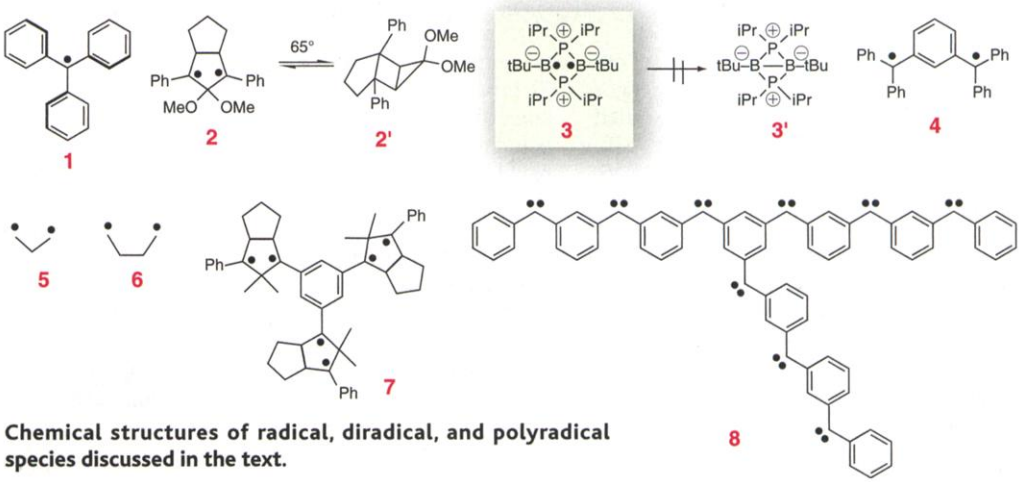
There is much current interest in generating molecules containing many nonbonding electrons. Free electrons in half-filled and high-lying nonbonding molecular orbitals could form a conduction band similar to that in metals (*7*) and may even lead to new superconducting materials. Furthermore, such molecules may show ferromagnetic or antiferromagnetic properties depending on spin and topology (*8*).

The first stable carbon-based diradical, Schlenk's hydrocarbon **4**, was prepared in 1915. It is stabilized by delocalization of the two free electrons over the aromatic rings, just as in **1** (*9*) and has a triplet ground state (*4*). Simple diradicals such as trimethylene **5** and tetramethylene **6** are involved in the thermal chemistry of hydrocarbons (*10*). Their singlet states are extremely short-lived intermediates that have only recently been observed directly by femtosecond spectroscopy (*11*, *12*). Triplet states of 1,3-diradicals have been observed by electron spin resonance (ESR) spectroscopy, but only in matrices at very low temperatures. Thus, four- and five-membered cyclic triplet diradicals have been observed below 20 K (*13*, *14*). Di-, tri-, and hexaradicals of the type **7** were remarkably long-lived at 77 K: Their ESR spectra were observable for months (*15*).

Diradical lifetimes can be influenced by substituents. The dimethoxy-substituted diradical **2** has a singlet ground state and is observable in solution at room temperature by ultraviolet spectroscopy. However, the room temperature lifetime of **2** is only 3.73 μs in chloroform (*5*). In a common reaction of hydrocarbon diradicals, the two radical electrons in **2** recombine to form a C–C single bond, resulting in the formation of **2′**. In contrast, Scheschkewitz *et al.*'s diradical **3** does not show any tendency to form an analogous bicyclic compound **3′** containing a B–B bond. Such a compound would be nonplanar. The x-ray structure of **3** clearly shows a planar four-membered ring with a B–B distance some 30% longer than the longest known B–B bond.

Magnetism requires the coupling of many electrons. High-spin molecules linked via appropriate "couplers," such as **7**, may have interesting magnetic properties. However, to be practical, these materials should be stable at room temperature.

Much valuable information on the magnetic properties of high-spin molecules has been gained from studying polycarbenes such as the nonacarbene **8**, which has 18 unpaired spins (*16*, *17*). A carbene can be regarded as a diradical where the two radical electrons are centered on the same carbon atom (*18*). However, polycarbenes are usually only stable at temperatures near 0 K.



Chemical structures of radical, diradical, and polyradical species discussed in the text.

The author is at the Department of Chemistry, School of Molecular and Microbial Sciences, The University of Queensland, Brisbane, Queensland 4072, Australia. E-mail: wentrup@chemistry.uq.edu.au

Recent research on long-chain complexes between polyradicals or carbenes and paramagnetic transition metal ions has led to superhigh-spin molecules with antiferromagnetic (Mn^{2+}) or ferromagnetic (Cu^{2+}) behavior at cryogenic temperatures (*19*). In these complexes, the organic moieties are carriers of the free spins as well as ligands of the paramagnetic metal ions.

The availability of stable diradicals at room temperature (*6*) will lead to attempts to generate stable polyradicals with ferromagnetic or antiferromagnetic properties. Work in other laboratories suggests that it may be possible to exploit substituent effects to induce singlet or triplet ground states of localized diradicals (*5*, *15*). It may be possible to link such localized diradicals in polymer or dendrimer chains. The scientific community will await further reports on the chemical and physical behavior of the new diradicals with keen interest.

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PERSPECTIVES: TRANSCRIPTION

Unlocking the Gates to Gene Expression

Christopher J. Fry and Craig L. Peterson

How activators regulate gene transcription has been hotly debated for more than a decade (*1*). Initial studies suggested that activator proteins bound to the promoter of the target gene might activate transcription by making contact with one or two key proteins within the core transcription machinery. However, it is now clear that activators must orchestrate the recruitment of numerous proteins including chromatin-remodeling enzymes before gene transcription can proceed. How is the recruitment of chromatin-remodeling enzymes coordinated with assembly of the core transcription machinery, and which transcription steps are regulated by these enzymes? Findings reported by Soutoglou and Talianidis (*2*) on page 1901 of this issue, together with other work, reveal that chromatin-remodeling enzymes can regulate nearly every step of the pathway leading to gene transcription.

In eukaryotes, genomic DNA is organized into chromatin. The basic subunit of chromatin, the nucleosome, is composed of ~147 base pairs of DNA wrapped around a complex of eight histone proteins. The most simple form of chromatin contains genomic DNA packaged into nucleosomes to form long strands that resemble beads on a string. The organization of chromatin poses a barrier to transcription because it prevents the transcription machinery from interacting directly with promoter DNA sequences. Given that chromatin in vivo is further folded into compact fibers (30 to 400 nm thick), how can the transcription machinery possibly access the genes hidden within the nucleosomal milieu? The solution lies in chromatin-remodeling enzymes that alter the folding, fluidity, and basic structure of chromatin. There are two classes of chromatin-remodeling enzymes: those that covalently modify nucleosomal histone proteins through acetylation, phosphorylation, or methylation, and those that alter chromatin structure through hydrolysis of the energy-rich molecule adenosine triphosphate (ATP) (*3*). Certain histone-modifying enzymes, such as the histone acetyltransferases (HATs) Gcn5p and P/CAF, and some ATP-dependent remodeling enzymes, such as SWI/SNF, directly interact with gene-specific activators to ensure that chromatin remodeling is targeted to the correct gene, in the proper cell, and at the right time.

In the early days of transcription research when chromatin was largely ignored, an activator was presumed to enhance transcription by promoting recruitment of proteins to the gene promoter and directing their assembly into a preinitiation complex (PIC), composed of RNA polymerase II and other general transcription factors. A more modern view is that activators must first recruit chromatin-remodeling enzymes in order to create a chromatin environment permissive for PIC assembly. This view, still too simplistic, may be valid only for in vitro systems, artificial reporter genes, and a small subset of endogenous genes. As illustrated in the following examples, it is now clear that other factors, such as the chromatin structure of the gene promoter and the phase of the cell cycle, also govern how chromatin-remodeling enzymes collaborate with each other to control steps before, during, or after PIC assembly.

Although the yeast *HO* gene is transcribed during G_1 phase of the cell cycle, the Swi5p activator recruits the SWI/SNF chromatin-remodeling complex to the *HO* upstream regulatory region during late mitosis of the previous cell cycle (*4*). Surprisingly, SWI/SNF activity is absolutely required for recruitment of the HAT complex Gcn5p, which also occurs during the previous mitosis (*4*, *5*). SWI/SNF action and Gcn5p-dependent histone acetylation facilitate the binding of a second gene-specific activator, SBF, to chromatin. Finally, RNA polymerase II and other general transcription factors are recruited, resulting in completion of PIC assembly and the initiation of *HO* gene transcription (see the figure, A). Thus, at the *HO* promoter, SWI/SNF action controls HAT recruitment, and subsequent chromatin remodeling governs the binding of an activator, a very early step in transcriptional activation. Interestingly, the interdependence of SWI/SNF and the Gcn5p HAT may be a general property of genes expressed at the end of mitosis (*6*). Condensation of the chromosomes during mitosis may confer an obligatory functional relationship on these two enzymes.

Activation of the human interferon-β (IFN-β) gene promoter involves a very different order of events (*7*). In this case, viral infection of human cells generates a signal that induces the binding of a group of activators to a nucleosome-free region of DNA upstream of the *IFN-β* gene. This DNA-activator complex, the enhanceosome, first promotes the rapid recruitment of the Gcn5p HAT, which acetylates nucleosomes encompassing the TATA box in

The authors are in the Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA 01605, USA. E-mail: craig.peterson@umassmed.edu