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"Frozen" Transition States: Pentavalent Carbon *et al.*

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Summary. Organic ligands have been designed for the stabilization of specific geometries of compounds of nonmetallic elements. These ligands have made possible the isolation, or direct observation, of large numbers of trigonal bipyramidal organo-nonmetallic species. Many of these species are analogs of transition states for nucleophilic displacement reactions and have been stabilized by the ligands to such a degree that they have become ground-state energy minima. Ideas derived from research on these species have been applied to carbon species to generate a molecule that is an analog of the transition state for the associative nucleophilic displacement reaction. The molecule is a pentavalent carbon species that has been observed by nuclear magnetic resonance spectroscopy.

The term "organo-nonmetallic chemistry," which I use in this article, has the intended effect of evoking echoes of the familiar term "organometallic chemistry." The latter term was coined in 1848 by the English chemist Edward Frankland (*1*) to describe the chemistry of compounds that have bonds joining carbon atoms of organic groups to a metal atom. Over the past three or four decades, chemists have greatly increased our understanding of the relation between the structure of the organic groups (the ligands) attached to the metals and changes in the reactivity patterns characteristic of the metal. This knowledge has made it possible to prepare organometallic species that are useful catalysts or reagents in various types of synthetic applications that are both scientifically interesting and useful to society. As a result, organometallic chemistry has become an important focus for research effort by inorganic and organic chemists.

It is now clear that organo-nonmetallic (*2*) species, in which carbon is bonded to nonmetallic elements rather than to metals, are as interesting and potentially as important as the organometallic ones. The systematic development of a system of ligands specifically designed to produce a desired pattern of reactivity about the central nonmetal in such species may lead to new chemical reactions as useful as the reactions that engendered the current interest in organometallic chemistry.

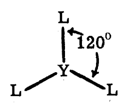
Research communities are now working in many areas of organo-nonmetallic chemistry. Organophosphorus, organosulfur, organosilicon, and organofluorine, for example, describe fields for which regularly scheduled international symposiums provide settings for the discussion of the organo-nonmetallic chemistry of the named element. In this article, I emphasize the point that much can be gained by broadening the focus of attention from a single central nonmetal to its neighbors, on either side, in the periodic table.

Over the past decade, work in our laboratory has been directed toward the synthesis of organo-nonmetallic compounds in which the bonding about the central nonmetal involves, at least formally, expansion of the valence octet of electrons—compounds with the kind of electron-rich multicenter bonding that has been called hypervalent (*3*). We have designed ligands that impart sufficient stability to these higher valent species to make many compounds with new hypervalent functional groups available for study.

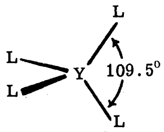
Figure 1 is a partial "periodic table" of hypervalent organo-nonmetallic species, arranged in a systematic manner to highlight the relations between them. Each species is given an *N-X-L* designation (*4*), where *N* is the number of valence-shell electrons formally assignable to the valence shell of the central atom, *X*, either as unshared pairs of electrons or as pairs of electrons in the sigma bonds joining a number, *L*, of ligands to *X*. The formulas enclosed in boxes represent types of compound for which isolable or directly observable examples have been prepared by exploiting the stabilizing effects associated with the system of ligands developed in our research. For those formulas enclosed in dotted lines, the evidence is not yet conclusive that we have really observed such species spectroscopically or have obtained evidence for the species as a very low energy transition state.

Ligand-Induced Stabilization

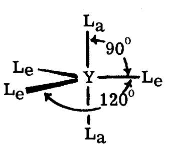
The pictured molecular geometries (Tr, Td, TBP, and Oc) are those most commonly encountered for organo-nonmetallic species. The TBP geometry is



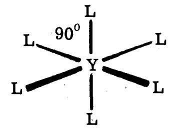
Trigonal
(Tr)



Tetrahedral
(Td)



Trigonal
Bipyramidal
(TBP)



Octahedral
(Oc)

the only one in this group that has two distinguishable types of ligand sites, the

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apical sites (occupied by L_a) and the equatorial sites (occupied by L_e). All ligand sites are identical in the Tr, Td, and Oc geometries. This feature of the TBP geometry provides an added element of interest to compounds with TBP molecular geometry. Much of our research has been directed toward the design of ligands that can provide extraordinary stabilization for such TBP species. Of the ten-electron ($N = 10$) species of Fig. 1, the ones in which all five ligand sites are occupied (the 10-*X*-5 species) can be considered to have TBP geometry. Species in which one, two, or all three of the equatorial ligands are replaced by lone pairs of electrons (10-*X*-4, 10-*X*-3, and 10-*X*-2 species, respectively) have pseudo–trigonal bipyramidal (ψ-TBP) geometry. Although many of the ten-electron species discussed in this article have bond angles somewhat distorted from those of ideal TBP or ψ-TBP geometry, it is useful to discuss them in terms of the idealized geometry.

The 12-electron species of Fig. 1 can, in a parallel manner, be considered to have either Oc or pseudooctahedral (ψ-Oc) molecular geometry, whereas eight-electron species are Td or pseudotetrahedral (ψ-Td).

In a ten-electron TBP species, the formal expansion of the valence octet of the hypervalent (*3*) central atom is in large measure accomplished by putting the extra electron pair into an orbital that puts most of the electron density on the apical ligands. The apical three-center, four-electron bond joining the two apical ligands to the central atom therefore has an accumulation of relatively negative charge on the apical ligands and relatively positive charge on the central atom. Since the TBP geometry has distinguishable apical and equatorial sites, this charge distribution can be stabilized by making L_a very electronegative in order to stabilize the negative charge developed at the apical positions. Not only should the central atom be more electropositive in order to stabilize the relatively more positive charge on the hypervalent atom, but the equatorial ligands, L_e, should be electropositive in order to stabilize the positive charge on the central atom to which they are attached. Since all of the ligand sites in the Oc, Td, or Tr geometries are identical, stabilization cannot be achieved by making one set of ligands more electropositive and the other set more electronegative.

The first reported examples of many of the species represented in Fig. 1 are like XeF_2 in that they have fluorine ligands attached to the central atom. Since fluorine is the most electronegative element, its ability to stabilize the negative charge at the apical positions of a hypervalent ψ-TBP species makes it easy to understand why such species are more easily prepared and isolated when they have apical fluorines. The apical fluorine ligand is, however, not always the most effective ligand for stabilizing a TBP structure. It has a disadvantage as a ligand in that, being monovalent, it has only one point of attachment to the central atom.

Ligands that are bidentate (two-toothed; that is, having two points of attachment to the central atom) are more versatile in that they can be used to build cyclic structures. If the rings are small—five-membered or smaller—little strain is introduced into the ring if the apical-equatorial angle of the TBP nonmetal (ideally 90°) is included in the ring. In contrast, the spanning of two ligand sites in a Td species (ideal bond angle, 109.5°) or two equatorial sites in a TBP species (120°) produces a very strained ring. One manifestation of the effect of a five-membered ring is therefore seen in the acceleration of reactions in which eight-electron Td or ψ-Td species, with the central atom included in a five-membered ring, are converted, by reaction with nucleophiles, into TBP or ψ-TBP species. The relief of strain that accompanies the conversion of a Td species into the less strained TBP species can provide significant driving force for such a reaction.

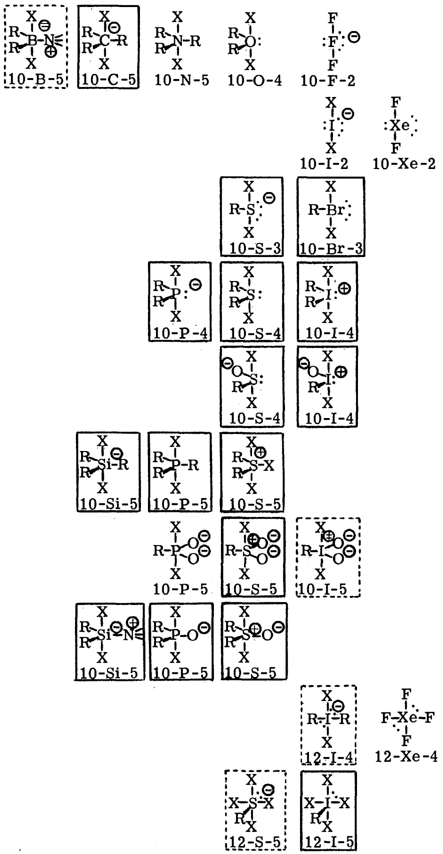
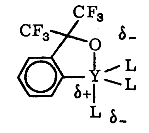


Fig. 1. A partial "periodic table" of hypervalent nonmetallic species, with *N-X-L* designations (see text).

The increased angle strain in species with a five-membered ring linking two equatorial sites of a TBP (ideal bond angle, 120°) also explains why such species are less stable than their isomers with an apical-equatorial ring.

The formation, or preservation, of the two bonds joining a bidentate ligand to the central atom can also be favored by other geometric features of the ligand. If the ligand is designed in such a way that once a single bond is joined to the central atom the second point of attachment of the ligand is closely juxtaposed to the central atom, the formation of the second bond is strongly favored.



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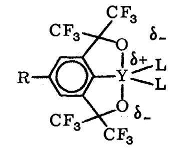
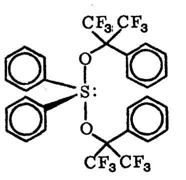


2 R = CH_3 or $(CH_3)_3C$

These factors are important in two ligands that are effective in providing unexpectedly stable examples of the species of Fig. 1. The bidentate ligand of **1** and the tridentate ligand of **2** provide stabilization to these ψ-TBP structures by several mechanisms: (i) They provide an apical ligand, the fluoroalkoxy oxygen, of great effective electronegativity strengthened by the inductive effect of the CF_3 groups. (ii) They provide an equatorial carbon ligand whose electropositive character helps to stabilize the positive charge that develops on the central atom of the hypervalent three-center bond. (iii) The five-membered ring linking an apical and an equatorial site of a TBP molecule is of the proper size to accommodate—essentially unstrained—bond angles such as the approximately 90° angle between the apical and the equatorial bonds in the ring. (iv) Steric constraints built into the ligand (the rigid benzene ring and the space-filling properties of the two CF_3 groups) favor conformations of the host ligand in which it is appropriately shaped to accept the guest nonmetal.

The validity of this analysis was established in a series of studies from our laboratory (*5*). The earliest demonstration of the effectiveness of the bidentate ligand of **1** in providing stability to a ψ-TBP molecule was provided in the contrast between the great reactivity of sulfurane **3** and the chemical inertness of the closely analogous spirobicyclic sulfurane **4**, similar in all respects except the geometry imposed by the five-membered rings.



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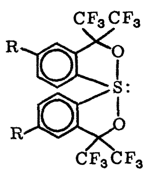
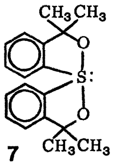


4 R = H or $C(CH_3)_3$

Sulfurane **3** is extremely reactive toward water, yielding the hydrolysis products alcohol **5** and sulfoxide **6** very rapidly even at low temperatures. In contrast, **4** does not react with aqueous acid even when boiled for long times.

$$\mathbf{3} \xrightarrow{H_2O} \begin{array}{ll} C_6H_5C(CF_3)_2OH & \mathbf{(5)} \\ + & \\ (C_6H_5)_2S{=}O & \mathbf{(6)} \end{array}$$

Various kinetic (*6*) and calorimetric (*7*) studies have shown that the five-membered ring effect provides 10 to 12 kilocalories of stabilization per mole for ψ-TBP sulfuranes such as **4** relative to their acyclic analogs (**3**).



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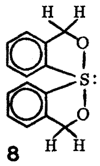

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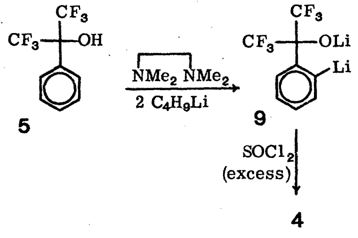
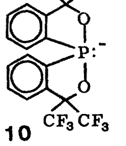
The analog of **4** in which the electron-withdrawing CF_3 groups have been replaced by methyl groups, sulfurane **7**, reacts slowly with water in aqueous methanol, in contrast to the complete inertness of **4** toward water under these conditions (*8*). The greater reactivity of **7** reflects the lessened ability of its bidentate ligands to stablize ψ-TBP sulfur species because of the decreased effective electronegativity of the apical oxygen in the absence of the CF_3 groups. Compound **8** with the much less bulky hydrogens replacing the methyl groups of **7** is even more rapidly hydrolyzed (*8*), in accord with point (iv) above.

The introduction of the bidentate ligand of **1** into an organo-nonmetallic species was made easy by the discovery (*9*) that the dilithiated species **9** is easily prepared from the readily accessible alcohol, **5**. Reaction of **9** with thionyl chloride gives **4** directly, in high yield.



In closely parallel reactions, **9** reacts with PCl_3 (*10*) to give phosphoranide anion **10** and is used (*11*) in a sequence of several steps to provide periodonium ion **11**. The fact that these represent the first reported examples of isolable organo-nonmetallic 10-P-4 and 10-I-4 species validates the hypothesis that led us to attempt their synthesis, namely, that the ligand which made **4** such a stable sulfurane would also stabilize isovalent, isostructural species related to **4** by replacing the sulfur of the latter by an atom immediately to its left in the periodic table (the phosphorus of **10**) or from the column of the periodic table to its right (the iodine of **11**).



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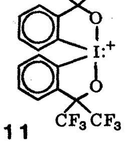

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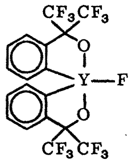
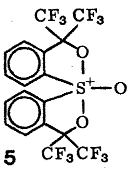
This triad of 10-*X*-4 species [anionic 10-P-4 (**10**), electrically neutral 10-S-4 (**4**), and cationic 10-I-4 (**11**)] has its counterparts in other parts of the periodic table of Fig. 1. The 10-*X*-5 species, for example, form a similar triad: **12**, an anionic 10-Si-5 siliconate (*12*); **13**, an electrically neutral 10-P-5 phosphorane; and **14**, a cationic 10-S-5 persulfonium (*13*).



12 ($Y = Si^-$)
13 ($Y = P$)
14 ($Y = S^+$)

In several of the species of Fig. 1 the charge on the central atom is intramolecularly neutralized by an equal and opposite charge on a ligand. This can make the species very stable. The oxidation of sulfurane **4**, for example, gives a neutral 10-S-5 species, sulfurane oxide **15** (*14*), in which the charge of a negatively charged equatorial oxygen neutralizes the postive charge on the central sulfur.

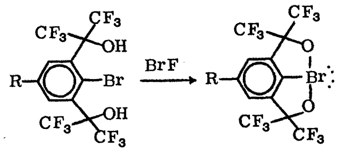


15

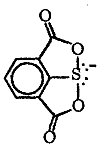
This compound is similar to **4** in its unreactivity. The internal charge cancellation is particularly effective in a case such as this one in which the placement of the charged ligand is proper for stabilizing the charge distribution of the hypervalent bond. In this case an electron-donating, negatively charged oxygen occupies an equatorial position, the proper site for stabilizing the compound.

The tridentate ligand of **2** turns out to be even more effective than the bidentate ligand of **1** at stabilizing ψ-TBP species.

The first isolated organo-nonmetallic 10-Br-3 species, brominane **17**, was prepared from bromodiol **16** by oxidation with the inorganic 10-Br-3 species BrF_3 (*15*). The contrast between **17** and the few known inorganic 10-Br-3 species (BrF_3 and its analogs) is great. The latter react, sometimes explosively, with organic solvents and are very reactive toward water, whereas **17** is stable above its melting point, 153°C, even though it has an easily oxidizable organic group as a part of its own structure, and is unreactive toward water. The "taming" of the bromine(III) species by this tridentate ligand is remarkable.



16 R = CH_3 or $C(CH_3)_3$ **17**



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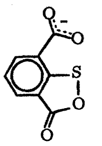
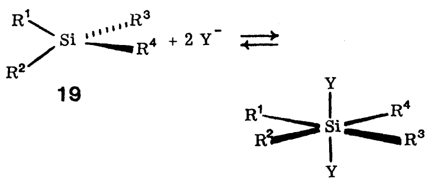


18a

A different tridentate ligand was used (*16*) to prepare the first 10-S-3 species, sulfuranide anion **18**. Evidence for the symmetrical structure of **18** is clearly demonstrated by solution infrared spectra in that only one carbonyl stretching frequency is observed (*16*). The unsymmetrical structure **18a** would be expected to show two carbonyl stretching frequencies.

Ligand Mediated Discrimination Between Td, TBP, and Oc Geometries

Silanes are particularly prone to react with nucleophiles. Both 10-Si-5 and 12-Si-6 species are well known, despite the fact that the latter places two formal negative charges on silicon. Corriu *et al.* (*17*) showed that in several cases optically active silanes (**19**) undergo nucleophile-promoted racemization by a process proceeding with a rate second-order in nucleophile (Y^-). The two molecules of nucleophile, which must be in the transition state for this reaction, are most probably involved in a 12-Si-6 dianionic Oc species such as **20**, which is achiral, hence a transition state or high energy intermediate along the pathway for racemization.



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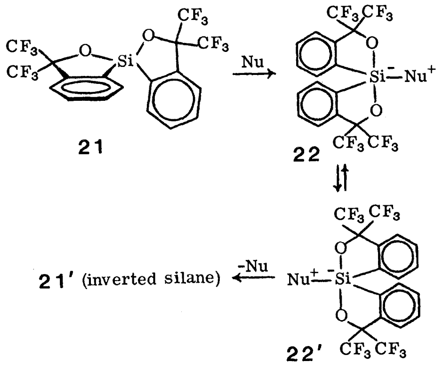
In silane **21**, the silicon has two ligands that are especially effective in stabilizing the TBP geometry. It is interesting to consider the processes by which silane **21** racemizes. As expected, **21** is found to be an exceptionally strong Lewis acid (*18*). The ^{19}F nuclear magnetic resonance (NMR) of **21**, when observed in hydrocarbon solvent, shows peaks for the two nonequivalent CF$_3$ groups expected for the pictured Td geometry. The addition of small amounts of very weak Lewis bases (nucleophiles) such as ether results in a coalescing of the ^{19}F peaks into a singlet, in a manner consistent with a nucleophile-assisted inversion of geometry at silicon, reminiscent of the racemization reactions of Corriu *et al.* (*17*). Silane **21** is, however, more than usually reactive toward weak nucleophiles. One-to-one complexes with substituted benzaldehydes—in equilibrium with free silane at low temperatures—are directly observable by NMR spectroscopy. The inversion at silicon seen at higher temperatures is catalyzed by these same nucleophiles, but for this silane the rate is first-order in nucleophile (Nu), not second-order as in Corriu's silanes. We propose that this first-order process proceeds through the intermediate TBP 10-Si-5 species **22**.

The inversion (**22** ⇄ **22′**) is an example of the commonly encountered structural flexibility of TBP derivatives of nonmetals. The intramolecular permutation of ligands among TBP sites can occur by a nondissociative process called pseudorotation (*5*), which has long been known for 10-P-5 species and was more recently established for 10-S-4 species (*5*).



21

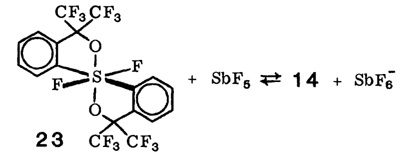
22

21′

22′

A single pseudorotation step involves pairwise exchange to two apical and two equatorial ligands by deforming the TBP, through a square pyramidal transition state, into another TBP ligand site occupancy pattern. A series of five such steps can convert a chiral TBP species into its enantiomer (for example, **22** → **22′**). Such a process could explain the first-order kinetic dependence on weak nucleophile concentration that we observe for the inversion of **21**. With stronger nucleophiles a stable 10-Si-5 species, which gives much slower inversion, is formed. Even at high concentrations of strongly nucleophilic species, no evidence is obtained for inversion at the silicon of **21** via 12-Si-6 Oc species such as **20**. The bidentate ligand of this silane therefore stabilizes the TBP structure (**22**) relative to the Oc and Td species since it can place carbon in the equatorial sites and very electronegative oxygens in the apical sites. Since all ligand sites are equivalent for Td and Oc geometries, these species are not as strongly stabilized by this ligand. We therefore find it easy to introduce the first nucleophile to convert Td to TBP geometry, but difficult to introduce a second nucleophile to convert the TBP to Oc geometry.

This kind of selective stabilization of the TBP geometry must also contribute to the ease with which Oc 12-S-6 persulfurane **23** is ionized to give the 10-S-5 persulfonium ion, **14c**. This TBP structure, the first observable 10-S-5 cation to be reported, owes its stability to the same bidentate ligand used to prepare other novel TBP structures.



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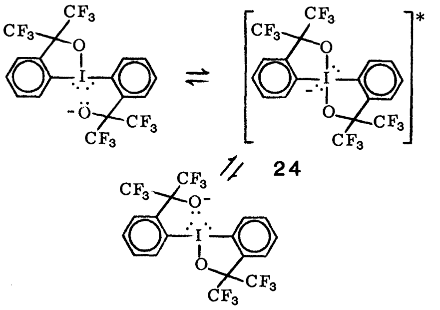
Frozen Transition States

The choice between symmetrical and unsymmetrical structures is not always as straightforward as in the 10-S-3 species **18**. In this case, infrared spectroscopy provided a structural probe effective on a time scale comparable to that of the vibrational deformations of the molecule (10^{13} to 10^{14} sec^{-1}), allowing the unambiguous ruling out of structure **18a**.

Many of the species of Fig. 1 were shown to be symmetrical in the solid state by x-ray crystallographic structure determinations. For others the evidence is based on solution-phase NMR spectroscopic evidence. the NMR time scale is, however, much longer (10 to 1000 sec^{-1}), leaving some ambiguity as to whether a spectrum consistent with a symmetrical structure analogous to **18** really reflects the symmetry of a species in which the ψ-TBP geometry is an energy minimum. The alternative interpretation, in which the ψ-TBP geometry is an energy maximum or a transition state for the rapid interconversion of the two identical unsymmetrical structures analogous to **18a**, is difficult to rule out if the activation energy for the interconversion is low. At the lowest temperature accessible for NMR spectroscopy, the interconversion can still be fast enough to give an averaged spectrum compatible with the symmetrical structure. Whether the ψ-TBP geometry is an energy maximum or an energy minimum depends, in many cases, on the structure of the ligand set around the central atom. Indeed, most of the ψ-TBP species of Fig. 1 have at one time or another been postulated to be transition states, or undetected high energy intermediates, in nucleophilic substitution reactions. Our goal has been to make these ψ-TBP structures global energy minima by the introduction of appropriate ligands.

In the case of 12-I-4 anion **24**, an analog of XeF$_4$, the room-temperature ^{19}F NMR spectrum showed a single sharp singlet consistent with the pictured symmetrical structure. At lower temperature, however, two ^{19}F singlets were seen, showing that **24** is a transition state that is higher in energy by 12 kilocalories per mole than the unsymmetrical ground-state structures (*11*).

In the case of nucleophilic displacements at sulfur, we have been successful in preparing examples for which the symmetrical ψ-TBP structures represent ground-state energy minima for the several types of sulfur-centered functional groups listed below. The first three examples of these "frozen" transition states for nucleophilic attack on sulfenyl (8-S-2) sulfur, on sulfonium (cationic 8-S-3) sulfur, or on oxysulfonium (cationic



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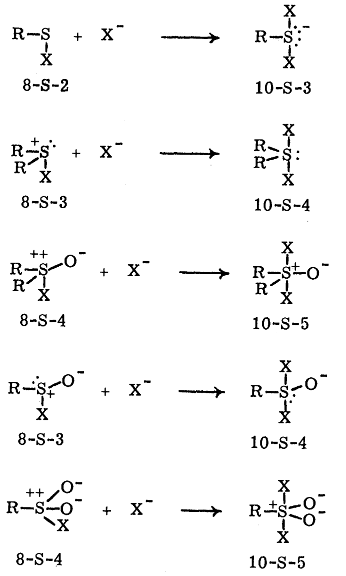
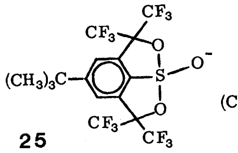
8-S-4) sulfur have already been discussed. We have only recently been successful in preparing sulfuranoxide **25** and sulfurane dioxide **26**, transition state analogs for nucleophilic attack on sulfinyl (8-S-3) sulfur or sulfonyl (8-S-4) sulfur, respectively (*19*). The TBP structure of both **25** and **26** has been confirmed by x-ray crystallography. The cover shows the x-ray structure of **26**.



The biologically important hydrolysis of phosphate esters (*20*) proceeds through a transition state, or high energy intermediate, for which the symmetrical phosphoranoxide anion **27** is an isolable model (*21*). Its structure has also been confirmed by x-ray crystallography.



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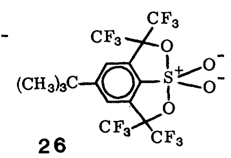

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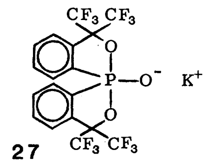

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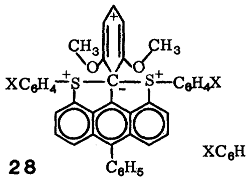
Pentavalent Carbon and Other Hypervalent First-Row Species

The transition state for the S_N2 (associative) nucleophilic displacement at carbon is one of the most familiar and most important transition states in organic chemistry. This TBP 10-C-5 species, midpoint geometry in the Walden inversion mechanism, differs from the other Fig. 1 species we have discussed in that carbon is a first-row element. The other hypervalent nonmetals we discussed are lower in the periodic table and therefore have empty atomic orbitals (for example, *d* orbitals) which are nearer in energy to the filled orbitals than is the case for first-row elements.

Chemists have traditionally considered the stability of species such as the well-known 10-P-5 phosphoranes to result from the availability of phosphorus *d* orbitals to accommodate the extra pair of electrons. In recent years, both theoretical calculations and experimental results with nuclear quadrupole resonance (NQR) or Mössbauer spectroscopy have agreed that the role of *d* orbitals in determining the energy of such species is not as crucial as many had thought (*5*, *22*). The approximate bonding scheme that Musher (*3*) advanced to describe hypervalent species uses only *p* orbitals and, as mentioned earlier, places the extra pair of electrons in an orbital that is primarily a ligand orbital rather than a central atom orbital. Pimentel's [see (*5*)] earlier molecular orbital description of the symmetrical hydrogen bond in the bifluoride anion, $(F\text{-}H\text{-}F)^-$ is similar to Musher's hypervalent bonding scheme. Indeed the bifluoride anion, a 4-H-2 species, can be considered a compound of hypervalent hydrogen.

Experiment and theory agree that very simple 10-C-5 species, such as the TBP midpoint geometry in the reaction between fluoride ion and methyl fluoride, are energy maxima rather than energy minima (*23*). We considered it possible, using the principles developed earlier in this article, that the introduction of suitable ligands about the central carbon, could lower the energy of the TBP geometry enough to make it the ground-state energy minimum rather than a maximum. After several preliminary attempts (*22*) we succeeded in preparing a compound to which we assign structure **28** (*23*).



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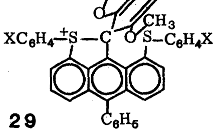

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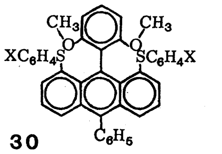
Although **28** is overall a dication, the bonding about the central carbon is 10-C-5. Various types of evidence support our claim that it is in fact a TBP ten-electron species rather than the Td 8-C-4 species, **29**.

The low-temperature ^1H NMR and the ^{19}F NMR spectra of **28** ($X = F$) that we reported earlier (*23*) are consistent with symmetrical structure **28** rather than unsymmetrical structure **29** down to −100°C in liquid sulfur dioxide.

Evidence from ^{13}C NMR and from the two-electron electrochemical oxidation of **30** (*24*) also supports the symmetrical structure of **28**.



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The ligands about the TBP carbon of **28** share many features with the tridentate ligand of **2**: (i) Electronegative positively charged 8-S-3 sulfur ligands occupy apical positions and three sigma donor carbons occupy the equatorial sites. (ii) The apical sites are linked to an equatorial site in five-membered rings. (iii) The rigid structure of the anthracene rings holds the interacting atoms in the 10-C-5 structure in the proper position for TBP formation—**29** is more strained.

Additional factors favoring the TBP structure devolve from the bidentate ligand linking two equatorial sites in a six-membered ring: (i) The two sigma donor carbons are pi acceptors that interact with the electron-rich apical hypervalent three-center bond to stabilize the TBP structure, and (ii) the geometry of the six-membered ring, made up of six benzene-like sp^2-hybridized carbon atoms, is strain free.

The evidence is strong that there are indeed five ligands bonded to the central carbon in **28**. If the conventional method of drawing structures is used, with each electron pair bond represented by a solid single line, the central carbon must be written as bearing a formal negative charge. In fact, this negative charge is delocalized into the pi-acceptor six-membered ring and to the apical ligands in much the same way that charge densities are altered from their formal values in all hypervalent species. As mentioned earlier, much of the electron density of the "extra" electron pair in a TBP ten-electron system is found on the apical ligands, making the central atom relatively more positively charged and the apical ligands more negative. The pictured negative charge on the carbon of **28** would likely be largely dissipated by this mechanism. Further work is under way to make simpler analogs of **28** that will be susceptible to x-ray crystallographic structure determination.

Evidence for the 10-F-2 trifluoride anion, a compound of hypervalent fluorine, has been reported (*25*). The species was observed at low temperature in a xenon matrix by Raman and infrared spectroscopy. Evidence for several lithiated first-row elements such as OLi_4, a 10-O-4 species, has also been discussed (*26*).

Conclusion

By the proper design of ligands, organo-nonmetallic species with unusual valence states or coordination numbers (or both) can be prepared and isolated. This article has illustrated this point by concentrating on a single class of compounds, the 10-*X*-*L* species with TBP geometry. Similar approaches are applicable to other classes of organo-nonmetallic species. The ability to fine tune the reactivity of such species offers considerable promise for the development of new reagents and catalysts of potential utility in synthetic chemistry. This promise has already been realized in applications of sulfurane reagents as dehydrating agents (*5*) and of organohalogen reagents as oxidizing agents (*15, 27*). Application of recent findings in hypervalent organosilicon chemistry (*18, 28*) in carbon-carbon bond-forming reactions currently appears promising.

References and Notes

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29. This research was supported in part by grants from the National Science Foundation (CHE 81-13142) and the National Cancer Institute (CA 13936). I thank P. von R. Schleyer for a copy of his manuscript.

Ribonucleotide Reductase—A Radical Enzyme

Peter Reichard and Anders Ehrenberg

It was with some trepidation that we suggested in 1972 that one of the two subunits (protein B2) of the enzyme ribonucleotide reductase might contain a stable free organic radical as part of its structure (*1*). The protein had spent about 2 weeks in aqueous media during our efforts to prepare a homogeneous enzyme. We knew that protein B2 contained stoichiometric amounts of iron (*2*) and decided to apply electron paramagnetic resonance (EPR) spectroscopy to characterize the state of the iron. Much to our surprise, we found a signal consisting of an asymmetric doublet centered at $g = 2.0047$ (curve A, Fig. 1) that had all the hallmarks of an organic free radical and thus apparently did not derive from the iron of protein B2.

The occurrence of free radicals in biological systems, in particular in connection with redox processes, was of course firmly established ever since the pioneering work of Michaelis (*3*). Characteristic features of such radicals are, however, high chemical reactivity as well as instability in aqueous solution and short life time. The existence of a stable organic radical in an enzyme, as an intrinsic part of its protein structure, had never been observed before.

Nature of the Organic Radical

Ribonucleotide reductases from several sources (*4–6*) show EPR spectra strikingly similar to that of protein B2 of *Escherichia coli* (Fig. 1, curves B to D). The characteristic doublet structure suggested hyperfine interaction with a proton and the nature of the free radical was therefore investigated by EPR experiments involving deuterated protein B2 (*7, 8*). With a genetically manipulated strain of *E. coli* (*9*) containing about 3 percent of its total protein as ribonucleotide reductase, the characteristic EPR signal of protein B2 could be measured directly on thick cell suspensions. When the bacteria were grown on a synthetic medium in D_2O a complete collapse of the doublet structure occurred. This phenomenon could be traced to the incorporation of deuterated tyrosine into B2. Bacteria grown on synthetic media in H_2O to which specifically deuterated tyrosines were added gave spectra with a similar collapse of the doublet structure or loss of the superhyperfine structure, depending on the site of the substitutions (Fig. 2). From such experiments we could assign the radical to a tyrosine residue of the protein with its spin density delocalized over the aromatic ring. Similar isotope substitution experiments with ribonucleotide reductases from other sources identified tyrosyl radicals also in these enzymes (*4, 5*).

In Fig. 1 it is seen that spectra A and B have great similarities. The other two spectra, C and D, are also similar to each other, but clearly different from the first two. These spectral differences may be explained by a twist of approximately 10°

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