to those for liquids. Since high-resolution solid-state spectra are now routinely obtained, even in the difficult case of quadrupolar nuclei, many of the versatile techniques pioneered in liquids can now be applied to solids. This should pave the way for many new applications of NMR to problems in chemistry and materials science.

While the DAS and DOR techniques have found early applications to inorganic materials such as minerals and zeolites, the techniques are equally applicable to organic and biological molecules in the solid state, and perhaps to some disordered systems such as glasses. Just as methods like cross-polarization were combined with MAS, the same may be done with DAS and DOR to increase the sensitivity obtained from nuclei such as ^{17}O. It is also important to note that while we have emphasized narrowing of the central transition of half-odd-integer quadrupolar nuclei, broadening due to other second-order effects such as dipole–quadrupole interactions should be eliminated by DAS and DOR as well. In particular, we see some further possibilities for the dynamical consequences of icosahedral symmetry in a number of recent NMR experiments and applications.[28,29]

We thank M. Munowitz for helpful comments. E.W.W. was supported by an NIH postdoctoral fellowship, and K.T.M. was supported by an NSF graduate fellowship. This work was supported by the Director, Office of Energy Research, Office of Basic Energy Sciences, Materials Sciences Division of the U.S. Department of Energy, under Contract No. DE-AC03-76SF00098.

(28) Tycko, R. *J. Chem. Phys.* **1990**, *92*, 5776–5793.
(29) Llor, A.; Olejniczak, Z.; Sachleban, J. R.; Pines, A. *Phys. Rev. Lett.* **1991**, *67*, 1989–1992.

Determinations of Transition-State Geometries by the Endocyclic Restriction Test: Mechanisms of Substitution at Nonstereogenic Atoms

PETER BEAK

Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

Received August 26, 1991

The description of a transition state on the basis of experimental evidence is the central, if sometimes elusive, goal of most studies of reaction mechanisms. The value of transition-state structures for understanding reactions is well established, and the concept is widely used.[1] Selection of a preferred transition state from reasonable alternatives is the classic approach to determining the mechanism of a reaction. Recognition of analogous structural features of transition structures for nominally different reactions provides a fundamental basis for establishing general reaction pathways. As the structures at the highest energy point over which a reactant must pass to become a product, transition states provide probes of the limits of chemical bonding and can serve as a test of theories. In synthetic chemistry, hypotheses about transition structures are useful for using and inventing reactions.

Studies of kinetics and stereochemistry are the most common experimental approaches to determinations of transition-state structures for reactions in solution. Reaction order and rate comparisons provide data which can be used to define the composition and electronic distribution in the transition state. The stereochemical consequences of a reaction provide information from which inferences are drawn about the arrangement of atoms in the transition-state structure. Classically, stereochemical analyses of reactions have been carried out by determinations of the course of a reaction at a stereodefined center. A reaction which has been thoroughly studied by the stereochemical approach is nucleophilic substitution at carbon. Over 50 years ago it was suggested that substitution at the stereogenic carbon of an optically active substrate to give a racemic product involves a planar symmetrical carbocation as an intermediate in an S_N1 reaction, while substitution with inversion at carbon involves a trigonal bipyramidal transition state which has the entering and leaving groups disposed at 180° in an S_N2 process.[2]

The geometries of substitution reactions at nonstereogenic atoms have not been widely investigated experimentally although this information could be of considerable value for understanding the mechanisms of a wide variety of reactions. For most reactions of this formal type in which an arrangement of atoms in a transition state has been suggested, the paradigm has been S_N1 and S_N2 substitutions at carbon. In a recent approach, due to Burgi and Dunitz, trigonal bipyramids have been inferred as transition-state structures for concerted substitutions at nonstereogenic atoms on the basis of correlations of interactions in the solid-state structures.[3]

Peter Beak did his undergraduate work at Harvard University and his graduate work at Iowa State University, where he worked with Ernest Wenkert. He joined the faculty at Illinois in 1961, and his research has focused on synthetic, structural, and mechanistic organic chemistry.

(1) Muller, K. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1. Houk, K. N.; Duh, H.; Wu, Y.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754. Carpenter, B. *J. Am. Chem. Soc.* **1985**, *107*, 5130.
(2) (a) Streitwieser, A., Jr. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1963. (b) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, 1969. (c) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper and Row: New York, 1981; Chapter 4.
(3) Burgi, H. B. *Inorg. Chem.* **1973**, *12*, 2321. Burgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. Burgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153.

0001-4842/92/0125-0215$03.00/0

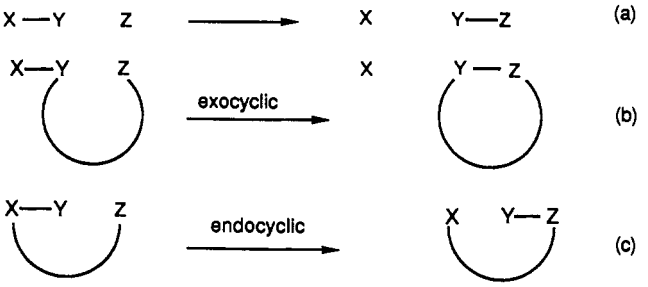


Figure 1.

In this Account we review the background of and discuss our recent work on the use of the endocyclic restriction test to provide experimental evaluations of transition-state geometries for substitutions at nonstereogenic atoms. Although this test has been known since the work of Eschenmoser[4] and Hogg[5] in 1970 and has been applied particularly to reactions at sulfur, it has not been widely used.

The Endocyclic Restriction Test. The test can be illustrated for a general substitution in which an atom or group Y is transferred from bonding to X to bonding to Z as shown for reaction a at the top of Figure 1. The second reaction (b) in Figure 1, in which there is a chain of atoms connecting Y to Z, shows a case in which the transfer is formally an exocyclic process. If Y is transferred in a structure in which the connecting tether is between Z and X as shown for c at the bottom of Figure 1, the reaction is formally endocyclic.

In the unconnected case (a), there is no external restraint imposed on the geometry of any possible transition-state structure for the reaction. In case b the tether may provide some limitation, but there will be a wide range of allowed reaction geometries, and in dilute solution the well-established advantage of intramolecularity would be expected to prevail to give a cyclic product.[6] In the endocyclic reaction of case c, however, the geometry of the possible transition states for intramolecular transfer of Y is restricted to those in which X and Z can remain tethered by the connecting chain for a concerted or associative transfer. This structural requirement is the essential feature of the endocyclic restriction test. If the transition-state structure required for the intramolecular reaction cannot be achieved within the limitation of an endocyclic mode, either no reaction or a different pathway of reaction, e.g., intermolecular transfer, will take place.

Transition-state geometry is fundamentally related to reaction mechanism. The three limiting types of mechanism for the transfer of Y from X to Z are concerted, associative, and dissociative bonding changes. These possibilities are illustrated in Figure 2 for a possible endocyclic reaction and can be discussed in terms of the intramolecular and intermolecular consequences. A concerted intramolecular reaction would be observed if the X---Y---Z bond angle required for the transfer were energetically accessible in an endocyclic transition state illustrated as A in the top of the figure.

(4) Tenud, L.; Farouq, S.; Seible, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2054.
(5) Hogg, D. R.; Vipond, P. W. *J. Chem. Soc. C* **1970**, 2142.
(6) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183. Czarnik, A. W. *Mechanistic Principles of Enzyme Action*; Liebman, J. L., Greenberg, A., Eds.; VCH Publishers: New York, 1988; Vol. 9, Chapter 3. Menger, F. M. *Tetrahedron* **1983**, *39*, 1013. Page, M. I.; Jencks, W. P. *Gazz. Chim. Ital.* **1987**, *117*, 455. Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1.

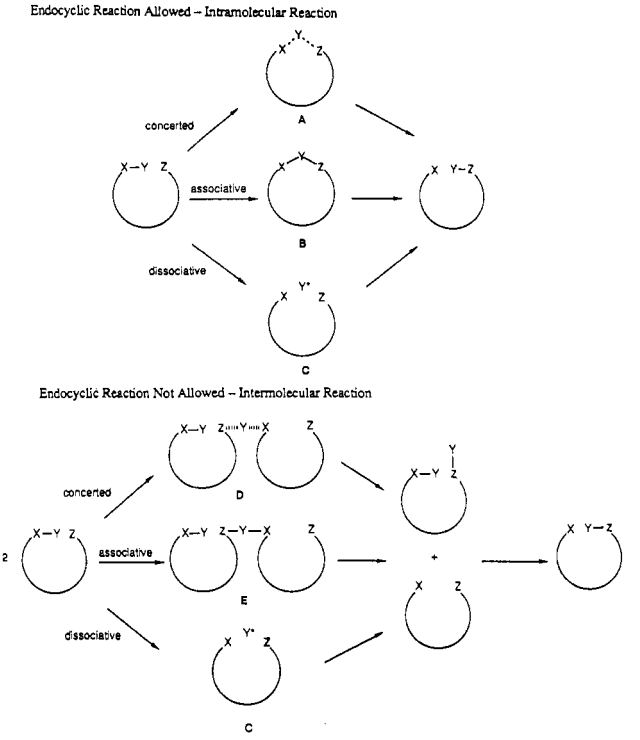
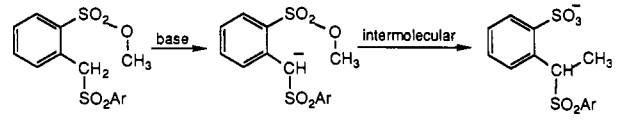


Figure 2.

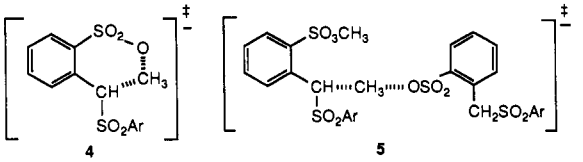
If the geometry required for concerted endocyclic transfer of Y were not attainable, the reaction could proceed by the intermolecular path shown as D in the bottom half of the figure. In the case of an associative pathway, intramolecular reaction would be favored if an intermediate with the endocyclic structure B, which accommodates the X–Y–Z bond angle, were on the reaction pathway. If such a structure were not accessible, an intermolecular reaction shown as E in Figure 2 could ensue. For a dissociative reaction, the species C with the X–Y bond broken could be formed initially, and the distinction between the intramolecular and intermolecular reactions would be determined by the fate of Y in recombination within or dissociation from that species. Rebonding within the solvent cage would be intramolecular while dissociation would be intermolecular.

Early Applications of the Endocyclic Restriction Test to Displacement Reactions. In 1970 the endocyclic restriction test was explicitly used as a probe of reaction geometry in two formal nucleophilic substitutions. In an important and influential paper, Eschenmoser et al. defined the exocyclic and endocyclic modes of nucleophilic substitution and showed by double-labeling experiments that the base-promoted methyl transfer in the conversion of **1** to **2** via **3** was an intermolecular reaction.[4] Because of the known advantage of six-membered rings in other reactions, casual analysis could have given the expectation of an intramolecular reaction. In demonstrating experimentally that the 180° bond angle between the entering and leaving groups characteristic of this S_N2 reaction cannot be achieved in the endocyclic six-membered intramolecular transition state **4**, with the consequence that the bimolecular reaction via **5** occurs, Eschenmoser provided a discussion of transition-state geometry which clearly is applicable to a number of reactions. In order to rule out alternative interpretations for discrimination against **4**, Eschenmoser showed that the conversion of

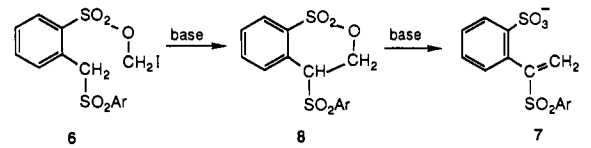
6 to **7** via **8** is intramolecular and the conversion of **9** to **10** is intermolecular. The intramolecular reaction of **6** to **8** can take place by an exocyclic S_N2 transition state while the S_N2 intramolecular conversion of **9** to **10** would be endocyclic and prohibitively strained. The transition structure is depicted as a trigonal bipyramid with the entering and leaving groups in apical positions. This geometry is consistent with the well-established inversion at carbon in the S_N2 reaction, with frontier orbital theory in which the σ^* LUMO of carbon accepts electrons from the nucleophile HOMO at 180° to the carbon–heteroatom bond, and with VSEPR theory.



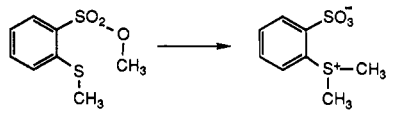
1 3 2



4 5



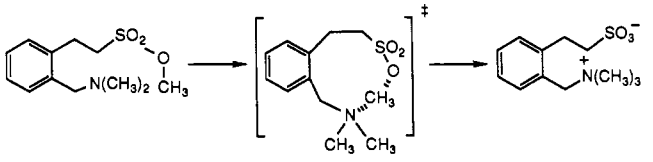
6 8 7



9 10

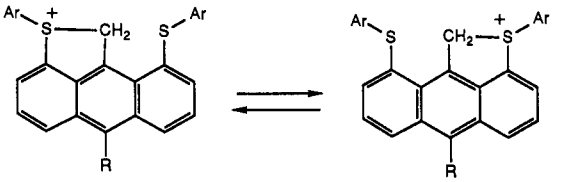
Ar = *p*-$CH_3C_6H_4$

In later work King et al. showed that 16% intramolecular methyl group transfer occurs in the conversion of **11** to **12** at 5×10^{-3} M.[7] A reasonable interpretation is that an S_N2 transition state with approximately 180° bond angles can be achieved in the nine-membered ring **13**. Hence the endocyclic process becomes a detectable, if minor, competitive pathway in this nucleophilic substitution at carbon.

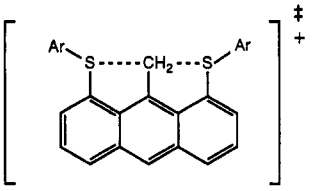


11 13 12

In 1973 Martin and Basalay, in a search for hypervalent carbon, found that compounds generalized as **14** undergo a rapid degenerate rearrangement, which was characterized by substituent effects as an S_N2 substitution.[8] They noted that this reaction, which, although exocyclic in two five-membered rings, is endocyclic in an eight-membered ring as shown for **15**, indicates that a deviation of 17° from linearity is allowed in the transition structure of this S_N2 process. The Martin and King work demonstrates how the structure of the tether between the nucleophile and the leaving group provides control of the size of the endocyclic ring and allows the endocyclic restriction test to be used to evaluate the angular limits for transition-state geometry.

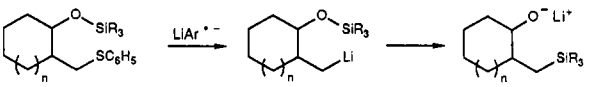


14 14



15

It is instructive to compare the above nucleophilic substitutions with a similar endocyclic substitution at silicon. The established ability of silicon to react with retention of configuration is consistent with the fact that a mixture of **16** and **17** is converted to **18** and **19** without crossover.[9] The reaction is considered to involve formation of **20** and **21**, which undergo front-side displacement at silicon via a hypervalent intermediate in an endocyclic ring. Thus the geometries of substitution at carbon and silicon as evaluated by attempted containment of the transition structures to an endocyclic ring are as expected.



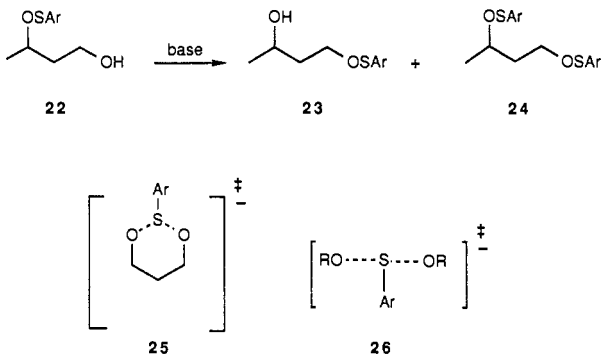
16, n = 1, R = CH_3
17, n = 2, R = $CH(CH_3)_2$

20, n = 1, R = CH_3
21, n = 2, R = $CH(CH_3)_2$

18, n = 1, R = CH_3
19, n = 2, R = $CH(CH_3)_2$

In 1970 Hogg and Vipond also reported recognition of the value of the endocyclic restriction test and applied it to nucleophilic substitution at a nonstereogenic sulfur atom.[5] They observed that the base-promoted isomerization of the sulfenate alcohol **22** to its isomer **23** also gives **24** and that the reaction is suppressed by dilution. Separate treatment of **23** with base gives **22** and **24**. These results were interpreted by Hogg and Vipond to be indicative of an intermolecular reaction which occurs because the intramolecular transition structure would require an angle at sulfur between the entering and leaving oxygens which cannot be achieved in the six-membered ring of **25**. The straightforward rationale is that the reaction proceeds via **26**, in which the bond angle needed for nucleophilic displacement at sulfur is approximately 180°. To the best of our knowledge the report of Hogg and Vipond is the earliest explicit application of the endocyclic restriction test for evaluation of geometry in a transition state for substitution at a nonstereogenic atom.

(7) McGarrity, M. J.; Stothers, J. B.; King, J. F. *Tetrahedron Lett.* **1982**, *23*, 4465. King, J. F.; McGarrity, M. J. *J. Chem. Soc., Chem. Commun.* **1982**, 175.
(8) Martin, J. C.; Basalay, R. J. *J. Am. Chem. Soc.* **1973**, *95*, 2572.
(9) Rücker, C. *Tetrahedron Lett.* **1984**, *25*, 4349. Daney, M.; La-Pougade, R.; Bouas-Lavert, H. *J. Org. Chem.* **1983**, *48*, 5015. Corriu, R. J. R.; Guerin, C.; Moreau, J. J. *Top. Stereochem.* **1984**, *15*, 43.



Ar = o-$NO_2C_6H_4$

In an important extension for analysis of reactions at sulfur, Kampmeier et al. in 1978 reported the use of the endocyclic restriction test for evaluation of the geometry of substitution at sulfur by carbon radicals and noted the general potential of the endocyclic restriction test for evaluation of substitutions at nonstereogenic atoms.[10] Kampmeier showed that **27** and **28** do not interconvert, a result which is consistent with a requirement of a large bond angle in the transition state for carbon radical substitution at sulfur.

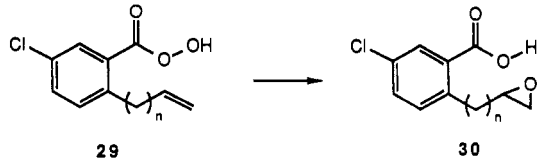
27 **28**

Endocyclic restriction has been used to provide information about a number of reactions. For carbon, the analysis by Stork of intramolecular epoxide ring openings and the generalizations of Baldwin in the rules for ring closure are well-known cases.[11,12] For phosphorus, the seminal work of Westheimer and the extensive work of Martin on a number of hypervalent systems have been rich and productive.[13,14] In the case of sulfur, applications to radical substitutions at sulfoxides by Beckwith and to nucleophilic substitutions at sulfones by Andersen are explicit recognitions of the value of this approach.[15] For nonstereogenic atoms applications to hydrogen[16] and acyl[17] transfers, to nitrene additions,[18] and to hypervalent iodonium species[19] are recent examples of the approach. The most general development of the endocyclic restriction test appears to have been in the work of Minkin. Minkin, Olekhnovich, and Zhdanov clearly outline the uses of this approach and summarize pertinent literature in their recent book.[20]

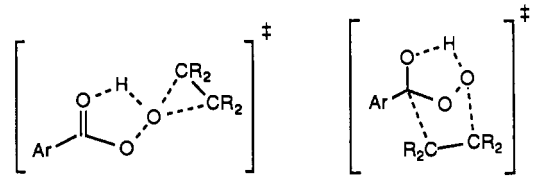
We have recently used the endocyclic restriction test to evaluate experimentally the geometries of formal nucleophilic substitutions at oxygen, nitrogen, and bromine. To the best of our knowledge, our results are the first experimental determinations of transition-structure geometries for substitutions at these atoms. In this Account we summarize how the information from this approach can provide the basis for a rational choice between alternative mechanisms for these atom-transfer reactions.

Transfer of Oxygen. Concerted, associative, and dissociative mechanisms have been suggested for oxidation reactions which involve formal transfer of an oxygen atom, but there has been little experimental information about the arrangement of atoms around oxygen in the transition structures for such reactions.

Epoxidation of an olefin by a peracid to give a peroxide with retention of olefin geometry is a widely used reaction, which is illustrated for the conversions of **29** to **30**. The generally accepted mechanism for the reaction was proposed by P. D. Bartlett in 1950 to involve a concerted reaction in which the olefin approaches the oxygen–oxygen bond of an internally hydrogen bonded peracid at 180° to give a transition structure, shown as **31**.[21a] An alternative which has been suggested more recently is a transition state represented as **32**, which resembles a 1,2-dioxolane but decomposes to the products directly.[22]



29 **30**



31 **32**

The expectations for the reaction of **29** under each mechanism are straightforward. If the transition state is **31** and the length of the tether between the peracid and the olefin is such that the 180° disposition of entering and leaving groups cannot be achieved endocyclically and intramolecularly, the reaction should be intermolecular. With a larger tether, the reaction should become intramolecular. On the other hand, if the reaction involves transition state **32**, the endocyclic ring required for the intramolecular transition structure should be favored for short tethers and could be less favorable with a longer tether. Double-labeling ex-

(10) Kampmeier, J. A.; Jordan, R. B.; Liu, M. S.; Yamanaka, H.; Bishop, P. J. *ACS Symp. Ser.* **1978**, *69*, 275. Franz, J. A.; Roberts, D. H.; Ferris, K. F. *J. Org. Chem.* **1987**, *52*, 2256.

(11) Stork, G.; Cama, L. D.; Coulsan, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 5268.

(12) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. Baldwin, J. E.; Kruse, L. I. *Ibid.* **1977**, 233. Baldwin, J. E.; Lusik, M. S. *Tetrahedron* **1982**, *19*, 2939.

(13) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70.

(14) Chopra, S. K.; Martin, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 5362 and references cited therein.

(15) (a) Beckwith, A. L. J.; Boate, D. R. *J. Chem. Soc., Chem. Commun.* **1986**, 189. (b) Andersen, K. K.; Gouda, G.; Jewell, L.; McGraw, P.; Phillips, B. T. *J. Org. Chem.* **1982**, *47*, 1884. Andersen, K. K.; Malver, O. *J. Org. Chem.* **1983**, *48*, 4803.

(16) Lewis, F. D.; Johnson, R. W.; Ruden, R. A. *J. Am. Chem. Soc.* **1972**, *94*, 4292. Hines, J.; Cholod, M. S.; King, R. A. *J. Am. Chem. Soc.* **1974**, *96*, 835. Berti, C.; Grierson, L.; Grimes, J. A. M.; Perkins, M. J.; Terem, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *29*, 653. Liotta, D.; Saindone, M.; Wagkobe, L.; Stephens, J.; Grossman, J. *J. Am. Chem. Soc.* **1988**, *110*, 2667. Zimmerman, S. C.; Korthals, J. S.; Cramer, K. D. *Tetrahedron* **1991**, *47*, 2649.

(17) Kemp, D. S.; Carey, R. I.; Dewan, J. C.; Galakatos, N. G.; Kerkman, D.; Leung, S. L. *J. Org. Chem.* **1989**, *54*, 1589.

(18) Atkinson, R. S.; Gringshire, M. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1135.

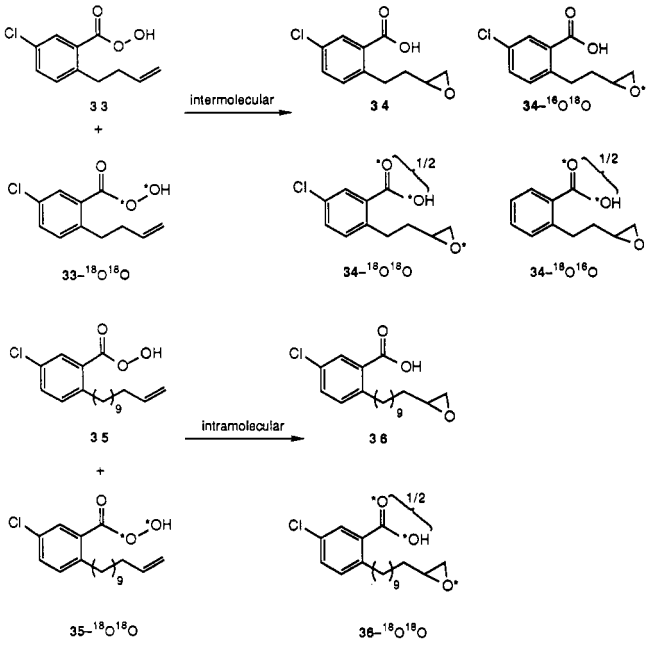
(19) Mohan, H.; Asmus, K. D. *J. Am. Chem. Soc.* **1987**, *109*, 4745.

(20) Minkin, V. I.; Olekhnovich, L. D.; Zhdanov, Y. A. *Molecular Design of Tautomeric Compounds*; D. Reidel Publishing Co.: Dordrecht, Holland, 1988.

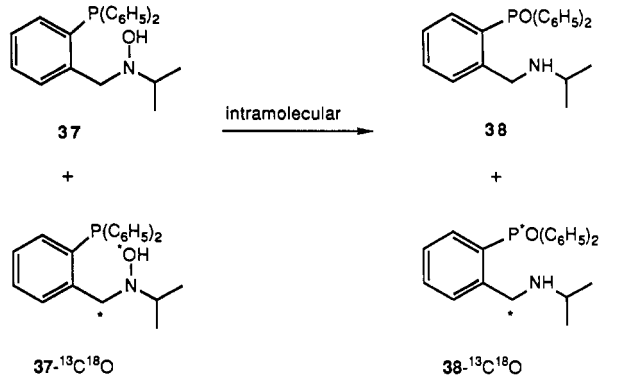
(21) Bartlett, P. D. *Rec. Chem. Prog.* **1950**, *11*, 47.

(22) Kwart, H.; Hoffman, D. M. *J. Org. Chem.* **1966**, *31*, 419. Kwart, H.; Starcher, P. S.; Tinsley, S. W. *J. Chem. Soc., Chem. Commun.* **1967**, 355. Mimoun, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 734.

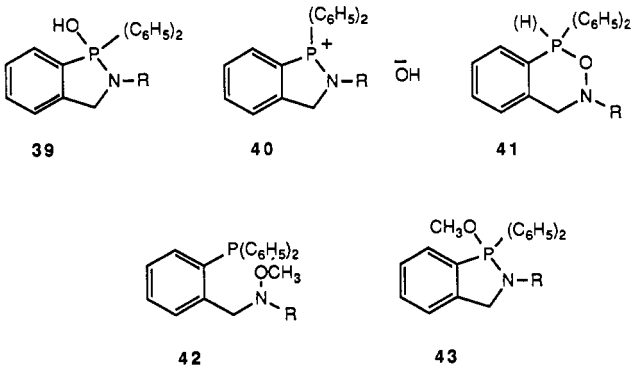
periments provide the experimental distinction.[23] For the short tether, a mixture of **33** and **33**-$^{18}O^{18}O$ at 0.01 M gave the products **34**, **34**-$^{16}O,^{18}O$, **34**-$^{18}O^{16}O$, and **34**-$^{18}O^{18}O$ in a statistical ratio as established by mass spectrometry. Control experiments established that the labels were stable in the product and in a model for the reactant. The conversion of **33** to **34** is intermolecular. A similar double-labeling experiment with **35** and **35**-$^{18}O^{18}O$ at ≤0.02 M showed predominantly intramolecular reaction, and at ≤0.005 M, **36** and **36**-$^{18}O^{18}O$ were obtained which had the same distribution of the label in the products as in the reactants. The epoxidation reaction with the longer tether is intramolecular. The difference in molecularity of the epoxidations of **33** and **35** is consistent with reaction by a transition state in which the carbon–oxygen bonds being formed and the oxygen–oxygen bond being broken are at a large bond angle. Such a geometry is required for **31** and is inconsistent with a transition state analogous to **32**. The geometry of the original Bartlett mechanism is supported by this endocyclic restriction test. This experimental result is also consistent with theoretical calculations of the transition-state structure.[24]



A formally similar oxygen-transfer reaction is illustrated by the conversion of **37** and **37**-$^{13}C^{18}O$ to **38** and **38**-$^{13}C^{18}O$.[25,26] The mechanistic pathways for this reaction which would be disfavored in an endocyclic reaction and therefore would lead one to expect an intermolecular reaction are a concerted classic S_N2 displacement at oxygen or a dissociative homolytic radial chain. However, as indicated by the labeling, **38** has the same label distribution as **37**, so the reaction is intramolecular, ruling out these possibilities. In addition, it was shown that the reaction exhibited first-order kinetics and the intermediates which would result from sequential transfer were not kinetically competent.



The fact that oxygen can be transferred from nitrogen to phosphorus formally endocyclically in a six-membered ring requires either a transition structure which can accommodate small bond angles around oxygen or a mechanism which is insensitive to the disposition of phosphorus and nitrogen. Possible intermediates which meet these requirements are shown as **39**, **40**, and **41**. The species **39**, which could give **38** by ring opening and proton transfer, could result from a biphilic insertion into the nitrogen–oxygen bond analogous to the pathway suggested for oxidation of phosphines by peroxides.[27] Alternatively, **39** could arise by internal return from the ion pair **40** formed by an initial exocyclic nucleophilic displacement by phosphorus of oxygen. A third possibility is the species **41**, a 10-P-5 species, which would involve association of oxygen at phosphorus in a six-membered ring. This species could proceed to **38** by breakage of the nitrogen–oxygen bond and proton transfer.

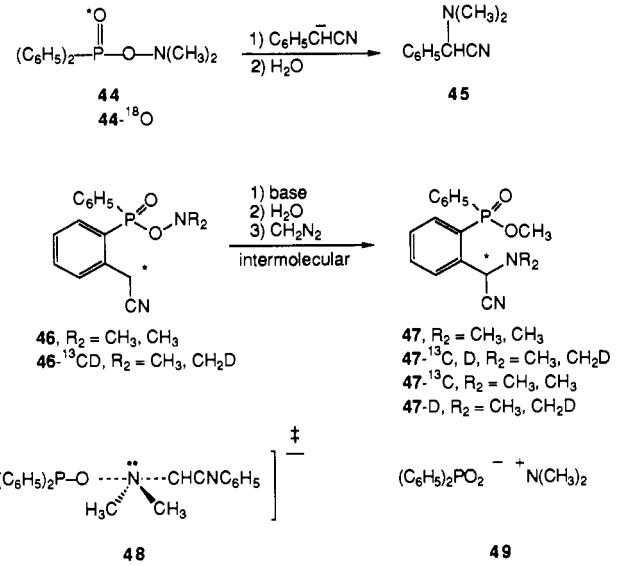


Reactions via **39** or **40** with internal return were ruled out by investigation of **42**. If either the biphilic reaction or the displacement recombination mechanism were operative, **42** would be expected to give **43** or a product resulting therefrom. It was found, however, that **42** was stable under the reaction conditions, thereby leaving the mechanism involving **41** as the favored pathway. Thus a reaction which might be viewed as a nucleophilic displacement at oxygen is more correctly formulated as an addition by oxygen involving valence expansion at phosphorus.

Transfer of Nitrogen. Substitutions which take place at nitrogen by first-row nucleophiles can be formulated to proceed by either concerted or dissociative

(23) Woods, K. W.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 6281.
(24) Bach, R. D.; Orensby, A. L.; Gonzalez, G.; Schleyel, H. B.; McDougall, J. J. W. *J. Am. Chem. Soc.* **1991**, *113*, 2338 and references cited therein.
(25) Kurtzweil, M.; Beak, P. Unpublished results for **37** and **38**. For a similar reaction of the analogous *N*-methyl systems, see: Beak, P.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 3834.
(26) Stec and Okruszek and Lukenbach (Stec, W. J.; Okruszek, A. *J. Chem. Res., Synop.* **1977**, 142. Lukenbach, R. *Tetrahedron Lett.* **1976**, 2017) were the first to report the reaction of a hydroxylamine and a phosphine to give an amine and a phosphine oxide.
(27) Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1984**, *49*, 793. Denny, D. B.; Denny, D. Z.; Hammond, P. J.; Huang, C.; Liu, L. T.; Teng, K. S. *Phosphorus Sulfur* **1983**, *15*, 281.

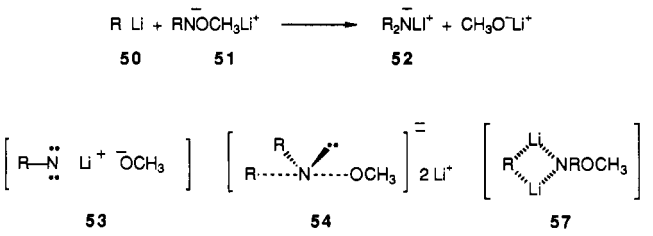
mechanisms. An aminative reaction of this type is illustrated by the delivery of a dimethylamino group from **44** to the carbanion of benzyl cyanide to give **45**. Similar reactions with aniline nucleophiles have been studied by Boche and co-workers, who found those reactions to be first order in each reactant.[28] Evaluation of the transition-structure geometry for this substitution at nitrogen was carried out by study of the conversion of **46** to **47**.[29] The two mechanistic possibilities are a classic S_N2 reaction, represented by transition state **48**, or nucleophile attack on an ion pair, which is shown as **49**. A double-labeling experiment showed that the reaction of **46** and **46**-$^{13}C^2H$ gave **47**, **47**-$^{13}C^2H$, **47**-^{13}C, and **47**-^2H with statistical scrambling of the label in accord with an intermolecular reaction. The labels were stable in the reactants and products under the reaction conditions. This result shows that the dimethylamino nitrogen is not transferred endocyclically in a six-membered ring. Recovery of labeled starting material for the intermolecular reaction of **44**-^{18}O to give **45** showed the label to be intact. This result is inconsistent with the equilibration of label which would be expected for the intermediacy of the reversibly formed ion pair **49** that would be required by the kinetic data for a dissociative mechanism. The transition state for this substitution at nitrogen is then consistent with the trigonal bipyramid of an S_N2 process, **48**, as suggested by Boche on the basis of kinetic data.[28]



44, **44**-^{18}O; **45**; **46**, $R_2 = CH_3, CH_3$; **46**-^{13}CD, $R_2 = CH_3, CH_2D$; **47**, $R_2 = CH_3, CH_3$; **47**-^{13}C, D, $R_2 = CH_3, CH_2D$; **47**-^{13}C, $R_2 = CH_3, CH_3$; **47**-D, $R_2 = CH_3, CH_2D$

48 **49**

A formal nucleophilic substitution at nitrogen which might be expected to proceed by a dissociative mechanism is illustrated by the conversions of **50** and **51** to **52**. The dissociative mechanisms would involve a nitrenoid illustrated as **53** while the concerted displacement is shown as **54**. The electron-deficient nitrene

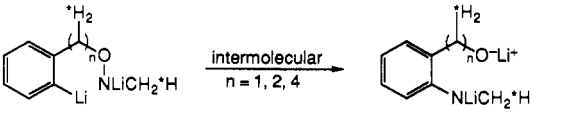


50 **51** **52**

53 **54** **57**

(28) Ulbrich, R.; Famulok, M.; Busold, F.; Boche, G. *Tetrahedron Lett.* **1990**, *31*, 1689 and references cited therein.
(29) Beak, P.; Li, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 2796.

would be expected to be attacked by a carbanion very rapidly, whereas for the concerted reaction displacement by a carbanion on a formally negative nitrogen would be required. Application of the endocyclic restriction test to this reaction is shown for the conversion of **55** to **56**.[30] Since the lifetime of a singlet nitrene would not be expected to allow intermolecular reaction, the expectation for the reaction of **55** via a dissociative-nitrene process is that it would be intramolecular. On the other hand, a classic concerted reaction via a trigonal bipyramidal transition state would be intermolecular for short tether lengths.[1] Double-labeling experiments showed that **55** and **55**-d_3 gave **56**, **56**-d, **56**-d_2, and **56**-d_3 and that the reaction is intermolecular for n = 1, 2, and 4. These results are then consistent with a concerted displacement involving **54** in which the entering and leaving groups about nitrogen are at a large bond angle.



55, *H = H
55-D_3, *H = D

56, *H=H
56-D, *H=D, *H_2=H_2
56-D_2, *H=H, *H_2=D_2
56-D_3, H*=D, *H_2=D_2

A reasonable rationale for this apparent reaction between two anions is that the lithium ions, which are well recognized to favor aggregation, promote the association shown for **57**, which allows the negatively charged groups to approach within bonding distance.[30] This species could provide the juxtaposition of favorable geometry required for subsequent reaction in the S_N2 mode. The importance of lithium ions to this process has been supported by theory although there are some differences between the transition structures from the different calculations.[31]

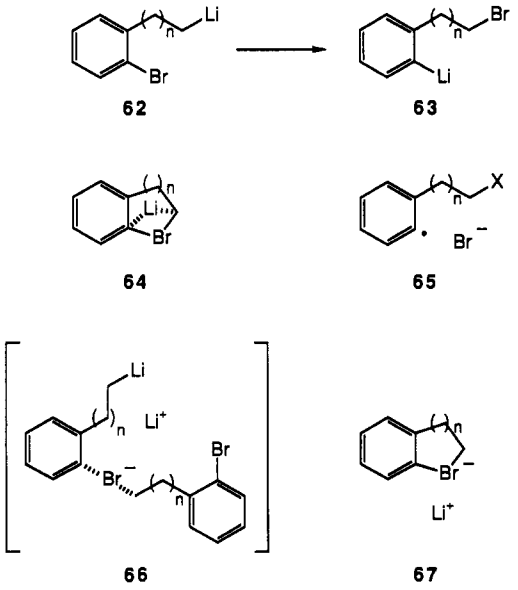
Transfer of Bromine. The halogen–lithium exchange reaction which is widely used for the synthesis of organolithium reagents can be viewed as a formal halogen transfer between carbanions. The reaction is illustrated for the conversion of **58** and **59** to **60** and **61**. The mechanisms which have been suggested for this process include a concerted four-center reaction, a dissociative single electron transfer sequence, a concerted S_N2 reaction at halogen, and an associative process via an ate complex.[32]

$$\underset{58}{RLi} + \underset{59}{BrAr} \rightarrow \underset{60}{RBr} + \underset{61}{LiAr}$$

Under the endocyclic restriction test shown for the conversions of **62** to **63**, these pathways would be expected to have different consequences.[33] With relatively short tethers, the four-center reaction should be intramolecular and most favored for transition structures which would have five- or six-membered rings as shown for **64**. A dissociative single electron transfer mechanism would not be expected to show a geometric

(30) Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016. Beak, P.; Selling, G. *J. Org. Chem.* **1989**, *54*, 5574.
(31) Boche, G.; Wagner, A. V. *J. Chem. Soc., Chem. Commun.* **1984**, 1591. Armstrong, D. R.; Snaith, R.; Walker, G. T. *J. Chem. Soc., Chem. Commun.* **1985**, 789. McKee, M. C. *J. Am. Chem. Soc.* **1985**, *107*, 859.
(32) For a recent review, see: Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1.
(33) Beak, P.; Allen, D. J.; Lee, W. K. *J. Am. Chem. Soc.* **1990**, *112*, 1629. Beak, P.; Allen, D. J. *J. Am. Chem. Soc.*, in press.

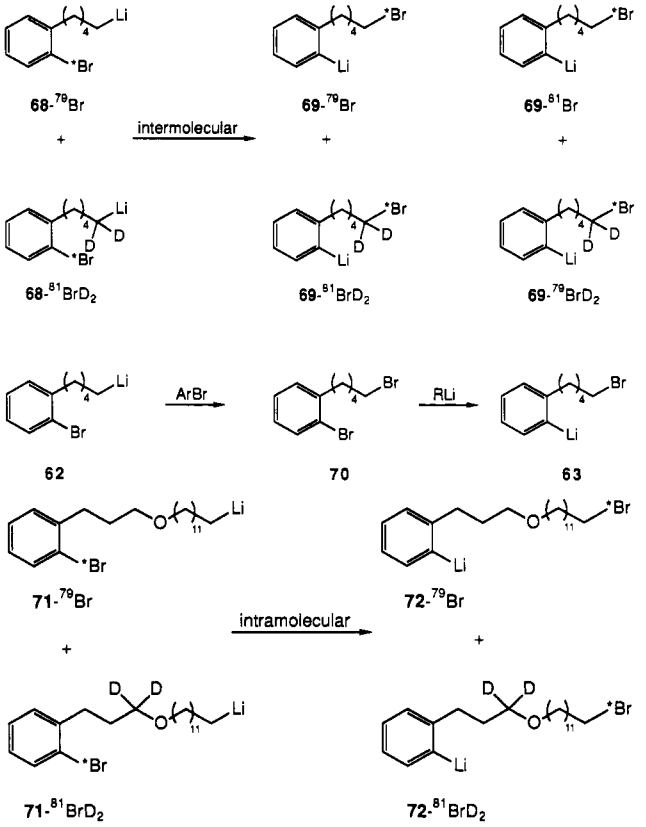
dependence and could be either intramolecular or intermolecular, depending on whether the bromide produced in the dissociative step shown as **65** escapes from the region of its origin. A classic S_N2 reaction which would be intermolecular for small endocyclic rings and intramolecular for large endocyclic rings is shown as **66**. Reaction via an ate complex would follow the same pattern as for the S_N2 processes if the ligands about bromine had to be bonded at a large bond angle. If a relatively oblique angle was allowed in such an ate complex, an intramolecular reaction via **67** could be observed with shorter tethers.



62 **63** **64** **65** **66** **67**

The experiments which reveal the course of the reaction with different length tethers between the reactive groups were carried out with ^{79}Br and $^{81}BrD_2$ labeling for the reactions of **62** with n = 1, 2, and 4. Labeling with both ^{79}Br and ^{81}Br was used to increase the accuracy of the assessment of intramolecular vs intermolecular reaction. The reactants were generated from the corresponding iodides, and the products of the reaction were analyzed by mass spectrometry after protonation. The results are illustrated for reaction of **68**-^{79}Br and **68**-$^{81}Br^2H_2$, which gives **69**-^{79}Br, **69**-$^{81}Br^2H_2$, **69**-^{81}Br, and **69**-$^{79}Br^2H_2$ in the ratios expected for an intermolecular reaction. Similar results were obtained with the shorter chains of **62** for n = 1 and 2. The bromine transfer in these conversions does not occur endocyclically within rings of five, six, or eight members. The bromine appears to be transferred intermolecularly through the dibromides **70**, which are also observed in these reactions. The dibromides have an isotopic content consistent with the sequence illustrated, in which **70** is an intermediate between **62** and **63**.

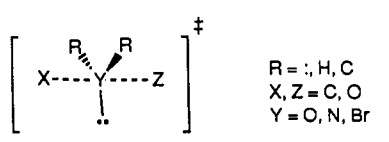
An endocyclic restriction test for bromine transfer was carried out with a larger prospective endocyclic ring as shown for the conversions of **71**-^{79}Br and **71**-$^{81}Br^2H_2$ to **72**-^{79}Br and **72**-$^{81}Br^2H_2$. At a dilution of 0.001 M, an intramolecular reaction is observed as shown and there is no dibromide formation observed in the course of the reaction. Thus, for a sufficiently large ring the bromine transfer is intramolecular, consistent with the requirement of a large angle between the entering and leaving groups about bromine. At this concentration **68** does not give products of bromine transfer.



68-^{79}Br **69**-^{79}Br **69**-^{81}Br **68**-$^{81}BrD_2$ **69**-$^{81}BrD_2$ **69**-$^{79}BrD_2$ **62** **70** **63** **71**-^{79}Br **72**-^{79}Br **71**-$^{81}BrD_2$ **72**-$^{81}BrD_2$

These results can be taken to rule out the four-center and radical mechanisms for the conversion of a primary alkyllithium reagent and an aryl bromide to a primary alkyl bromide and an aryllithium reagent. The possibility of a bromide transfer via a dissociative intermolecular single electron transfer reaction also is discounted by the failure of lithium bromide to be incorporated into the products in reactions of labeled bromide with the shorter tethers. The results are consistent with an S_N2 reaction at bromine or formation of an ate complex which has large bond angles for the substituent groups, consistent with reaction via **66** as a transition state or an intermediate.

Summary. The geometries of formal substitutions of nucleophiles at oxygen, nitrogen, and bromine have been evaluated experimentally by application of the endocyclic restriction test. For reactions in which the nucleophile is carbon, the electrophile is oxygen, nitrogen, or bromine, and the leaving group is oxygen or carbon, the transition structures are trigonal bipyramids. A generalized transition structure shown as **73** is consistent with frontier orbital and VSEPR theory and donor–acceptor models.[2c,34] In the case of transfer of oxygen to phosphorus, reaction can occur at a small angle, consistent with valence expansion at phosphorus.



73

In conjunction with kinetics, isotopic labeling, and alternative generation of possible intermediates, the geometries of many transition structures should be amenable to evaluation by the endocyclic restriction

(34) Huheey, J. E. *Inorganic Chemistry*; Harper and Row: New York, 1983; pp 207–208. Bent, H. A. *Chem. Res.* **1987**, *87*, 587.

test. An advantage of this approach is that the arrangements of atoms can be determined regardless of the stereogenicities of the atoms involved. Control of the tether allows systematic variation of the possible geometries of transition structures, and variations in concentration and reactant groups may be used to probe the available modes of a reaction. It is to be noted that the conclusions which can be drawn from this approach are independent of the yield of the rearranged product. We hope that this Account may help to stimulate applications of this approach to other atoms and other kinds of reactions.

The experimental results from our laboratories were achieved by the colleagues cited in the references. They and many others in Urbana have made this work possible, and I am very grateful to them for their effort and accomplishments. We also very much appreciate support by the National Science Foundation and the National Institutes of Health for this work.

Chemistry of Organochromium(III) Complexes

JAMES H. ESPENSON

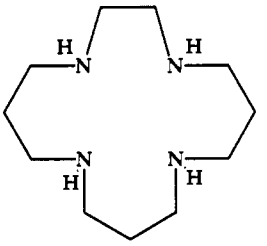
Ames Laboratory and the Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received July 22, 1991 (Revised Manuscript Received February 3, 1992)

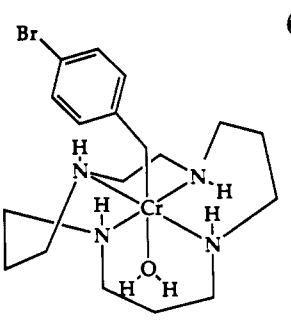
Compounds with a bond between chromium and carbon are now reasonably common. Here we consider species containing trivalent chromium, which tend therefore to involve σ donor ligands rather than π acceptors. Their general formula is R_nCrL_m; this includes such species as $R_3Cr(THF)_3$, $(H_2O)_5CrR^{2+}$, $RCr(THF)_3Cl_2$, $RCr(acac)_2(NC_5H_5)$, etc. Only for the family with the general formula $(H_2O)_5CrR^{2+}$ have reaction mechanisms been explored systematically, and in this Account I summarize these results. Earlier work was reviewed about a decade ago,[1,2] and the chemistry of other series such as $[(\eta^5\text{-}C_5Me_5)CrRCl_2]_2$ has been reviewed with particular attention to applications as polymerization catalysts.[3] For mechanistic studies the existence of a single alkyl group is highly advantageous since it is difficult to deconvolute the sequential and similar reactions of a species like $R_3Cr(THF)_3$.

Structures and Trans Effects. As yet, not one member of the $(H_2O)_5CrR^{2+}$ series has been isolated as a pure solid, or in a form suitable for crystallography. By coating the chromium with other ligands, however, so as to reduce hydrogen bonding to the solvent, crystal structures have been obtained[4-6] for derivatives, including *trans*-$RCr(acac)_2(NC_5H_5)$ with R = $CHCl_2$ and CH_2Cl and [*trans*-$RCrL(H_2O)](ClO_4)_2$ with L = 1,4,8,12-tetraazacyclopentadecane (1) and R = 4-$BrC_6H_4CH_2$ (2, 3). The crystallographic data substantiated the structures inferred from chemical and spectroscopic data (but not, of course, from NMR owing to paramagnetism).

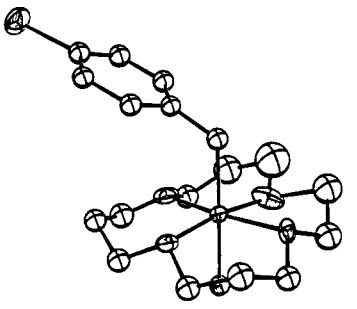
A notable feature of the structures is the elongated bond between chromium and its trans ligand, compared to that in species lacking the chromium–carbon bond. For example, the complexes *trans*-$ClCH_2Cr(acac)_2B$ have trans distances as follows: d_{CrN} = 220.1 pm (B = NC_5H_5), d_{CrO} = 213.4 pm (B = H_2O), and d_{CrO} = 215.6 pm (B = CH_3OH).[4,5] In comparison, d_{CrO} values are 210, 196.5, and 197.5–209.0 pm for *mer*-$Cr(CF_3CO_2)_3(NC_5H_5)_3$,[7] *trans*-$[CrCl_2(CH_3OH)_4]^+$,[8] and various other $CrOH_2$ compounds.[5]



1



2



3

The discovery of the elongated trans distances confirms the kinetic measurements. The reactivity of $(H_2O)_5CrR^{2+}$ and other metal–alkyl complexes, including organocobaloximes, toward ligands entering into the

James H. Espenson was born in Los Angeles in 1937. He received a B.S. degree from Caltech in 1958 and a Ph.D. degree from the University of Wisconsin in 1962 under Edward L. King. He then was a postdoctoral fellow at Stanford University with Henry Taube. He joined Iowa State University as an instructor in 1963, where he is now distinguished professor and chairman of the Chemistry Department as well as senior chemist and program director at the Ames Laboratory. His research interests concern the mechanisms of inorganic and organometallic reactions.

(1) Espenson, J. H. *Adv. Inorg. Bioinorg. Mech.* **1982**, *1*, 1.
(2) Espenson, J. H. *Prog. Inorg. Chem.* **1983**, *30*, 189.
(3) Theopold, K. H. *Acc. Chem. Res.* **1990**, *23*, 263.
(4) Ogino, H.; Shoji, M.; Abe, Y.; Shimura, M.; Shimoi, M. *Inorg. Chem.* **1987**, *26*, 2542.
(5) Abe, Y.; Ogino, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 56.
(6) Shi, S.; Espenson, J. H.; Bakac, A. *J. Am. Chem. Soc.* **1990**, *112*, 1841.
(7) Dikareva, L. M.; Antsyshkiva, A. S.; Porai-Kochits, M. A.; Zevirov, Yu. V.; Ostrikova, V. N. *Koord. Khim.* **1983**, *9*, 1426.
(8) Hardcastle, K. I.; Skovlin, D. O.; Eidawad, A.-H. *J. Chem. Soc., Chem. Commun.* **1975**, 190.

0001-4842/92/0125-0222$03.00/0