preparation and stability, diazo carbonyl compounds are most amenable to synthetic utilization. Their aliphatic counterparts, including diazomethane, are less stable and, consequently, they are more prone to undergo preferential dimerization or polymerization in the presence of a transition metal catalyst. Stoichiometric methods based on the direct use of metal carbenes are presently better adapted for aliphatic carbenoid addition reactions.

The attractiveness of catalytic cyclopropanation reactions for organic synthesis has been limited by low selectivities associated with the transformation. Now, however, control of stereoselectivity and regioselectivity can be achieved through the use of structurally modified catalysts and diazo compounds.[52]

Catalytic entry to ylide intermediates has perhaps the greatest potential for new synthetic developments. Rhodium catalysts are superior to previously employed copper catalysts, and even ylide generation from allyl halides and ethers can now be conveniently achieved without excessive competition from cyclopropanation. Although current examples of ylide transformations in catalytic reactions are limited to the [2,3]-sigmatropic rearrangement and direct insertion, a variety of other processes should also be possible.

I am deeply indebted to the many co-workers who have given their time, energy, and ideas to make the projects described here possible. I also acknowledge with great appreciation the support of the National Science Foundation and a loan of transition-metal compounds from the Johnson Matthey Co. I thank Hope College, where a majority of this research was accomplished, and Trinity University for providing environments in which research is an educational priority.

(52) Catalysts that enhance syn selectivity have recently been reported: Callot, H. J.; Metz, F. *Tetrahedron* **1985**, *41*, 4495.

Stereo- and Regiocontrol by Complex Induced Proximity Effects: Reactions of Organolithium Compounds

PETER BEAK*

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

A. I. MEYERS*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received February 3, 1986 (Revised Manuscript Received July 28, 1986)

The sensible idea that chemical reactions can be promoted by structures which bring potentially reactive groups close together emerged naturally as chemists applied models of bonding to understanding reaction pathways. The famous Fisher "lock and key" model for enzyme action, the well-recognized advantages of intramolecularity, and the often-invoked chelate and complexation effects embody proximity as an important factor for understanding and controlling the course of chemical reactions.[1]

In organolithium chemistry mechanistic rationales of regio- and stereochemical results often involve bonding between lithium and electron pairs of substrates in critical intermediates.[2] For example, reviews of ortho-lithiations of aromatic compounds and of lithiations and additions to nonaromatic compounds suggest complexation to be a major effect in many cases.[3] Such ideas are firmly based on information from X-ray spectroscopy about the structure of lithium in solids, the propensity of lithium for association in solution, and theoretical calculations of lithium binding in the gas phase.[4]

In most cases association between lithium and the functional group of a substrate enforces not only proximity but also resonance, stereoelectronic, inductive, and steric effects. As a result, evaluation of the relative contributions of these factors can be difficult. However, reactions have been described which suggest that a complex-induced proximity effect (CIPE), operating in a preequilibrium complex, can be as important as the classical effects in controlling the course of the ensuing transformations.

One of the clearer demonstrations of dominance by a CIPE process is the β-lithiation of γ,δ-unsaturated

Biographies of the authors have appeared previously.

---

(1) For recent discussions and diverse applications of this ubiquitous concept, see: (a) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128. (b) Weinreb, S. M. *Ibid.* **1985**, *18*, 16. Kozikowski, A. P. *Ibid.* **1984**, *17*, 410. Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Ibid.* **1984**, *17*, 35. (c) Hibbert, F. *Ibid.* **1984**, *17*, 115. (d) Breslow, R. *Ibid.* **1980**, *13*, 170. (e) Mutterties, E. *Chem. Soc. Rev.* **1982**, *11*, 283. (f) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Lancharich. *Science* **1986**, *231*, 1108. (g) Beak, P.; Ziegler, J. M. *J. Org. Chem.* **1981**, *46*, 614.

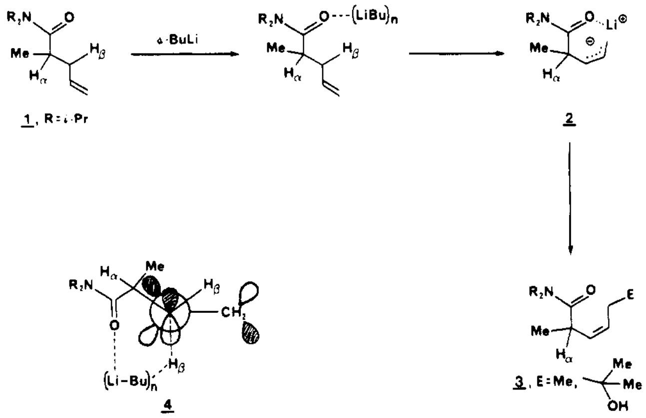
(2) (a) Wakefield, B. J. *Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974. (b) Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375.

(3) (a) Gschwend, H. W.; Rodriquez, H. R. *Org. React.* (N.Y.) **1979**, *26*, 1. H. Gilman [Gilman, H.; Marten, J. W. *Org. React.* N.Y. **1954**, *8*, 258] credits Roberts and Curtin [Roberts, J. D.; Curtin, D. Y. *J. Am. Chem. Soc.* **1946**, *68*, 1658] for demonstrating this effect in ortho lithiations. (b) Klumpp, G. W. *Rec. Trav. Chim. Pays-Bas* **1986**, *105*, 1.

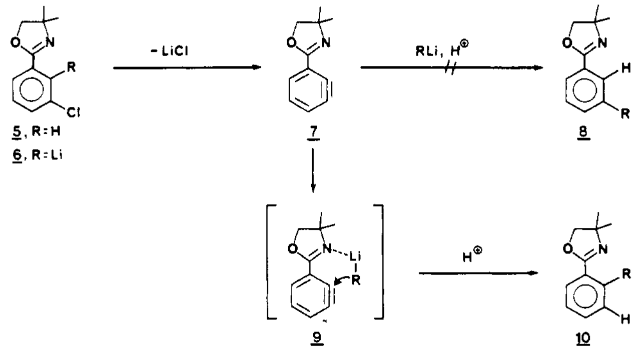
(4) For recent examples and leading references, see: Amstuz, R.; Laube, T; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1984**, *67*, 224. Jastrzebski, J. T. B. H.; van Koten, G.; Konijn, M.; Stem, C. H. *J. Am. Chem. Soc.* **1982**, *104*, 5490. Al-Aseer, M. A.; Allison, B. D.; Smith, S. G. *J. Org. Chem.* **1985**, *50*, 2715. Frankel, G.; Henrichs, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 255. Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. Jackman, L. M.; Scormoutzous, L. M. *J. Am. Chem. Soc.* **1984**, *106*, 4627. Buese, M. A.; Hogen-Eisch, T. E. *Ibid.* **1985**, *107*, 4509. McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Looli, H. R. *Ibid.* **1985**, *107*, 1810. Kaufmann, E.; Clark, T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1984**, *106*, 1856. Streitwieser, A., Jr. *Acc. Chem. Res.* 1984, *17*, 353, and references cited therein.

0001-4842/86/0119-0356$01.50/0

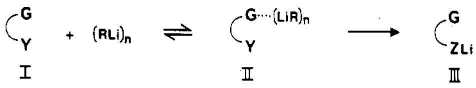
tertiary amides. Thus, the reaction of 1 with *sec*-butyllithium to give 2 requires kinetic removal of the β-proton in the presence of an α-proton which is ca. 10 $\mathrm{p}K_a$ units thermodynamically more acidic.[5] The intermediacy of 2 is established by the formation of δ-substituted products, 3, on treatment with electrophiles. Control and isotopic substitution experiments show the reaction does not involve initial α-deprotonation or the formation of dianions. Both resonance and inductive effects should favor removal of the α-proton; hence the observed loss of a β-proton is taken to indicate regiocontrol by a CIPE process. The kinetic deprotonation of 1 to give 2 is interpreted to involve a transition state represented as 4. In this complex, the organolithium base is delivered with the proper geometry to allow overlap between the HOMO of the α-C-H bond being broken and the LUMO of the π^* orbital of the double bond. It is interesting that a transition state involving a seven-membered ring appears to be favored over the six-membered ring which would be involved in enolate formation. The angle of the carbon–oxygen–lithium bond as well as the possible complexation of the double bond with the lithium are critical features which still must be defined for this reaction.



A different type of reaction representative of a CIPE process is the unexpected regiochemistry of addition of organolithium reagents to the benzyne, 7.[6] The latter, derived by metalation of 5 to the ortho lithio derivative 6, reacts with alkyl and aryl lithium reagents to furnish the ortho-alkylation products 10. In view of the well-known regiochemical outcome for benzynes containing an electron-withdrawing group,[7] the product of this addition was expected to produce the meta-substituted product 8. The formation of 10 as the major product (10:8 = 6:1) can be understood in terms of a complex 9 which places the organolithium in the proximity of the ortho carbon of the benzyne. Again, a proximity-assisted reaction of an organolithium complex can be seen as vital in regiochemical control.



Scheme I



G = Functional Group
Y = Reactive Site
Z = Transformed Site

In a general sense, a CIPE process can be defined as shown in Scheme I. The functional group G in the general structure I provides a residence site for the reagent, *prior* to subsequent reaction. The group G, in the preequilibrium complex, II, may be neutral or ionic. In effect, the formation of this complex makes the subsequent conversion to III intramolecular in nature. The suggestion that reactions of organolithium compounds involve complexes is, as noted above, well precedented.[2-4] Most recognized cases of CIPE transformations involve either formation of unexpected kinetic products, instead of the apparently available thermodynamic alternatives, or dramatic accelerations of normally unfavorable reactions.

We wish to emphasize that unusual or unexpected products attributable to a CIPE process appear to arise in a wide variety of reactions of organolithium compounds. In this Account we provide selected examples which are consistent with the general process outlined in Scheme I. Indeed, these examples are so numerous that within the space constraints of this article we could not include many pertinent cases and offer our apologies to those investigators whose work may not be described herein. We have sought coverage and have cited cases not in other summaries. We offer this Account with the intent that our attempt at unification will be useful for understanding reaction pathways and in the design of regio- and stereospecific syntheses.

Metalations under Complex Induced Proximity Effects

The well-known lithiation of heteroatom-substituted aromatics, wherein the ortho proton is removed and

---

(5) Beak, P.; Hunter, J. E.; Jun, Y. M. *J. Am. Chem. Soc.* **1983**, *105*, 6350. This $\Delta \mathrm{p}K_a$ estimate is based on the $\mathrm{p}K_a$'s of *N,N*-dimethylacetamide (34–35) and propene (44) from the work of Bordwell, Streitwieser, and Breslow.

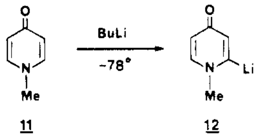
(6) Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1983**, *24*, 4935; **1984**, *25*, 2941.

(7) Hoffmann, R. W. *Dehydrobenzenes and Cycloalkynes*; Academic Press: New York, 1967.

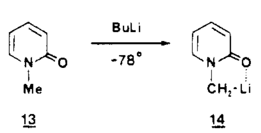
(8) Complex-induced proximity effects have been or can be invoked for a wide variety of reactions. Many reactions of allylic alcohols are considered to demonstrate such an effect. Examples include cyclopropanation by the Simmonds–Smith reagent [Staroscik, J. D.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 738], hydroboration [House, H. *Modern Synthetic Reaction*; W. A. Benjamin: New York, 1972; pp 115–117] and, hydrogenations catalyzed by iridium and rhodium [Evans D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866]. Regio- and stereospecific reductions and alkylations of double bonds are also recent synthetically useful examples. Gammill, R. B.; Bell, L. T.; Nash, S. A. *J. Org. Chem.* **1984**, *49*, 3039. Moret, E.; Schlosser, M. *Tetrahedron Lett.* **1985**, 4423. Iron and palladium insertion into sites remote from the directing functionality also illustrate CIPE process. For examples, see: Groves, J. T.; Subramanian, D. V. *J. Amer. Chem. Soc.* **1984**, *106*, 2177. Heumann, A.; Backvall, J. E. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 207. Baldwin, J. E.; Jones, R. H.; Najera, C.; Yus, M. *Tetrahedron* **1985**, *41*, 699. Perhaps the most dramatic current example is the gas-phase insertion of cobalt into a carbon–carbon bond, postulated to involve initial complexation with an proximate hydroxyl group. Tsarbopoulos, A.; allison, J. *J. Am. Chem. Soc.* **1985**, *107*, 5085.

replaced with a C–Li bond, has been extensively reviewed[3a] and will not fall within the purview of this report. In these cases, only ortho-lithiation can be expected, with varying degrees of efficiency, to be mediated by virtually any substituent other than a hydrocarbon. We will, therefore, focus on those metalations where alternative, often thermodynamically favored, sites of proton removal exist but which appear to follow a CIPE-controlled process to give a kinetic product.

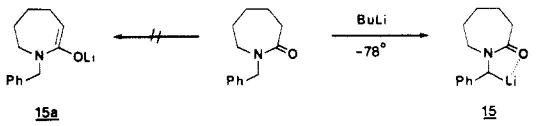
The lithiation of the 4-pyridone **11** exclusively on the ring proton to give **12**[9] is consistent with early work on dipole stabilized carbanions[10a] which showed that the 2-H in **11** is exchanged in basic deuterium oxide. However, when the 2-pyridone **13** is metalated, the proton of the *N*-methyl group is removed, presumably via a CIPE process, to give **14**. A special role for lithium is indicated in this case because treatment of **13** with sodium deuteroxide in deuterium oxide leads to substitution of the 6-H.[10b] A recent study on various *N*-benzylcaprolactams indicates that the benzyl protons are exclusively removed to give **15**.[10c] The thermodynamically favored reaction would be removal of the α-methylene protons to give the amide enolate, **15a**.[10b] The former process is considered to be a kinetic deprotonation, directed by the CIPE phenomenon, in conjunction with an unfavorable conformation in the complex wherein the α-proton to the carbonyl is not properly aligned for removal.



11 **12**

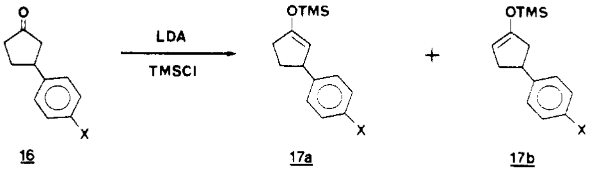


13 **14**



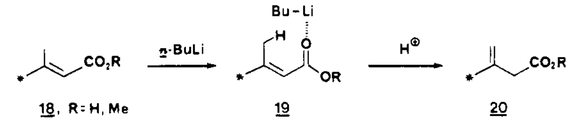
15a **15**

In another example of a CIPE process, Posner[11] described the regioselective enolization of 3-arylcyclopentanones **16**. The deprotonations were selective (3–7:1) forming **17a** over **17b** leading to the suggestion of a π-arenelithium complex which places the base in the proximity to the C-2 carbon.



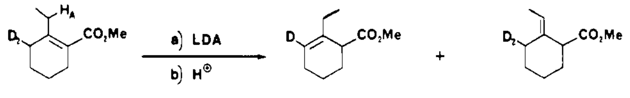
16 **17a** **17b**

It has been shown in several examples, that a γ-C–H bond syn to a functional group in an α,β-unsaturated system is selectively vulnerable towards lithium bases.[12] The case of deprotonation of the esters **18**, to give **20**, via **19**, is illustrated.[13a] Weiler[13b] also reported that metalation (LDA–THF–HMPA) of **21**, containing deuterium in the anti-allylic position, gave only **22**, which seems contradictory to the results observed for **18**. However, if the HMPA was omitted from the metalation step, a 60:40 mixture of **23**:**22** was obtained. This may be rationalized as interference with a CIPE process by HMPA which provides alternative complexation for the lithium. The delicate balance that occurs between CIPE processes and other classical effects is demonstrated in this case.



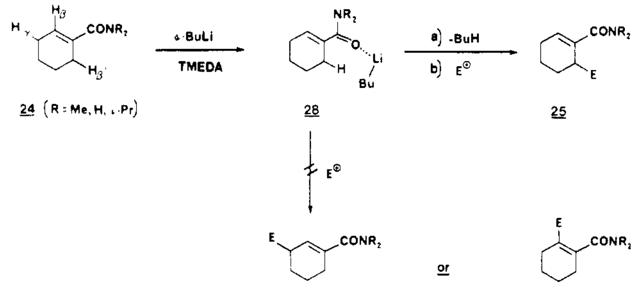
18, R = H, Me **19** **20**

* = CD_3



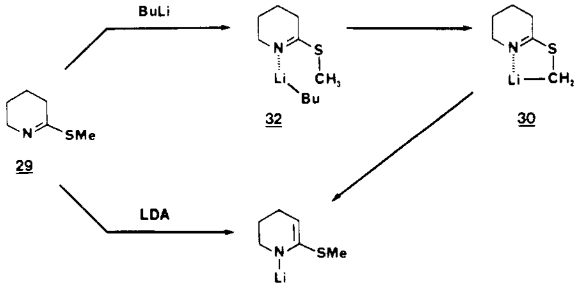
21 **22** **23**

In another study, a CIPE process has been found to operate more exclusively in the cyclohexenecarboxamides **24**.[14] Of the three possible deprotonation sites (H_β, H_γ, and $H_{\beta'}$) in both secondary and tertiary amides, only the β′-proton is removed. The products obtained after addition of electrophiles were **25**. The alternative product **26** was never observed, and the formation of **27** (E = CHO), observed in a single case, is considered to arise by isomerization of **25**. These results are readily rationalized by invoking a complex **28** in which the base is in proximity to the β′-proton for a kinetic deprotonation.



24 (R = Me, H, *i*-Pr) **28** **25** **26** **27**

Another interesting CIPE process was noted by Trost[15] for the imino thioether **29** which gave only de-



29 **32** **30** **31**

---

[9] Patel, P.; Joule, J. A. *J. Chem. Soc., Chem. Comm.* **1985**, 1021.

[10] (a) Beak. P.; Bonham, J. *J. Am. Chem. Soc.* **1965**, *87*, 3365. (b) Beak, P.; Monroe, E. M. *J. Org. Chem.* **1964**, *34*, 589. (c) Meyers, A. I.; Kunnen, K., unpublished results.

[11] Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.

[12] For a more recent case and a suggestion of the importance of complexation, see: Majewski, M.; Green, T. R.; Snieckus, V. *Tetrahedron Lett.* **1986**, *27*, 531. For an example in which a sulfone group is suggested to be involved in a similar reaction, see: Block, E.; Eswarakrishnan, V.; Gebreges, K. *Tetrahedron Lett.* 1984, *25*, 5469.

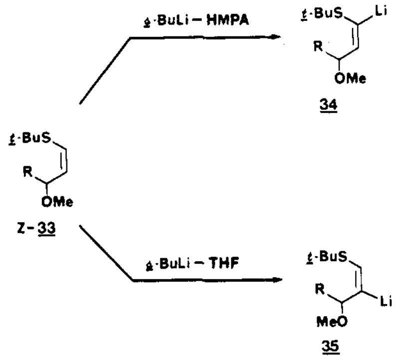
[13] (a) Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1985**, *26*, 1939; **1984**, *25*, 1333. (b) Harris, F. L.; Weiler, L. *J. Chem. Soc., Chem. Comm.* **1985**, 1124.

[14] Beak, P.; Kempf, D. J.; Wilson, K. D. *J. Am. Chem. Soc.* **1985**, *107*, 4745.

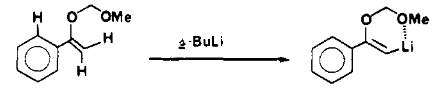
[15] Trost, B. M.; Vaultier, M.; Santiago, M. L. *J. Am. Chem. Soc.* 1980, *102*, 7929.

protonation of the thiomethyl group to provide **30** under kinetic conditions while the ring methylene protons of **29** are removed to give **31** under thermodynamic conditions. Apparently the preequilibrium complex **32** can achieve proper alignment for kinetic removal of the proton from the thiomethyl group while the methylene groups at C-3 are too remote to be accessible to the complexed butyl group. When the base used is LDA, either an equilibrium favoring the thermodynamically more acidic methylenes is favored or a different mechanism is operative.

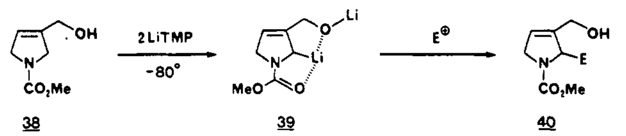
An example of a less activated CIPE process was provided by Julia[16] who showed that metalation of (*Z*)-thioenol **33** with strong base in the presence of HMPA furnishes the lithiated product **34** wherein thermodynamic acidity prevailed. However, in the absence of the ion-solvating cosolvent, metalation proceeded to **35**, apparently the result of more favorable lithium ion coordination to the methoxyl group and abstraction of a nearby available proton. Allylic deprotonation does not occur with (*Z*)-**33** but is the predominant path when *E* isomer of **33** was employed. Perhaps this difference reflects the relative stability of the allylic anions and once again shows how CIPE process may be balanced by other factors.



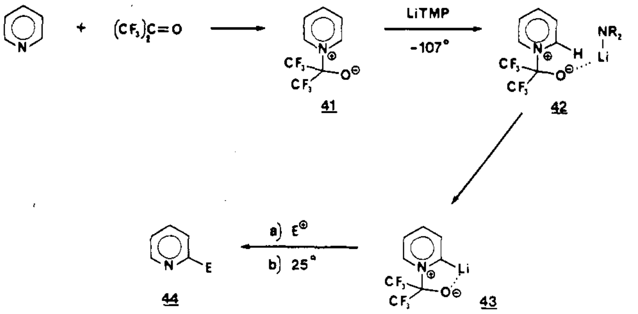
When the competitive deprotonations involve an aromatic ring, CIPE may be seen to determine the outcome. McDougal[17a] recently showed that the enol ether **36**, which can metalate either at the ortho position, as is well-known for methoxymethylbenzyl ethers,[17b] or at the vinyl carbon, gave exclusively **37**. Electrophile addition to the latter furnished the β-substituted vinyl products with only the *E* configuration. Again, a critical transition-state geometry must be achieved in the complex for removal of the vinyl hydrogen.

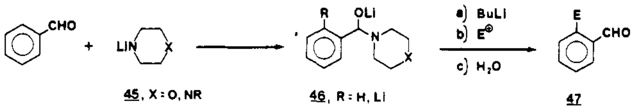


When two equivalent carbon acids are present, the inclusion of a complexing group can alter the relative kinetic acidities and provide regioselective metalations and control of subsequent alkylations. In this manner, MacDonald[18] was able to metalate **38** with a strong base making use of the lithium alkoxide, initially formed, to direct the second equivalent of base into the 2-position to give **39**. Alkylation gave 2-alkyl pyrroline **40**, in greater than 97% yield.



Another strategy which may involve a CIPE process is the transient introduction of a complexing group to bring the lithium base into proximity for proton abstraction. Although metalation may be the expected reaction, the in situ introduction of a complexing moiety is worthy of note. Martin[19] demonstrated this technique by addition of hexafluoroacetone (HFA) to pyridine in THF–ether to form the adduct **41** which was stable at −107 °C. Addition of lithium tetramethylpiperidide to this species forms the lithium HFA complex **42** which directs the base to the 2-proton, now also made more acidic by the positively charged nitrogen. Metalation furnishes the lithio complex **43** which is alkylated with various electrophiles. Warming the solution caused the decomposition of the hexafluoroacetone complex leaving the 2-substituted pyridine, **44**. A further demonstration of a transient CIPE process was described by Comins.[20] While benzaldehydes are not useful in direct ortho-metalation due to the very reactive carbonyl which accepts most lithio bases, this property can be exploited. Addition of lithio morpholines or piperazines **45** to benzaldehyde to give the adducts **46** (R = H), which with its oxygen substituent functioning as a ligand, can now direct a lithium base via the CIPE process to afford the lithio benzene, **46** (R = Li). Usual alkylation with electrophiles followed by aqueous workup and decomposition of the carbinolamine then regenerated the ortho-substituted benzaldehyde, **47**.[21]





Complex Induced Proximity Effects in Halogen–Metal and Metal–Metal Exchanges

Impressive proximity effect behavior has been noted when the competitive reactions involve halogen–metal exchange vs. deprotonation. It is well-known that

---

(16) Ekogha, C. B. B.; Ruel, O.; Julia, S. A. *Tetrahedron Lett.* **1983**, *24*, 4825, 4829.

(17) (a) McDougal, P. G.; Rico, J. G. *Tetrahedron Lett.* **1984**, *25*, 5977. (b) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923. Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101. For a recent example on cyclohexenyl metalation see: Stork, G.; Shiner, C.; Cheng, C. W.; Polt, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 304.

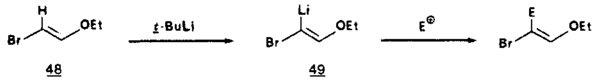
(18) MacDonald, T. L.; Narayanan, B. A. *J. Org. Chem.* **1983**, *48*, 1131.

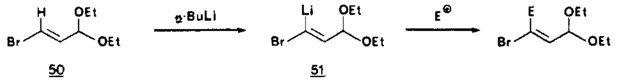
(19) Taylor, S. L.; Lee, D. Y.; Martin, J. C. *J. Org. Chem.* **1983**, *43*, 4158.

(20) (a) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. (b) For a recent example of transient introduction of a complexing group in tetrahydroisoquinoline alkylations, see: Katritzky, A. R.; Akutagawa, K. *Tetrahedron* **1986**, *42*, 2571.

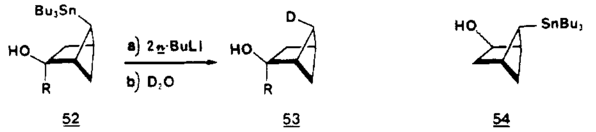
(21) This technique was used earlier by Gschwend and co-workers for ortho metalation of *N*,*N*-dimethylbenzamides. Barsky, L.; Gschwend, H. W.; McKenna, J.; Rodriquez, H. R. *J. Org. Chem.* **1976**, *41*, 3651.

halogen metal exchange can be fast,[2a] yet if a molecule contains structural features which permit a CIPE process to occur, the latter may be favored. Schlosser[22] described the deprotonation of the (*E*)-bromovinyl ether **48**, by virtue of a lithium complex placing the base in close proximity to the proton, kinetically enhancing the metalation to **49**. Similarly, the (*E*)-bromovinyl acetal **50**, by initial complexation of the lithium base to the suitably placed ethoxyl group, gave 88% vinyl deprotonation **51** and only 12% bromine–lithium exchange products.[23] It is pertinent that the *Z* isomer of **48** led only to bromine–lithium exchange, which suggests that halogen–metal exchange processes also may be sensitive to complexing proximity effects.



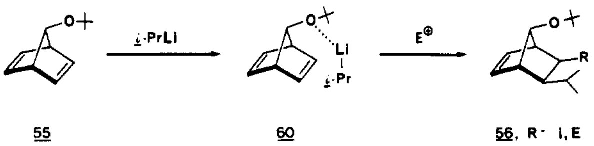


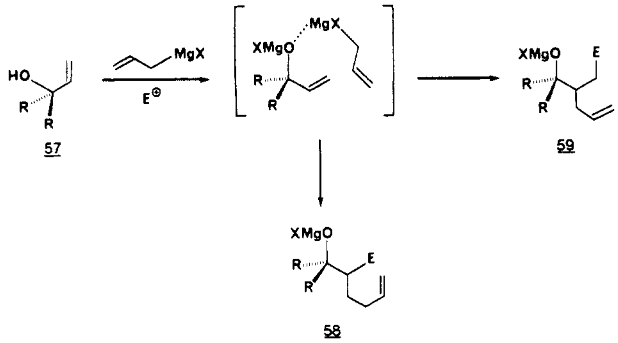
A more unusual example of this exchange has recently been reported by Carpenter[24] who found extremely high stereoselectivity and regioselectivity when **52** was transmetalated with *n*-butyllithium followed by deuterium oxide to give the deuterated alcohol **53**. Since transmetalation of tin compounds by organolithiums are known to usually proceed with loss of configuration, this result was rationalized by a CIPE process. That is, the initially formed lithio alkoxide serves as a complexing agent for the second equiv of butyllithium necessary to generate the "ate" complex on the tin. It was also found that the isomer **54** did not exchange lithium for tin, supporting the postulated proximity effect.



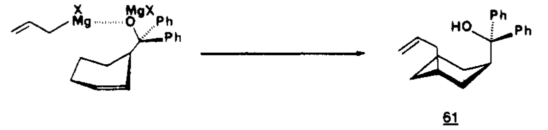
Additions to Carbon–Carbon Multiple Bonds

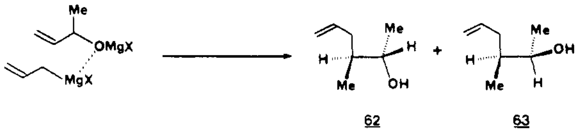
One of the earlier recognitions of the CIPE phenomena was recorded for the addition of a lithium or Grignard reagent to a carbon–carbon multiple bond adjacent to an alcohol or amine.[4] The pioneering work of Wittig and Klumpp for organolithium species and of Eisch and Felkin for Grignard reagents involved the addition of isopropyllithium to **55** to give **56**[25,26] and of allylmagnesium bromide to the allyl alcohols **57** to give **58** and **59**.[27,28] Two different complex-induced processes were suggested. The formations of **56** and **58** were rationalized via an intracomplex pathway in which the group bonded to the metal associated with oxygen is the addend. Felkin suggested for the Grignard additions that the magnesium associated with oxygen acts as a Lewis acid to promote addition to the double bond by an allyl group of an external Grignard reagent.





The intramolecular addition to give **60** is clearly supported by the **exo** structure of the product **56**. Addition by an external isopropyllithium would be expected to give an isomeric endo-substituted product. In the case of addition by the allyl Grignard to **57**, the two different mechanisms would provide different diastereomers. Further experiments suggested both modes may be operative. Thus the reaction of (2-cyclohexenyl)diphenylcarbinol with allylmagnesium bromide gives **61** via delivery of the allyl group from the same side of the ring as the magnesium alkoxide.[29] On the other hand, the reaction of allylmagnesium bromide with α-methallyl alcohols favors the erytho isomer **62** by eight to one over the threo isomer **63**. It is reasonable that **62** arises by addition of an external allyl group to the double bond. A number of other studies show variable stereochemistry and presumably different modes of CIPE process for similar additions by allyl, benzyl, and tertiary Grignard reagents.[30]





Additions of primary, secondary, and aryl organolithium reagents to allyl alcohols give 2-substituted-1-propanols analogous to **59**. The predominant product from α-methallyl alcohol and allyllithium is the threo isomer **63** in accord with addition by an allyl group which is part of the complex. Similar additions to allenes and acetylenes for multiple bonds within three carbon atoms of the directing group, and other additions directed by ethers or metals (e.g., Ni^{2+}, Zn^{2+}) have been reported from a number of laboratories including

---

(22) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595.

(23) Meyers, A. I.; Spohn, R. F. *J. Org. Chem.* **1985**, *50*, 4872.

(24) Newman-Evans, R. H.; Carpenter, B. K. *Tetrahedron Lett.* **1985**, *26*, 1141.

(25) Wittig, G.; Otlen, J. *Tetrahedron Lett.* **1963**, 601.

(26) Klumpp, G. W.; Veerkind, A. H.; deGraff, W. L.; Bickelhaupt, F. *Justus Liebigs Ann. Chem.* **1967**, *706*, 46.

(27) Eisch, J. J.; Husk, G. R. *J. Am. Chem. Soc.* **1985**, *89*, 4194.

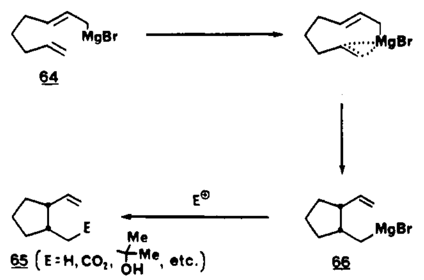
(28) Cherest, M.; Felkin, H.; Frajerman, C.; Lion, C.; Roussi, G.; Swierczewski, G. *Tetrahedron Lett.* **1966**, 875.

(29) Eisch, J. J.; Merkley, J. H.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 587.

(30) For a review, see: Vara Prasad, J. V. N.; Pillai, C. N. *J. Organometall. Chem.* **1983**, *259*, 1.

those of Richey, Crandall, and Klumpp.[3b,30,31] These additions provide methodology for the regio and stereospecific formation of a new carbon–carbon bond simultaneously with the generation of a reactive organometallic. Although this approach has not yet been widely used, it appears to offer considerable potential for target-oriented syntheses.

A formally related reaction, devised by Felkin,[32] is the intramolecular addition of an allylic Grignard to a carbon–carbon double bond.[32] The process is illustrated for the cyclization of 64 to 65. It may involve magnesium association with the vinyl group as shown for the formation of 66. The synthetic advantages of this formal ene reaction have been recognized by Oppolozer.[33] In this case the CIPE concept was used by Felkin to invent a new and useful reaction.

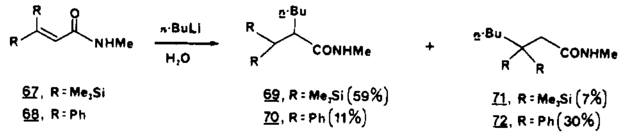


64

65 (E = H, CO_2, etc.)

66

A remarkable demonstration of the formation of an unexpected product in a possible CIPE process has been reported recently by Klumpp[34] for the reactions of *n*-butyllithium with the secondary amides 67 and 68.



67, R = Me_3Si
68, R = Ph

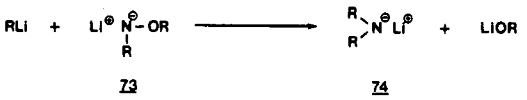
69, R = Me_3Si (59%)
70, R = Ph (11%)

71, R = Me_3Si (7%)
72, R = Ph (30%)

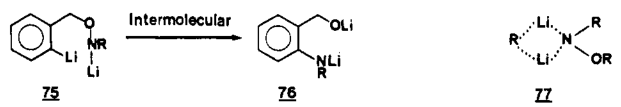
The products 69 and 70 are the result of an "anti-Michael" reaction. Presumably, the reaction is promoted by formation of a complex between the organolithium and the amide group, albeit with product stabilization provided by β-substituents. The expected products 71 and 72 are also obtained from the ene-amides but the anti-Michael pathway is dominant with ynamides. In more recent work, Klump has suggested a similar "anti-Michael" reaction may be a single-electron process.[34c] A complex could, of course, play a critical role in a variety of mechanisms. In the case of an SET process, the location of the radical at the time of its formation within a solvent cage could be critical in determining reaction regiochemistry.

Displacements under Complex Induced Proximity Effects

It has recently been recognized that a CIPE process can promote displacement reactions which would unlikely be based on conventional considerations. The reactions of lithium alkoxyamides, 73 with organolithium reagents to give lithium amides 74, provides a useful amination of organolithium reagents.[35] The key step, formal attack by an anionic carbon atom on an anionic nitrogen, would appear to involve a prohibitive charge–charge repulsion. The reaction has been shown to proceed in an intermolecular mode for the conversion of 75 to 76, a result which is interpreted to favor an S_N2 reaction in a complex represented as 77.[36] The notable feature of 77, which is modeled after structures of aggregated organolithium species, is that the lithium atoms bring the formally negative carbon and nitrogen into juxtaposition for addition of the LUMO of the formal carbanion to the HOMO of the nitrogen–oxygen bond. Theoretical analysis provides agreement that the lithium ions are critical to the process although there is some disagreement over the geometry of the species.[37]


$$RLi + Li^{\oplus}\overset{\ominus}{N}(R)\text{-}OR \longrightarrow R_2N^{\ominus}Li^{\oplus} + LiOR$$
73

74

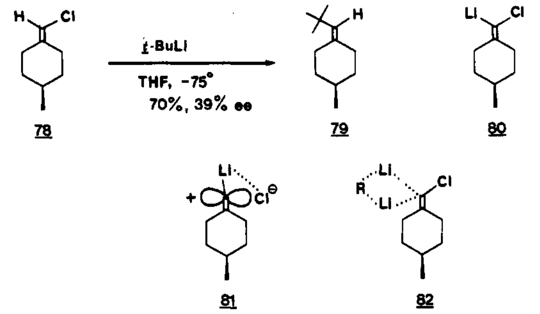


75

76

77

Walborsky[38] has reported a novel reaction wherein a vinyl chloride 78 is displaced with inversion by *tert*-butyllithium to give 79. The mechanism has been suggested to involve initial deprotonation to give 80 which reacts as a carbenoid in a subsequent reaction in which the lithium provides metal assistance for heterolytic bond cleavage of the halide, a process involving the intermediate 81. A CIPE alternative would have the lithium of 80 as part of an aggregate with *tert*-butyllithium which brings the displacing group into a position to add to the σ* orbital of the carbon chlorine bond, shown as 82. The possibilities may not be exclusive; depending on the size and geometry of the aggregate, both factors could be involved in the transition state of the displacement.



78

79

80

81

82

Dilithiations Mediated by Complexing Effects

The dilithiations which provide 83, 84, and 85 may also be considered examples of CIPE processes.[39]

---

[31] Crandall, J. K.; Clark, A. C. *J. Org. Chem.* **1972**, *37*, 4236. Richey, H. G., Jr; Heyn, A. S.; Erickson, W. F. *Ibid.* **1983**, *48*, 3821.

[32] Felkin, H.; Swierczewski, G.; Tambute, A. *Tetrahedron Lett.* **1969**, 707.

[33] (a) Oppolozer, W.; Pitteloud, R.; Strauss, H. R. *J. Am. Chem. Soc.* **1982**, *106*, 6476. Oppolozer, W.; Heland, R. P. *Ibid*, 6478. (b) The reaction may occur with allyllithium reagents as well: Edwards, J. E.; McQuillin, W. H. *J. Chem. Soc., Chem. Comm.* **1977**, 838.

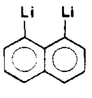
[34] (a) Klumpp, G. W.; Mierop, A. J. C.; Vrielink, J. J.; Brugman, A.; Schakel, M. *J. Am. Chem. Soc.* **1985**, *107*, 6740. For cases of normal Michael additions to secondary amides see: (b) Mpango, G. B.; Mahalanabis, K. K.; Mahadavi-Damghani, Z.; Snieckus, V. *Tetrahedron Lett.* **1986**, *21*, 4823. (c) Kruthof, K. J. H.; Mateboer, A.; Schakel, M.; Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 63.

[35] Kokko, B. J.; Beak, P. *Tetrahedron Lett.* **1983**, 561, and references cited therein.

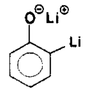
[36] Beak, P.; Basha, A.; Kokko, B. *J. Am. Chem. Soc.* **1984**, *106*, 1511.

[37] Boche, G. *J. Chem. Soc., Chem. Comm.* **1984**, 1591. McKee, M. *J. Am. Chem. Soc.* **1985**, *107*, 859. Armstrong, D. R.; Smith, R.; Walker, G. T. *J. Chem. Soc., Chem. Comm.* **1985**, 789.

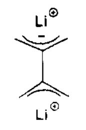
[38] Duraisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1984**, *106*, 5035.



83



84

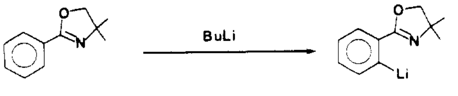


85

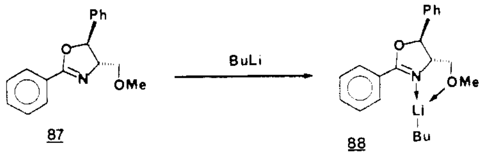
Conventionally it would be expected that the first lithiation would deactivate the system towards further lithiation. Although the second lithiations are difficult, the fact they do proceed may indicate that the first metalation provides a lithium species which acts to direct the second deprotonation in an aggregated species.

Suppression of Reactions under Complex Induced Proximity Effects

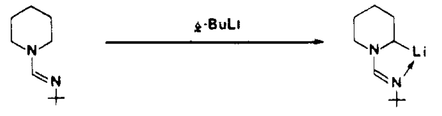
An interesting consequence of complexation can be an apparent halt to an otherwise expected reaction due to formation of a complex in which the lithium base is positioned inappropriately for reaction. Two examples of suppressed lithiations from our laboratory illustrate the point. Metalation of phenyl oxazolines has been shown by Gschwend and Meyers[3a] to be a facile process furnishing the lithiated species 86. However when the methoxy-substituted phenyloxazoline 87 is treated with butyllithium, no metalation occurs under a wide variety of forcing conditions. It is suggested that the lithium base is complexed, as shown in 88, in a manner which holds the base away from the proton to be removed.[40] Another case of complex interference is found in the piperidine formamidines 89 and 91.[41] In the former, metalation proceeds readily to give the lithiated piperidine 90, whereas in the alkoxy substituted formamidine, 91 the lithium base, via coordination to give 92, is considered to be locked in a position too remote for metalation, and only addition to the $C{=}N$ link is observed.



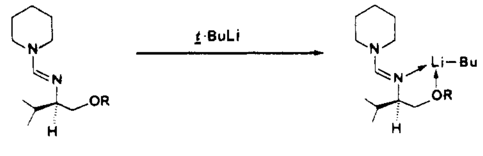
86



87 88



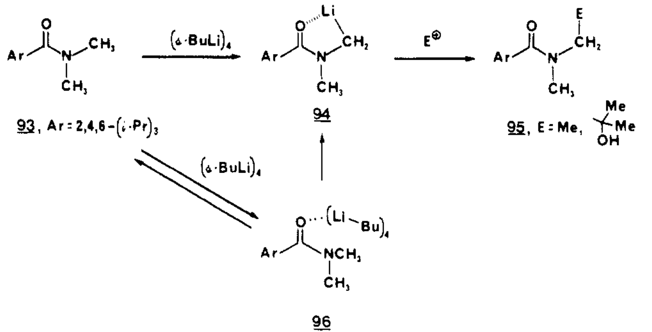
89 90



91 92

Evidence for Complex Induced Proximity Effects

However appealing the hypothesis of a complex-induced proximity effect may be it must be recognized as a convenient qualitative rationale in most cases. Indeed the demonstrated complexity of reactions of organolithium species suggests caution for claims of understanding of the details of these reaction pathways.[4,42]



96

In order to illustrate the point we will discuss the lithiation of the amide 93 which occurs adjacent to the amide nitrogen. The α' lithiated species 94 is considered to be formed by loss of a proton which is orthogonal to the amide π system and syn to the carbonyl oxygen. Evidence for these assignments is provided by the structures of the products 95 in systems with restricted rotation and the assumption that lithiation and trapping proceed with retention.[43] An investigation of the course of this reaction by a stopped-flow infrared technique reveals the presence of an amide lithium complex, assigned as 96, in which the organolithium base is brought into the vicinity of the syn α' proton.[44] Calculations of the energy of 94 suggest a net stabilization of about 25 kcal/mol relative to an α-lithio amine. Two-thirds of this value is due to dipole stabilization and one-third to bonding by the lithium.[45] Such calculations are, of course, for the gas phase, and while they do reveal fundamental effects, it is not clear how they apply to solution or to the transition state leading to 94. It was also found,[44b] however, that solvent polarity plays a significant role in the equilibrium concentration of the lithium complex in analogous formamidines, while certain solvents are not compatible with this process.[44c] Moreover, it is not yet established that 96, although clearly present in the reacting system, is on the pathway between 93 and 94. The possibility

---

(39) Boche, G.; Decker, G.; Etzrodt, H.; Mahdi, W.; Kos, A. J.; Schleyer, P. v. R. *J. Chem. Soc., Chem. Comm.* **1984**, 1483. Posner, G. H.; Canella, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 2571; Bates, R. B.; Gordan, B., III; Highsmith, J. H.; White, J. J. *J. Org. Chem.* **1984**, *49*, 298.

(40) Meyers, A. I.; Hanagan, M. A.; Trefonas, L. M.; Baker, R. J. *Tetrahedron* **1983**, *39*, 1991.

(41) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *106*, 7974.

(42) Solid state and solution structures, which provide convincing evidence for complexation in ground states, can be extrapolated to effects in reactive species as strong but circumstantial support for mechanistic hypothesis. For a recent case, see: Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *98*, 1373.

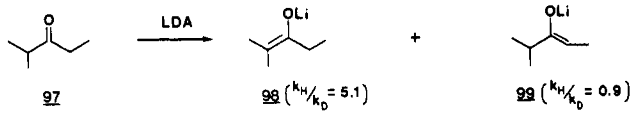
(43) Wykypiel, W.; Lohmann, J.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 1337; Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010, and references cited therein.

(44) (a) Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080. (b) Similar conclusions were drawn for α-lithio formamidines: Meyers, A. I.; Fuentes, L. M.; Rieker, W. F. *J. Am. Chem. Soc.* **1983**, *105*, 2082. (c) Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1984**, *49*, 209.

(45) Rondan, N. G.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Org. Chem.* **1981**, *46*, 4316.

that reactions occur via small amounts of undetected species is well precedented, and more detailed studies of possible CIPE reactions are needed before the suggested mechanisms can be considered definitive.

It should also be noted also that complexes involving lithium may play a major role in reactions for which classical resonance and inductive effects have been considered dominant. For example, Saunders has observed dramatically different isotope effects for two different sites in the kinetic enolization of 2-methyl-3-pentanone **97** by lithium diisopropylamide. Lithiation at the 2-position (**98**) has a k_H/k_D of 5.1 while substitution at the 4-position (**99**) shows a k_H/k_D of 0.9. Saunders[46] suggests that isomeric lithium complexes are involved. The normal isotope effect for the tertiary hydrogen results when deprotonation of the *syn*-isopropylcarbonyllithium complex is slow relative to reversal of complexation by lithium syn to the isopropyl. The negligible isotope effect for the secondary hydrogen reflects fast deprotonation relative to slow reversal of the complexation for the species with the lithium syn to the ethyl group. As Saunders notes, this proposal is reasonable on steric and electronic grounds. Once again, an unexpected result is understood by considering a complex-induced proximity effect.[47]



97 98 (k_H/k_D = 5.1) 99 (k_H/k_D = 0.9)

Summary

In this Account we have drawn attention to the use of the complex-induced proximity effect (CIPE) as a rationale for a number of novel reactions of organolithium compounds. The importance of such complexation has been recognized for some time (vide supra), but recent work suggests that proximity in a transition state related to the initial complex can be dominant over classical effects in determining the course of a reaction. CIPE processes are notable in the formation and reactions of a variety of carbanionic synthetic equivalents, ranging from α-lithioamines, allyl anions, and electrophilic nitrogen to enolates. The regio- and stereocontrol provided in these reactions is a matter of continuing interest. The geometry of the relevant transition states need to be probed in more detail as does the nature of the specific reactants. Detailed understanding of these reactions is at an early stage and the CIPE proposal should be a useful guide for correlating observations, devising new reactions, and designing mechanistic probes.

We are grateful to our co-workers in Urbana and Fort Collins for their continuous efforts, to the National Science Foundation and the National Institutes of Health for support, and to Professor G. W. Klumpp for providing information from his laboratories prior to publication and to Professor Victor Snieckus for comments on the manuscript.

---

(46) Miller, D. J.; Saunders, W. H., Jr. *J. Org. Chem.* 1982, *47*, 5039.

(47) *Note Added in Proof.* For recent cases which further illustrate CIPE processes in novel reactions see: (a) Ritter, R. H.; Cohen, T. *J. Am. Chem. Soc.* 1986, *108*, 3718. Dickman, D. A.; Meyers, A. I. *J. Am. Chem. Soc.*, in press.

Toward Functional Models of Metalloenzyme Active Sites: Analogue Reaction Systems of the Molybdenum Oxo Transferases

RICHARD H. HOLM*

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

JEREMY M. BERG*

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

Received April 21, 1986 (Revised Manuscript Received August 8, 1986)

A significant portion of research in bioinorganic chemistry has been directed toward the synthesis of representations of the metal-containing sites in metallobiomolecules.[1] These are usually intended to serve as stereochemical and electronic analogues of these sites, and have the substantial advantage of being amenable to characterization at a very high level of detail. Leading examples include Fe–S complexes as related to ferredoxin sites[2] and, more recently, binuclear μ-oxo Fe(III) species,[3] which convey many of the essential

A biographical note of Richard H. Holm has appeared several times in this journal. He rejoined the Department of Chemistry at Harvard University in 1980, where he is currently Higgins Professor of Chemistry.

Jeremy M. Berg was born in Palo Alto, California, in 1958. He received his B.S. and M.S degrees from Stanford University and his Ph.D. from Harvard University (with R. H. Holm). After 2 years as a postdoctoral fellow in the Department of Biophysics at the Johns Hopkins University School of Medicine, he moved to the Homewood campus of Johns Hopkins as an Assistant Professor of Chemistry. His interests include inorganic, structural, and biophysical chemistry.

---

(1) Ibers, J. A.; Holm, R. H. *Science* (Washington, D.C.) 1980, *209*, 223.

(2) Berg, J. M.; Holm, R. H. In *Metal Ions in Biology*; Spiro, T. G., Ed.; Interscience: New York, 1982; Vol. 4, Chapter 1.

(3) (a) Armstrong, W. H.; Spool, A.; Papaefthymiou, G. C.; Frankel, R. B.; Lippard, S. J. *J. Am. Chem. Soc.* 1984, *106*, 3653. (b) Armstrong, W. H.; Lippard, S. J. *J. Am. Chem. Soc.* 1984, *106*, 4632. (c) Spool, A.; Williams, I. D.; Lippard, S. J. *Inorg. Chem.* 1985, *24*, 2156. (d) Lippard, S. J. *Chem. Br.* 1986, *22*, 222. (e) Wieghardt, K.; Pohl, K.; Gebert, W. *Angew. Chem., Int. Ed. Engl.* 1983, *22*, 727. (f) Chaudhuri, P.; Wieghardt, K.; Nuber, B.; Weiss, J. *Ibid.* 1985, *24*, 778.

0001-4842/86/0119-0363$01.50/0