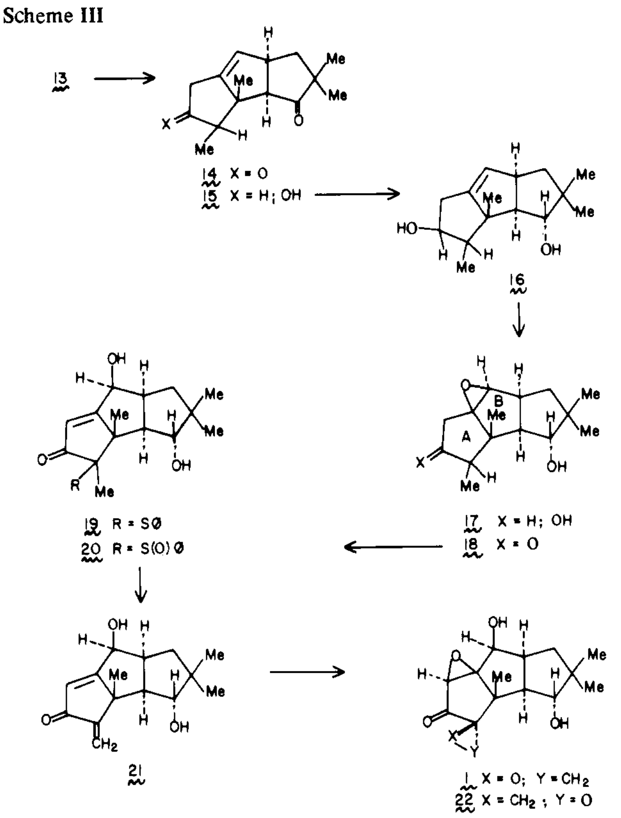
Scheme III



afforded (70%) **14**^{13,22} which gave, after reduction with 3 equiv of Dibah (THF, −78 °C, 2 h), the homoallylic alcohol epimers **15**^{24} in 85% yield. The latter, upon further reduction (Li, NH_3, and methanol) affords quantitatively **16**,^{24} bearing the more stable α alcohol in the A ring. Epoxidation of **16** (MCPBA, methylene chloride, room temperature, 10 min) clearly provides **17**.^{24} *The desired β sense of this epoxidation could be predicted with confidence since the alternate and undesired α mode would result in an energetically unacceptable trans fusion of the A and B rings.*

Selective oxidation of the more accessible alcohol according to Corey and Suggs^{25} affords **18**.^{13,24} Treatment of **18** with (4 mmol, i.e., 1.3 equiv) of lithium diisopropylamide from −30 → 0 °C, followed by quenching at 0 °C with phenylthiophenylsulfonate,^{26} affords **19**^{13} in 40% yield. This key transformation was shown to first proceed through β elimination of the epoxide. This is then followed by in situ enolization of the enone dialkoxide in the α' sense.^{27} In this way, no protecting groups are employed in the entire synthesis. Oxidation of **19** (MCPBA, methylene chloride, −78 °C) gave **20** which suffers smooth elimination (ethyl acetate, reflux, 30 min)^{27} to afford **21**.^{13} Finally, treatment of **21** with alkaline hydrogen peroxide affords *dl*-coriolin (**1**), along with its spiroepoxide epimer **22**^{13a} in an ~7:5 ratio. These were readily separated by preparative LC to provide *dl*-coriolin, mp 151–154 °C, whose chromatographic mobility and infrared and NMR (600 MHz) spectra were identical with those of a specimen of natural coriolin kindly furnished by Drs. Umezawa and Takita.

Experiments addressed to improving the yields of this 19-step total synthesis, attainment of stereospecificity in the creation of the spiroexpoxide, and suitable modifications to embrace several active coriolin congeners are well in progress and their outcome will be disclosed in due course.

Acknowledgment. This research was supported by PHS Grant CA-12107-15 and by a grant from the Merck Co. An NRC Fellowship to R.Z. is gratefully acknowledged. NMR measurements at 600 MHz were obtained on facilities housed at Mellon Institute and supported by RR 00292-14 for the MPC (Mellon-Pitt-Carnegie) Corp. We also thank Professors H. Umezawa and T. Takita of the Institute of Microbial Chemistry (Tokyo) for a sample of coriolin.

References and Notes

(1) For an excellent compilation of these and related sesquiterpenes see: Little, R. D.; Bukhari, A.; Venegas, M. G. *Tetrahedron Lett.* **1979**, 305.
(2) For a compilation of pertinent references including citations to the biological literature see: Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1979**, *101*, 7129.
(3) Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Tetrahedron Lett.* **1971** 1829. Lansbury, P. T.; Nazareno, N. *Ibid.* **1971**, 1833.
(4) Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Tetrahedron Lett.* **1972**, 2053.
(5) Hashimoto, H.; Tsuzuki, T.; Sakan, F.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1974**, 3745.
(6) Trost, B. M.; Shuey, C. D.; DiNinno, F., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 1284.
(7) For pertinent structure and stereochemical information on coriolin see: (a) Takahashi, S.; Naganawa, H.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Tetrahedron Lett.* **1971**, 1955. (b) Nakamura, H.; Takita, T.; Umezawa, H.; Kunishima, M.; Nakayama, Y.; Iitaka, Y. *J. Antibiot.* **1974**, *27*, 301.
(8) Ishizaka, M.; Inuma, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1972**, *25*, 320.
(9) Umezawa, H.; Kumimoto, T. *Biochem. Biophys. Acta* **1973**, *318*, 78.
(10) Tatsuta, K.; Akimoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 6116.
(11) The preparation of the diethoxy ketal methyl ester version of **2**, for another purpose, had been described by J. Quick, Thesis, University of Pittsburgh, 1973.
(12) Agosta, W. C.; Smith, A. B., III *J. Am. Chem. Soc.* **1971**, *93*, 5513.
(13) (a) The structure of this compound is in accord with its infrared, NMR, and (b) mass spectra.
(14) In fact several Michael reactions to enedione **7** resulted, exclusively, in angular entry of nucleophile: M. Kahn, unpublished results.
(15) (a) Mock, G. A.; Holmes, A. B.; Raphael, R. A. *Tetrahedron Lett.* **1977**, 4539. (b) Danishefsky, S.; Yan, C. F. *Synth. Commun.* **1978**, *8*, No. 4, 211.
(16) The stereochemistry of the secondary methyl group can not be rigorously assigned.
(17) The issue of the directionality of Diels-Alder reactions of enedione **5** with various dienes has been studied in some detail. The results will be discussed in a separate publication.
(18) (a) Reich, H. J.; Renga, J.; Reich, I. L. *J. Am. Chem. Soc.* **1973**, *95*, 5813. (b) Sharpless, K. B.; Lauer, R.; Teranishi, A. Y. *Ibid.* **1973**, *95*, 6137. (c) Reich, H. J.; Renga, J. M.; Reich, I. L. *Ibid.* **1975**, *97*, 5434.
(19) Although the reaction is regiospecific as shown, there appears to be produced a 9:1 ratio of epimers in this addition. These are carried on together.
(20) The intermediates in this degradative sequence have not been characterized.
(21) Stork, G.; Clarke, F. H., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 3114.
(22) This reaction results in epimerization of the secondary methyl group to varying extents. The two epimers are not separated for subsequent reactions.
(23) Ringold, J.; Malhotra, S. K. *Tetrahedron Lett.* **1962**, 669.
(24) Three epimers **15a–c** in an isolated yield ratio of 55:20:10 were obtained in pure form from this reduction. Each was carried forth separately in the sequence shown. The secondary alcohol epimers **15a** and **15c** converge at the stage of compound **18a**. Epimer **15b** leads to compound **18b**. Epimers **18a** and **18b** converge at sulfide **19** of undetermined configuration at the thiophenyl center. We now believe that the sequence from **15** → **19** could be carried out on the mixture. However, this has not been fully demonstrated.
(25) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(26) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405.
(27) Lee, R. A.; McAndrews, C.; Patel, K. M.; Reusch, W. *Tetrahedron Lett.* **1973**, 965.
(28) (a) Address correspondence to the Department of Chemistry, Yale University, New Haven, Conn. 06520; (b) National Research Council (Canada) Fellow.

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Reactions of Arc Generated Carbon Atoms with Benzene

Sir:

The reaction of atomic carbon with benzene is of interest in that it provides a potential entry onto the interesting C_7H_6 energy surface. Two possible pathways for this reaction are C–H insertion to generate phenylcarbene (**1**) and addition to

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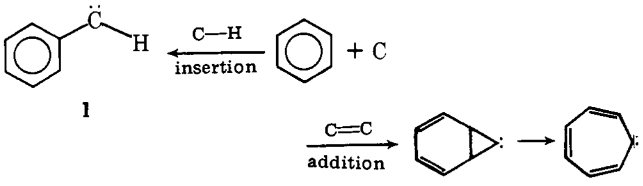
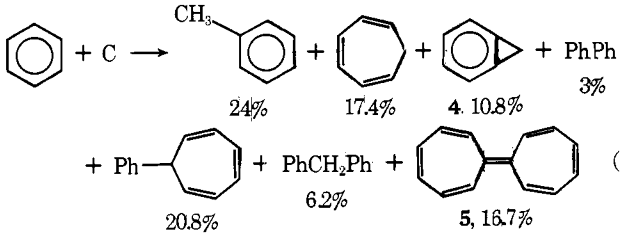
the double bond to produce the novel norcaradienylidene (**2**), which may open to cycloheptatrienylidene (**3**) [2]



Previous studies of this reaction have generally employed nucleogenic carbon-14[2] or carbon-11[3] atoms produced under energetic conditions, or high energy carbon-14 ions which are neutralized prior to reaction.[4] To investigate this reaction under conditions which may be less energetic, we have used the method developed by Skell and co-workers in which atomic carbon is generated in a carbon arc and reacted in the condensed phase at −196 °C.[5]

The reaction of arc generated carbon with benzene yields the products shown in eq 1.[6] An examination of eq 1 reveals

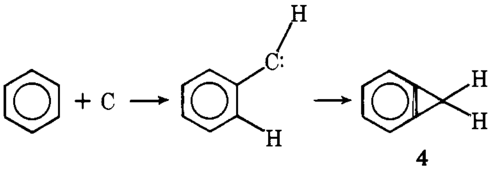


(1)

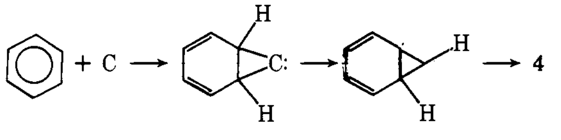
two interesting compounds, benzocyclopropene (**4**) and heptafulvalene (**5**), which have not been previously identified in this reaction.

The heptafulvalene undoubtably results from the dimerization of cycloheptatrienylidene (**3**)[8] and is the first definitive evidence that this carbene is an intermediate in the reaction of carbon with benzene. The phenylcycloheptatriene and diphenylmethane, which have been reported previously, are most likely products of the reaction of phenylcarbene (**1**) with benzene. This reaction has been observed when phenylcarbene is generated by conventional methods.[9]

An interesting C_7H_6 product of this reaction is benzocyclopropene (**4**). To generate **4**, two carbon–carbon bonds and two carbon–hydrogen bonds must be formed. Two limiting mechanistic possibilities are presented in eq 2 and 3. The



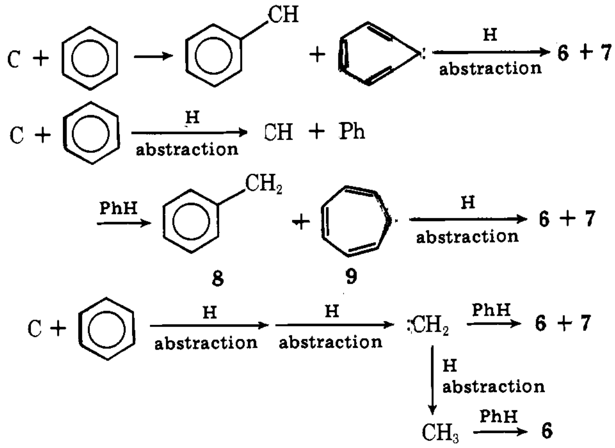
(2)



(3)

process in eq 2 involving two consecutive C–H insertions may seem unattractive as **1**, generated by conventional methods, does not undergo intramolecular C–H insertion to generate **4**. However, production of **1** by a C H insertion is exothermic by over 100 kcal/mol and it is possible that a second C–H insertion occurs before the ground-state geometry of **1** is reached. In other words, a second C–H insertion may begin before carbene **1** is fully formed and **4** may be generated without ever going through carbene **1** in its ground-state geometry. Equation 3 depicts a process in which formation of the two C–C bonds is followed by the formation of the two C–H bonds. The completely concerted alternative to eq 2 and 3 is generation of **4** by two simultaneous C–H insertions; it seems probable that the mechanism of the formation of **4** lies somewhere between that depicted in eq 2 and 3 and this concerted process.

Toluene (**6**) and cycloheptatriene (**7**), products that are always observed in the reaction of carbon with benzene,[2,3,10] are also generated in the present study. Possible mechanisms for the formation of **6** and **7**, which are the result of the addition of two hydrogens to the carbon plus benzene system, are shown in eq 4–6. The mechanism in eq 4 does not appear likely as



(4)

(5)

(6)

hydrogen abstractions by carbene **1** to generate toluene[11] and by **3** to produce cycloheptatriene[8] have not been observed. Also, the hydrogen abstractions by benzyl radical (**8**) and cycloheptatrienyl radical (**9**) from benzene should be thermodynamically unfavorable. The mechanism in eq 5 again suffers from the fact that radicals **8** and **9** are required to perform thermodynamically unfavorable hydrogen abstractions. However, a series of hydrogen abstractions by atomic carbon to generate methylene is thermodynamically attractive and would provide a convenient rationale for the formation of **6** and **7** by reaction of methylene with benzene, a process with ample analogy.[12] A further hydrogen abstraction by methylene generates methyl radicals which also may react with benzene to produce toluene.[13] This formation of toluene by methylation of benzene rationalizes the fact that more toluene than cycloheptatriene is formed, a situation that would not be expected if **6** and **7** were formed solely by the addition of methylene to benzene.[12] Lemmon, in his studies of the reaction of ^{14}C with benzene, has reached the conclusion that **7** is the result of a methylene reaction[14] while **6** arises by the reaction of both methylene and methyl radicals with benzene.[15]

To establish if hydrogen abstractions are stepwise, we have reacted carbon with a 1:1 mixture of benzene and benzene-d_6. Table I gives the ratio of several deuterated toluenes and cycloheptatrienes obtained from this reaction. It can be seen that the cycloheptatriene-d_8:-d_7:-d_6 ratio is consistent with a series of stepwise abstractions by carbon to generate methylene which reacts with benzene to give **7**. The toluene, however, contains appreciable amounts of the d_5 compound and shows an isotope ratio that is qualitatively consistent with formation of toluene by methylation and methylene insertion. Table I also gives the ratio of toluene-d_8:-d_7:-d_6:-d_5 when benzene-d_6 is reacted with carbon atoms in the presence of an equimolar amount of propane. Since the hydrogens on propane are more readily abstracted than those on benzene, there is a larger amount of toluene-d_5 than is formed in the 1:1 benzene and benzene-d_6 case.

The multiplicity of the methylene and its precursors is not certain at this time. However, the fact that methylene is formed and partially reacts by hydrogen abstractions raises the possibility that it is in the triplet state. In this connection, it is interesting to note that reaction of carbon with benzene and propane does not produce detectable amounts of cyclohepta-

Table I. Partial Isotopic Composition of Toluenes and Cycloheptatrienes Produced in the Reaction of Carbon with Benzene[a]

deuterated species	percent of deuterated species in product		
	cycloheptatriene	toluene	toluene[b]
$C_7D_5H_3$	0 ± 4.1	14.1 ± 8.0	43.3 ± 1.6
$C_7D_6H_2$	25.3 ± 6.2	31.1 ± 5.0	30.6 ± 1.4
C_7D_7H	49.5 ± 3.5	36.9 ± 6.1	19.1 ± 1.0
C_7D_8	25.2 ± 3.7	17.9 ± 4.9	7.0 ± 0.8

[a] Only toluenes and cycloheptatrienes containing five or more deuteriums are reported; quantitative determination of the others was not possible owing to the presence of some of the benzocyclopropenes which were incompletely separated by GC in this experiment. [b] Toluene from reaction of carbon with benzene-d_6 and an equimolar amount of propane.

triene. This observation may be rationalized if one assumes that the reactant is triplet methylene which prefers to abstract hydrogen from propane rather than react with benzene.

The fact that biphenyl is formed is indicative of hydrogen abstractions from benzene to yield phenyl radicals. An analysis of the biphenyl produced in the reaction of carbon with benzene and benzene-d_6 reveals biphenyl-d_0, -d_5, and -d_{10} in a ratio of 1:2:1. Similarly, an analysis of phenylcycloheptatriene reveals an isotope distribution of d_0:d_6:d_{12} of 1:2:1, the ratio expected from the reaction of phenyl carbene with benzene.

In summary, atomic carbon reacts with benzene to produce both carbenes **1** and **3** as primary products. An additional C_7H_6 product is benzocyclopropene which may result from rearrangement of energetic **1** or **2** or by a direct addition of carbon to benzene. A competing process in the reaction of carbon with benzene is a series of hydrogen abstractions to generate methylene and methyl radicals which may react with benzene to produce cycloheptatriene and toluene.

Acknowledgments. We are grateful to Professor W. M. Jones for a generous gift of heptafulvalene. We thank the National Science Foundation for support of this work under Grant CHE 77-24624.

References and Notes

(1) For recent reviews of the Chemistry of carbenes **1** and **3** see: (a) Jones, W. M.; Brinker, U. H. In "Pericyclic Reactions", Marshand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. I, Chapter 3, pp 109–198. (b) Wentrup, C. *Fortschr. Chem. Forsch.* **1976,** *62*, 173.

(2) Visser, R.; Redvanly, C. R.; Sixma, F. L. J.; Wolf, A. P. *Recl. Trav. Chim. Pays-Bas*, **1961,** *80*, 533.

(3) (a) Williams, R. L.; Voight, A. F. *J. Phys. Chem.* **1969,** *73*, 2538. (b) Rose, T.; MacKay, C.; Wolfgang, R. *J. Am. Chem. Soc.* **1967,** *89*, 1529.

(4) Lemmon, R. M. *Acc. Chem. Res.* **1973,** *6*, 65, and references cited therein.

(5) Skell, P. S.; Havel, J. J.; McGlinchey, M. J. *Acc. Chem. Res.* **1973,** *6*, 97, and references cited therein.

(6) With the exception of **5**, products were identified by GC–mass spectrometry. Mass spectra were compared with those of authentic samples. The identity of **4** was further confirmed by its silver ion catalyzed reaction with dimethylamine to yield benzyldimethylamine.[7] The heptafulvalene was identified by TLC and by a comparison of its NMR spectrum with that of an authentic sample. Atomic carbon appears to be rather unreactive toward benzene. The total yields in eq 1 are only ~1% based on the C_1 vaporized. Most of the vaporized carbon appears as graphite.

(7) Billups, W. E. *Acc. Chem. Res.* **1978,** *11*, 245.

(8) Jones, W. M.; Ennis, C. L. *J. Am. Chem. Soc.* **1969,** *91*, 6391. A referee has raised the interesting possibility that the heptafulvalene results from reaction of C_2 with two molecules of benzene followed by ring opening of the two norcaradienes. While this possibility cannot be ruled out, the literature contains no reports of the addition of C_2 to a double bond. Carbon atoms, on the other hand, often add to double bands and such a reaction is expected in the present case.

(9) (a) Gutsche, C. D.; Bachman, G. L.; Coffey, R. S. *Tetrahedron* **1962,** *18*, 617. (b) Shen, K.; McEwen, W. E.; Wolf, A. P. *Tetrahedron Lett.* **1969,** 827. (c) Nozaki, H.; Noyori, R.; Sisido, K. *Tetrahedron* **1964,** *20*, 1125.

(10) Sprung, J. L.; Winstein, S.; Libby W. F. *J. Am. Chem. Soc.* **1965,** *87*, 1812.

(11) Moss, R. A.; Dolling, U. *J. Am. Chem. Soc.* **1971,** *93*, 954.

(12) (a) Doering, W. von E.; Knox, L. H. *J. Am. Chem. Soc.* **1950,** *72*, 2305. (b) Lemmon, R. M.; Strohmeier, W. *Ibid.* **1959,** *81*, 106. (c) Russell G. A., Hendry, D. G. *J. Org. Chem.* **1963,** *28*, 1933.

(13) Formation of toluene in the reaction of methyl radicals with benzene has been reported: (a) Eliel, E. L.; Rabindran, K.; Wilen, S. H. *J. Org. Chem.* **1957,** *22*, 859. (b) Corbett, G. E.; Williams, G. H. *J. Chem. Soc.* **1964,** 3437.

(14) Erwin, W. R.; Gordon, B. E.; Lemmon, R. M. *J. Phys. Chem.* **1976,** *80*, 1852.

(15) Erwin, W. R.; Spicer, L. D.; Lemmon, R. M. *J. Phys. Chem.* **1978,** *82*, 654.

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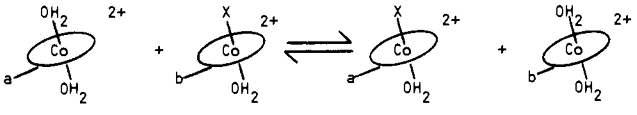
Transition-State Binding Energies and the Nature of the Reaction Coordinate in Inner-Sphere Electron-Transfer Reactions: A Unified Approach to Methyl- and Halogen-Bridged Reactions[1]

Sir:

While cobalt mediated methylations are of considerable biological significance,[2] they present many puzzling mechanistic features. This has even been the case for methyl-transfer reactions between transition metals in aqueous solution.[3,4] These reactions are best described as inner-sphere electron-transfer reactions; yet they are orders of magnitude slower than the halide or pseudohalide analogues. The common mechanistic description of halide and methyl-bridged electron-transfer reactions has been particularly challenging since the coordinated methyl group lacks a nonbonding pair of electrons believed necessary for bonding to the reducing metal in the precursor complex.[5]

Much of the advance in understanding of outer-sphere electron-transfer reactions can be attributed to the systematic separation of "intrinsic", $\Delta G^{\ddagger}{}_{i}$, from free-energy, $\Delta G°$, dependent components of the reactivity.[5-8] A similar level of understanding of inner-sphere electron-transfer reactions has been difficult to achieve in large part because these factors are much more difficult to separate. However, very recent work[9] has shown that intrinsic factors can be systematically examined for inner-sphere electron-transfer reactions in which the metal centers are coordinated to macrocyclic ligands. In such cases an inner sphere self-exchange reaction (a = b) can be investigated (eq 1). Although the inner-sphere self-exchange rate constants are $\sim 10^7$ times larger (X = Cl, Br, or N_3) than the corresponding outer-sphere self-exchange rate constant (i.e., $\Delta G_i(\text{IS}) \ll \Delta G_i(\text{OS})$), the halide and pseudohalide-bridged reactions still exhibit sensitivity to variations in structural parameters.[9]



(1)

We have now used reactions of macrocyclic cobalt complexes (**1**) to isolate the intrinsic reactivity factors for methyl-bridged electron-transfer reactions.[10] We find that for these reactions $\Delta G_i(\text{IS, X} = \text{CH}_3) \gg \Delta G_i(\text{IS, X} = \text{Cl, Br, or N}_3)$; see Table I. The ~$10^6$-fold slower methyl- than halide-bridged self-exchange reactions are not easily rationalized in terms of the simple reorganizational argument presented previously.[9a,11,12]

The reaction coordinate in the inner sphere electron-transfer reactions involves bond breaking and should be described by a potential energy function which takes this into account (e.g., a Morse function). This requires that the Co-X homolysis energy be a factor in the mechanistic analysis. The consideration of homolysis energies in addition to the usual kinetic parameters permits a unified description of methyl- and halide-bridged electron-transfer reactions.

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