Pergamon

Tetrahedron Letters 40 (1999) 4297–4300

TETRAHEDRON
LETTERS

A Proposal for (slight) Modification of the Hughes-Ingold Mechanistic Descriptors for Substitution Reactions

Robert E. Gawley

Department of Chemistry, University of Miami
P. O. Box 249118, Coral Gables, FL 33124-0431, USA

Received 15 March 1999; revised 13 April 1999; accepted 15 April 1999

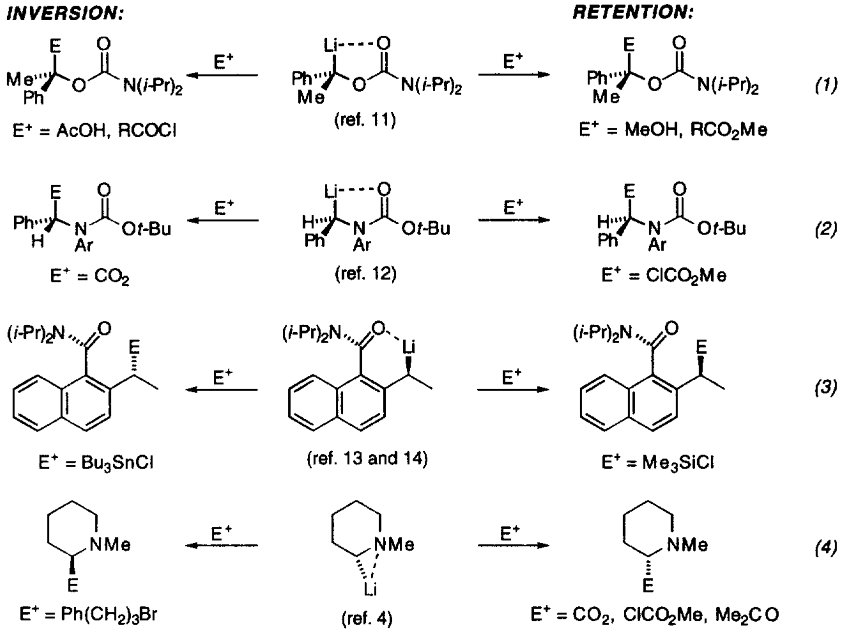
Abstract: The term "S_EAr" is proposed to represent electrophilic aromatic substitution, leaving the term "S_E2" to refer exclusively to electrophilic substitutions where a steric course is possible. To describe the steric course of an aliphatic substitution reaction, the suffixes "ret" and "inv" are proposed, referring to retention and inversion of configuration, respectively. The rationale for these proposals is discussed.

Many years ago, a series of terms were coined to describe reaction pathways, as summarized in the first and second edition of Ingold's book.[1,2] The most common descriptors for substitution reactions are S_N1 and S_N2, with a number of modifications such as $S_{RN}1$, S_N2cA, etc., being introduced later, as summarized in the latest edition of March.[3] During the course of an investigation into the steric course of electrophilic aliphatic substitutions of α-aminoorganolithiums,[4,5] it became obvious that recent advances have revealed some weaknesses in the terminology. Specifically, there is no way to specify the steric course of an aliphatic substitution. Ten years ago, an IUPAC committee proposed an alternative to Ingold's system,[6] but the new system has not been widely adopted, and it also lacks the means to specify steric course. Herein, the Ingold descriptors for nucleophilic and electrophilic substitutions are analyzed and suffixes are proposed to clarify the descriptors and extend their meaning.

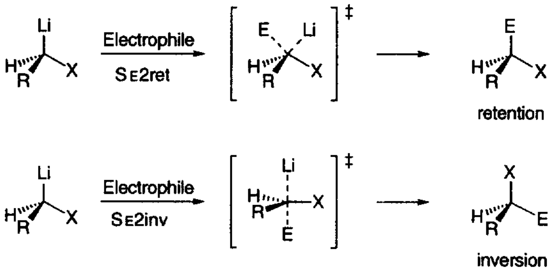
The term "S_E2", meaning bimolecular electrophilic substitution, was originally intended to include electrophilic aromatic substitution, while S_N2 reactions originally included nucleophilic aromatic substitution.[7-9] In modern usage, both S_E2 and S_N2 are restricted to aliphatic substitutions.[3] The term "S_NAr" is now commonly used for nucleophilic aromatic substitution,[10] but a similar descriptor for electrophilic aromatic substitution has not emerged. It seems obvious to coin a term analogous to S_NAr for electrophilic aromatic substitution: S_EAr.

It is appropriate, then, to formally exclude aromatic electrophilic substitution from the term "S_E2", and restrict its use to electrophilic substitutions such as electrophilic reactions of organometallics. For such substitutions, it is appropriate to include a modifier to describe the steric course (when known), since numerous stereochemical studies of electrophilic substitutions have revealed dichotomous pathways, depending only on the electrophile (for instance). Examples of several such dichotomous S_E2 reactions of configurationally stable organolithiums are shown in Eq. 1-4.[4,11-14]

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00780-7

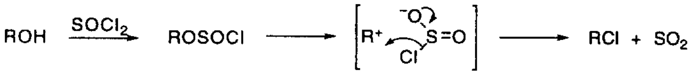


To distinguish reactions that go with inversion and retention, the suffixes "inv" and "ret" are proposed. Therefore, an aliphatic electrophilic substitution that undergoes inversion at the metal-bearing carbon would be "S_E2inv"; one that goes with retention would be "S_E2ret" (Scheme 1). Note that these suffixes could also be used to modify the IUPAC descriptors, in line with the recommendation to do so when more information needs to be included.[6]



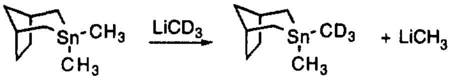
Scheme 1

Rationale, vs. alternative terms. The term S_Ei, substitution-electrophilic-internal, was introduced by analogy to the term "S_Ni";[15] both terms involve substitution reactions with retention of configuration. However, there is a further mechanistic implication in these terms: that the reagent interacts with the leaving group in some way. In nucleophilic substitutions, the classic example is the reaction of thionyl chloride with an alcohol to produce an alkyl chloride with retention (in some solvents), as shown in Equation 5.



(5)

It is possible that nucleophilic substitutions could proceed with retention of configuration by mechanisms other than S_Ni (especially at atoms other than carbon). The term S_N2ret has no mechanistic implication beyond being bimolecular and stereoretentive, so S_Ni reactions should be considered a subset of S_N2ret reactions. The tin-lithium exchange shown in Eq 6 is an S_N2 reaction that proceeds with retention of configuration at tin,[16] but not by an S_Ni mechanism. The appropriate descriptor for the reaction at tin would be S_N2ret. One might even further modify the term to indicate the atom in question: $S_N2ret(Sn)$.



(6)

$$CH_3HgBr + Hg^*Br_2 \rightleftharpoons CH_3Hg^*Br + HgBr_2 \qquad (7)$$

Reactions that have been proposed to proceed by an S_Ei mechanism include mercury exchange reactions in organomercurials, such as shown in Eq. 7.[17] Note however, that it may not be possible to distinguish between an open transitition state and a closed one (the latter is required for S_Ei).[15] According to the symmetry rules for chemical reactions,[18] both S_E2ret and S_E2inv (concerted) mechanisms are allowed (via open transition states), but the S_Ei reaction is symmetry forbidden if concerted.[19] Figure 1 shows the orbital symmetry analysis for an alkyllithium and an alkyl halide, which requires like symmetry between the HOMO of the organolithium (the carbanionic orbital) and the LUMO of the electrophile (the σ^* orbital of an alkyl halide), and that the electron flow goes from the carbanion HOMO to the electrophile LUMO. This is possible with the illustrated S_E2ret and S_E2inv transition states, but not with the S_Ei transition state.

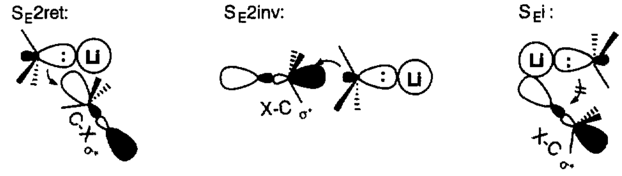
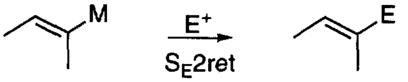


Figure 1

A stepwise S_Ei mechanism is also unlikely with an alkyl lithium and an alkyl halide for mechanistic reasons, because it requires retention of configuration at the carbon of RX. Since the S_Ni mechanism is the only S_N mechanism allowing retention at carbon, it follows that S_Ni at RX must accompany S_Ei at RLi. In other words, reaction of RX with RLi would have to give LiX plus a carbanion and a carbocation in the same solvent cage. For these reasons, the term S_E2ret is preferable to S_Ei. It is also apparent from Figure 1 that the steric requirements for S_E2inv can be rather severe, perhaps explaining why they are less common than S_E2ret reactions.

If a unimolecular reaction proceeded with a nonrandom steric course, the suffixes could be used to specify the steric course, such as S_N1inv, etc. In certain instances, the molecularity may be unknown or uncertain, whereas the steric course could still be specified as S_Nret/S_Ninv or S_Eret/S_Einv.

The terms "S_E2(retention)" and "S_E2(inversion)" have been used to designate the steric course of aliphatic and vinylic susbstitutions of organotransition metal compounds,[20] but "S_E2ret" and "S_E2inv" seem somewhat less cumbersome. They could also be used to indicate the steric course of electrophilic substitution at an sp^2 center, such as reactions of vinyl zirconium,[21] nickel,[22] silver or copper complexes,[23,24] which take place with retention of configuration (Eq 8).



(8)

"$S_E2$ret" and "$S_E2$inv" are preferable to "S_E2(front)" and "S_E2(back)" used by March,[25] since they provide a more appropriate description of the steric course, and they do not imply concertedness. Other possible descriptors of steric course were considered (*e.g.*, "R" for retention, "I" for inversion), but these seemed likely to be confusing since "R" is already a symbol of absolute configuration and the designator of a generic alkyl group, and "I" (meaning inversion) could be confused in conversation with "i" (meaning internal).

Acknowledgements. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (32984-AC1) and to the National Institutes of Health (GM 56271) for financial support. I am grateful to Professors J. Bunnett and D. Seebach for helpful suggestions and comments on these terminology proposals.

References

(1) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell University: Ithaca, NY, 1953.
(2) Ingold, C. K. *Structure and Mechanism in Organic Chemistry, 2nd Edition*; Cornell University: Ithaca, NY, 1969.
(3) March, J. *Advanced Organic Chemistry, 4th Edition*; Wiley-Interscience: New York, 1992.
(4) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763.
(5) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *submitted* **1999**.
(6) Guthrie, R. D. *Pure Appl. Chem.* **1989**, *61*, 23.
(7) Ingold, C. K. In *Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca, 1953, p 279.
(8) Ingold, C. K. In *Structure and Mechanism in Organic Chemistry*; Cornell University: Ithaca, NY, 1953, p 802.
(9) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: Amsterdam, 1968.
(10) March, J. In *Advanced Organic Chemistry, 4th Edition*; Wiley-Interscience: New York, 1992, p 641.
(11) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097.
(12) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561.
(13) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755.
(14) Clayden, J. *Synlett* **1998**, 810.
(15) Ingold, C. K. In *Structure and Mechanism in Organic Chemistry, 2nd Edition*; Cornell University: Ithaca, NY, 1969, p 563.
(16) Reich, H. J.; Borst, J. P.; Coplein, M. B.; Phillips, N. H. *J. Am. Chem. Soc.* **1992**, *114*, 6577.
(17) Charman, H. B.; Hughes, E. D.; Ingold, C. K.; Volger, H. C. *J. Chem. Soc.* **1961**, 1142.
(18) Pearson, R. G. *Acc. Chem. Res.* **1971**, *4*, 152.
(19) Slack, D. A.; Baird, M. C. *J. Am. Chem. Soc.* **1976**, *98*, 5539.
(20) Flood, T. C. In *Topics in Inorganic and Organometallic Stereochemistry*; Geoffroy, G. L., Ed.; Wiley Interscience: New York, 1981; Vol. 12, p 37.
(21) Labinger, J. A.; Hart, D. W.; Seibert III, W. E.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 3851.
(22) Dodd, D.; Johnson, M. D. *J. Organometall. Chem.* **1973**, *52*, 1.
(23) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379.
(24) Normant, J. F.; Cahiez, G.; Chuit, C.; Villieras, J. *J. Organometall. Chem.* **1974**, *77*, 269.
(25) March, J. In *Advanced Organic Chemistry, 4th Edition*; Wiley-Interscience: New York, 1992, p 569.