

## Mechanisms of reactions at non-stereogenic heteroatoms: Evaluation of reaction geometries by the endocyclic restriction test

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**Abstract.** Experimental evaluations of reaction geometries for formal nucleophilic substitutions at oxygen, nitrogen and bromine which have been carried out by the endocyclic restriction test are summarized. This information is used to distinguish between concerted, dissociative and associative mechanisms for these heteroatom transfers.

Heteroatom transfers are among the most ubiquitous reactions in chemistry. Oxidations, aminations and halogenations are widely used reactions which can involve transfer of an oxygen, a nitrogen or a halogen, from a heteroatom carrier to a heteroatom acceptor. The mechanisms which need to be considered for these transfers are concerted, associative, and dissociative processes. Distinction between alternative mechanisms can be provided by experimental information which distinguishes the arrangements of the atoms in the different possible transition structures.

### Heteroatom Transfers



Y = heteroatom eg: O, N, Br

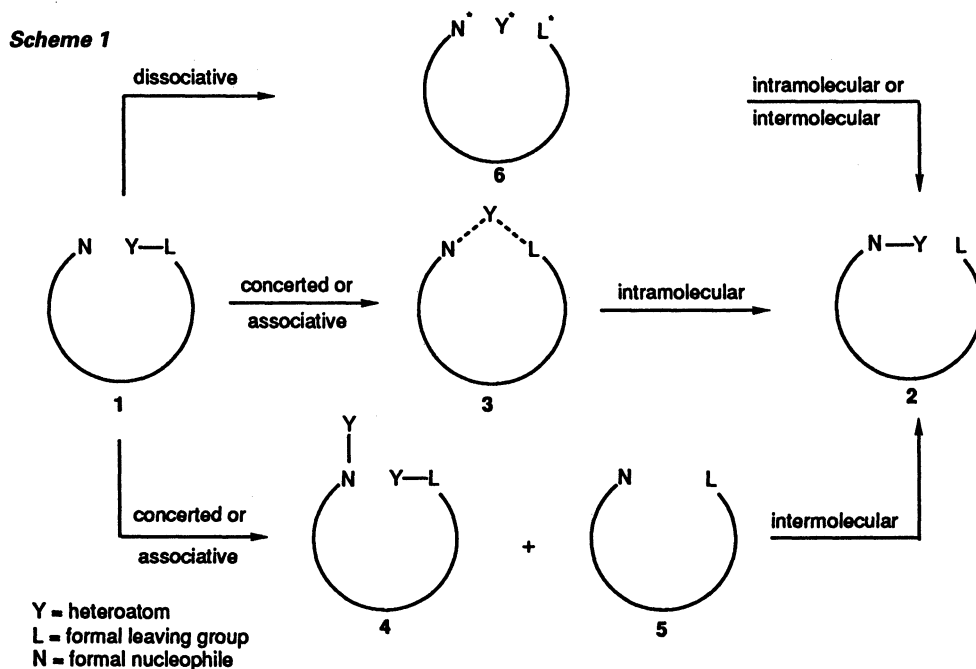
N = formal nucleophile

L = formal leaving group

In 1970 papers by Eschenmoser *et al.* and by Hogg and Vipond appeared which drew attention to endocyclic restriction of atom transfer as an approach for evaluation of reaction geometry. Eschenmoser and co-workers showed by a double labeling experiment that transfer of a methyl carbon to a carbanion was not achievable intramolecularly in a six-membered ring consistent with the need to bond attain the bond angle of  $180^\circ$  for this  $S_N2$  reaction (1). In the same year Hogg and Vipond reported that transfer of a sulfur between oxygens could not be achieved within a six-membered endocyclic ring (2). The endocyclic restriction test, as outlined in these seminal papers, provides a method for the evaluation of transition structure geometry which is independent of the stereogenicity of the atom transferred. Although the approach has been used a number of times for studying the geometry of reactions at sulfur, it has not been widely applied to other atoms. In this manuscript we will summarize our recent work using the endocyclic restriction test to provide information about the geometries of oxygen, nitrogen and bromine transfers which allows choices to be made between alternative mechanisms for these reactions (3,4,5).

The relationship of the mechanism of reaction and the endocyclic restriction test is shown in Scheme 1 for the conversion of 1 to 2 where Y is the heteroatom, L is the formal leaving group and N is the formal nucleophile for a heteroatom transfer. The critical feature is the structure of the tether linking N and L which determines the geometry of the NYL bond angle which would be allowed for an endocyclic intramolecular reaction. For a concerted or associative process in which that angle is allowed intramolecularly, the reaction should proceed in the intramolecular via transition structure 3.

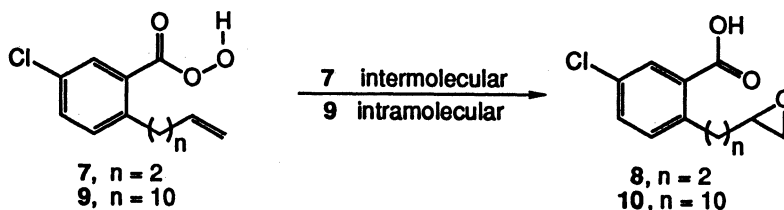
For a concerted or associative mechanism in which the NYL bond angle is not allowed endocyclically, the reaction could still proceed but would be intermolecular via 4 and 5. A dissociative mechanism involving 6 which could be either intra or intermolecular must also be considered for these reactions.



#### TRANSFERS OF OXYGEN

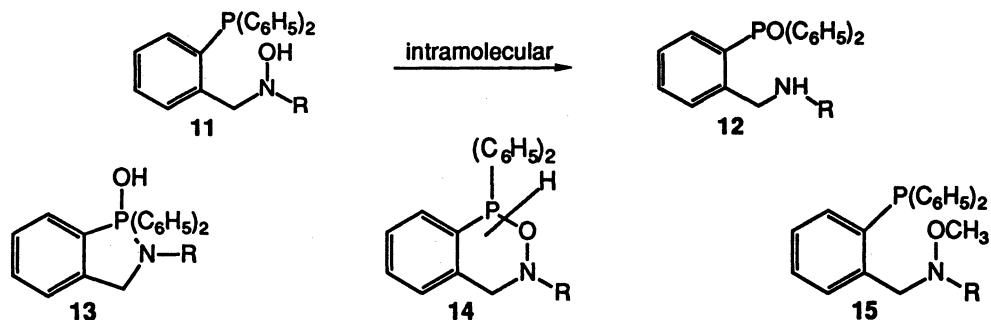
Epoxidation of an olefin by peracid is classic reaction in which oxygen is transferred from a percarboxylic acid to an olefin. The classic "butterfly" mechanism due to Bartlett requires the olefin to approach the oxygen-oxygen bond from a large bond angle (6). An alternative mechanism could proceed through a formal 1,3-dipolar cycloaddition to give a dioxolane which collapses to give the epoxide product (7). For the reaction of 7, the reaction would be expected to be intramolecular for the 2,3-dipolar cycloaddition and intermolecular for the  $S_N2$  reaction. For the reaction of 9, the reaction would be expected to be intramolecular for both mechanisms at the appropriate dilution.

The intramolecular and intermolecular modes of reaction were distinguished using a double labeling experiment in which both oxygens of the peroxy function were labeled with oxygen-18 and the isotopic compositions of the respective products determined by mass spectrometry. The experimental results show that the conversion of 7 to 8 is intermolecular and the reaction of 9 to give 10 is intramolecular (8). These results rule out the concerted cycloaddition mechanism and supports the original Bartlett proposal of an  $S_N2$  reaction at oxygen.



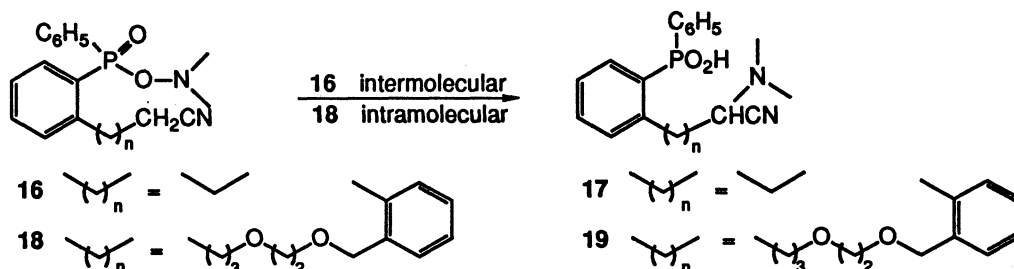
A transfer of oxygen from nitrogen to phosphorus is illustrated for the conversion of 11 to 12 (9). Possible mechanisms for this reaction include: a classic  $S_N2$  displacement by phosphorus at oxygen and a dissociative radical chain process both of which would be intermolecular; a classic  $S_N2$  substitution at nitrogen followed by return of the hydroxyl to phosphorus to give 13 which could ring open to give 12 and could be intra or intermolecular; a concerted biphillic addition to give 13 directly which would be intramolecular; or an associative process via a valence-expanded phosphorus shown as 14 which could be intramolecular. A double labeling experiment showed the reaction of 11 to give 12

to be intramolecular. The possibility that the mechanism involves **13** was discounted by the stability of the methoxyl amine **15** to the reaction conditions. Thus, the mechanism for this reaction is consistent with an associative process to give the intermediate **14** in which the oxygen can be accommodated within a six-membered ring (**10**).

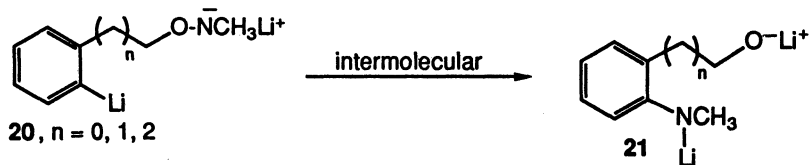


### TRANSFERS OF NITROGEN

The amination of a carbanion by transfer of a nitrogen from a hydroxyl amine derivative is illustrated for the conversion of **16** to **17** which can be initiated by reaction with base (11). The possible mechanisms for the reaction are a dissociative process involving an ion pair of a nitrenium ion and a concerted reaction involving nucleophilic substitution at nitrogen. Double-labeling studies show that for the conversion of **16** to **17** the reaction is intermolecular while for the conversion of **18** to **19** the reaction is intramolecular. The results are consistent with the concerted nucleophilic displacement at nitrogen in which the entering and leaving group are at a large bond angle. The possibility of a nitrenium ion pair which reacts selectively from side external to the leaving group has been discounted by failure of oxygen **18** to scramble in the aminating agent (**12**).



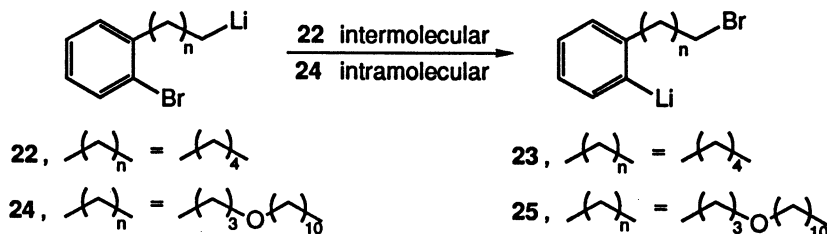
Amination by a lithium alkoxide might be expected to take a different route. Reaction via a singlet nitrene which would be expected to be intramolecular might be considered to alleviate the formal repulsion of negative charge which would appear to be involved in an  $S_N2$  reaction. An endocyclic restriction for this reaction is shown for the conversion of **20** to **21**. The organolithium reagent **20** is produced from the corresponding iodide and the product **21** is converted to the corresponding amino alcohol by protonation. The reactions of **20** to **21** are intermolecular as shown by double labeling techniques (12). Apparently this reaction is a nucleophilic displacement at nitrogen which has large bond angles for the entering and leaving groups about nitrogen. Lithium bridging in an aggregate is considered to overcome the formal repulsion of the negative charges in an  $S_N2$  transition structure.



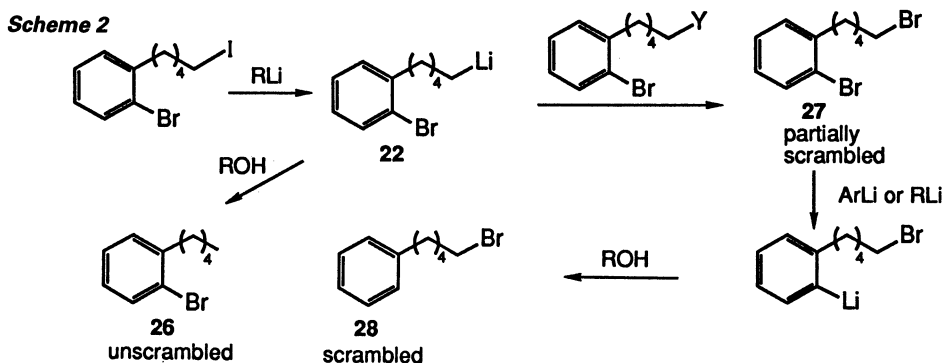
### TRANSFER OF BROMINE

The bromine-lithium exchange reaction between a primary alkyl lithium and aryl bromide is illustrated for an endocyclicly restricted case by the conversion of **22** to **23** (14). The organolithium reagents **22** and **24** are produced from the corresponding iodides and the products are converted to bromoarenes by

protonation. The mechanistic alternatives for the reaction includes a concerted four center process which would be expected to be intramolecular in a small ring, a single electron transfer dissociative bromide process which could be intramolecular or intermolecular, an associative mechanism through an ate-complex which would be intramolecular if small bond angles were allowed in the ate-complex and intermolecular if the structure was restricted to large bond angles, and a concerted classic  $S_N2$  reaction which would be intermolecular in a small ring and intramolecular in a larger ring. The results of a double labeling experiments show the reaction to be intermolecular for the conversion of **22** to **23** and intramolecular for the conversion of **24** to **25** (15).



The reaction of **22** can be rationalized as shown in Scheme 2. The isotopic contents of **26**, **27** and **28** are consistent with this sequence for the intermolecular reaction.



These results can be taken to rule out the 4-centered reaction and a single electron transfer as well as an ate-complex which would have small bond angles. In addition, a radical reaction which would involve a dissociative formation of a bromide can be ruled out by a failure of the reaction in the intermolecular case to incorporate external bromide into the product. These results are consistent with a substitution at bromine which requires large bond angles of a classic  $S_N2$  reaction or an ate complex (15).

### SUMMARY

The above results demonstrate the use of the endocyclic restriction test as a valuable tool for the determination of reaction geometries and therefore, for the evaluation of alternative mechanisms for reactions at heteroatoms. On the basis of this test, the geometries and mechanisms of heteroatoms transfers which we have investigated are consistent with the  $S_N2$  transition structures **29**. These reactions are displacement at oxygen of an oxygen by a double bond, displacement at nitrogen of an oxygen by a carbanion, and displacement at bromine of a carbon by a carbanion. In the latter case, formation of an ate-complex as an intermediate also seems quite reasonable. The transition structure geometries determined for these reactions are consistent with Frontier Orbital Theory, with VSEPR structures and with Donor-Acceptor paradigms. On the other hand, displacement at oxygen of a nitrogen by phosphorus can occur at an oblique angle consistent with an association at phosphorous.



Y = heteroatom  
N = formal nucleophile  
L = leaving group

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