

ELECTRONIC EFFECTS ON THE STEREOCHEMISTRY OF ATTACK ON TRIGONAL ATOMS IN SIX MEMBERED RINGS

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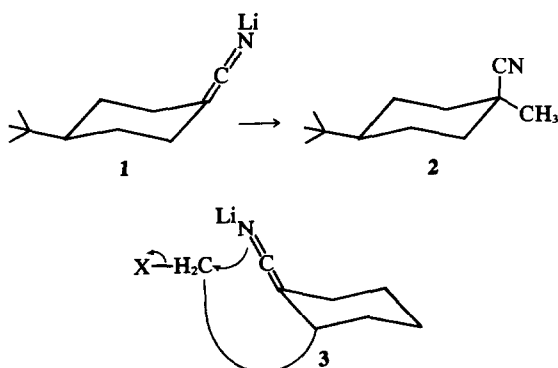
Abstract—The steric course of attack on a trigonal atom in a six-membered ring is attributed to electronic effects due to the interaction of the p-orbital of the trigonal atom with the symmetric σ orbital of the β C–C bonds. This interaction leads to a different electron density on the two faces of the plane containing the trigonal atom. Nucleophilic attack involves preferential axial approach, but electrophilic attack involves preferential equatorial approach to the ring, in the absence of steric effects. Polarization by the reagent makes the σ -p interaction stronger. These principles are used to explain addition to trigonal carbon, sulfur, and pyramidal nitrogen.

A rule has been proposed recently for the steric course of attack on exocyclic double bonds of cyclohexanones and methylenecyclohexanes. This rule¹ states that in unhindered compounds, and in the absence of polar effects, electrophiles attack from the equatorial and nucleophiles from the axial side. This steric course is attributed to electronic effects due to σ - π interaction of the double bond with the symmetric β C–C σ bond orbital, leading to an unequal electron density on the diastereotopic faces of the double bond. In particular, issue was taken with the view that the usually observed axial attack during metal hydride reductions of unhindered cyclohexanones is determined by steric hindrance to approach from the equatorial side.^{2,3} Examples of electrophilic attack from the equatorial side on exocyclic double bonds were also given.^{1,4,5}

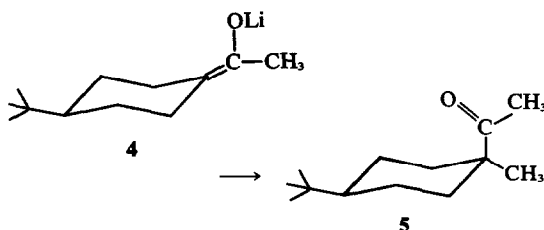
We wish to discuss further examples of known reactions on exocyclic double bonds in the light of our generalization and to extend this rule to six-membered rings containing a trigonal atom (carbon or other) even when no exocyclic double bond is present.

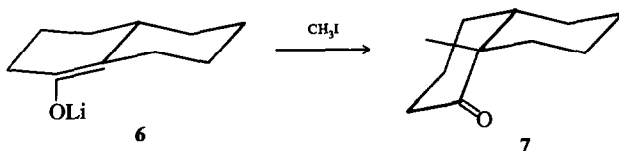
The reaction of the anion **1**, derived from a nitrile, with methyl bromide gave preponderantly the product of equatorial⁶ attack **2**. Intramolecular reactions of anions derived from nitriles with a C–X group in the molecule were shown⁷ to proceed from the equatorial side **3**, although in doing so the side chain has to assume an axial position.⁷ Similarly, alkylation of lithium enolate of 1-acetyl-4-tert butylcyclohexane **4** takes place from the equatorial direction preponderantly⁶ to give **5**.

Our rule of equatorial electrophilic and axial nucleophilic attack applies to compounds containing a single and not two neighbouring trigonal



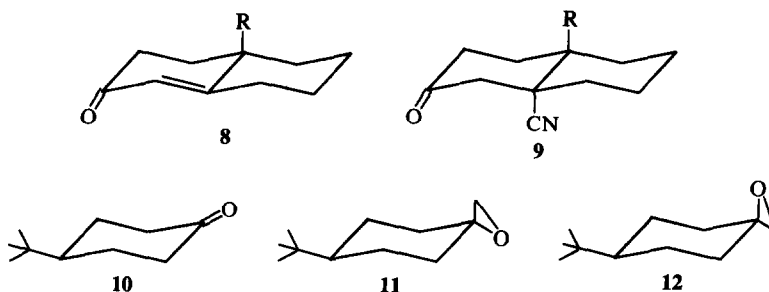
atoms in the ring. Electrophilic attack on endocyclic double bonds, such as protonation or halogenation of olefins and enols, proceeds from the axial direction. Even alkylation of endocyclic enols, particularly of those carrying a substituent, is preferentially axial.⁸⁻¹¹ However, methylation of **6**, although axial to the ring with the endocyclic double bond, takes place like other electrophilic reactions from the equatorial direction¹¹ to the ring with the exocyclic double bond, giving the product **7**. On the other side, nucleophilic attack of **8** by cyanide ion proceeds axially to both rings¹² to give **9**.





Another example of nucleophilic axial attack is the reaction¹³ of **10** with dimethylsulfonium methylide which leads to **11**. However, reaction of the same substrate with dimethylsulfoxonium methylide yields the product of equatorial reaction **12**. This is due not only to the larger size of dimethylsulfoxonium methylide but also to the reversibility¹⁴ of the first stage of the reaction of **10** with this reagent, which permits thus to obtain the more stable product.

electrophilic attack of aluminium on the double bond, when the intermediate complex is formed, or due to the large bulk of the organometallic reagent, and to solvation effects. However, when the ratio is 1:2 the reaction proceeds by an axial attack of trimethylaluminium on the carbonyltrimethylaluminium complex. Solvation does not here hinder axial attack by an increase of the bulk of the organometallic reagent, since it is intramolecular by the coordinated trimethylaluminium. This is a




Nucleophilic attack on unhindered cyclohexanones **13** by methyl lithium or methylmagnesium derivatives is from the equatorial^{15,16} side **14** and is determined largely by the bulk of the solvated organometallic compound that makes the axial approach difficult. However, with the decrease of the ionic character of the carbon-metal bond as in dimethylzinc and dimethylcadmium, the proportion of axial attack to form **15** increases.¹⁶ This is a consequence of the influence of the position of the transition state on the reaction coordinate on the degree of $\sigma-\pi$ interactions. Hyperconjugative effects are considered to be rather weak in the ground states of uncharged molecules, but the electronic requirements of reactions or charges present in molecules enhance this effect.¹⁷⁻²¹ The transition state of the reaction of **13** with dimethylcadmium is more product-like than with methyl lithium, the $\sigma-\pi$ interaction stronger and more axial attack follows.

The interesting observation that the stereochemistry of the reaction of **13** with trimethylaluminium depends on the ratio of **13** to the aluminium compound²² can be explained along similar lines. The equatorial attack, when this ratio is 1:1 might be considered either as a result of an

genuine nucleophilic reaction. It is of interest that triphenylaluminium, when in a 1:1 ratio with **16**, gives more axial attack than trimethylaluminium despite its larger bulk. This is again a manifestation of a stronger $\sigma-\pi$ hyperconjugation due to a transition state that is more advanced from the starting materials in the case of triphenylaluminium than in that of trimethylaluminium.

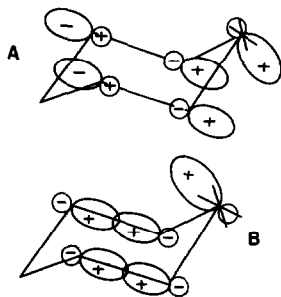
The $\sigma-\pi$ interaction to which we attribute the control of the stereochemistry of the reaction is here a composite and differential effect. The β C-C and the β C-H bonds could in principle interact with the trigonal atom. The two bond systems are disposed antisymmetrically relative to the plane of

 C, containing the trigonal atom X, and their effect is expected to be in opposite directions. It seems that the β C-C bond interaction with the trigonal centre is stronger^{19,21-24} than that of the C-H one. This might be due to the larger polarisability of these bonds. The interaction between the occupied bonds on the α and β carbons is also of importance.¹ There is also the possibility that the involvement of the β C-C and the axial β C-H bonds is different in electrophilic and nucleophilic reactions. The in-



teraction of these bonds with the electrophile and nucleophile can also play a role.

The control of the stereochemistry of the reaction by electronic factors is not limited to compounds containing exocyclic double bonds. Similar electronic effects are involved in the steric course of reactions on a trigonal atom in a six-membered ring, even when this atom is not part of an exocyclic double bond. The different electron densities on the two diastereotopic faces of such a trigonal atom are a consequence of the interaction of the filled p-orbital with the antibonding symmetric β C-C σ orbital (as in A), which makes the electrophilic attack preferred from the equatorial direction. On the other hand, the interaction of the vacant p-orbital with the bonding β C-C σ orbital (as in B) promotes nucleophilic attack from the axial direction.



4-t-Butylcyclohexyllithium shows a very high conformational preference for equatorial lithium.²⁵ Similarly, 2-lithio-1,3-dithians have the lithium in an equatorial conformation even when a methyl is located on the same carbon.²⁶ This preferential location of lithium on a six-membered ring can be attributed to the ionic contribution of the C-Li bond which makes the lithium, as an electrophile,

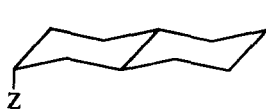
*Cohen and Solash³⁰ advance a different explanation involving a retention reaction in a solvated ion pair (S_Ni). However, their mechanism was not supported by a parallel retention in the equatorial bromide reaction.

occupy the equatorial position. The lower propensity²⁵⁻²⁷ of the C-Mg than that of the C-Li bond to take up an equatorial position can be explained by a lower ionic contribution to the first bond. However solvation effects may play a role in making the solvated metal atoms larger and enhance their preference for equatorial positions.

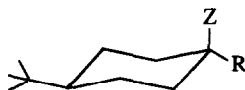
The formation of cyclohexylcarbonium ion during the solvolysis of tosylates is not established definitively since the prevalent mode of the displacement is an inversion process.^{28,29} However the silver perchlorate-catalysed displacement of bromide by acetonitrile* in *trans-trans*-2-bromodecalin **16** to yield the N-(*trans-trans*-2-decalyl) acetamide **17** can be considered as a result of an axial nucleophilic attack on the *trans*-2-decalyl carbonium ion. The lead tetraacetate oxidative decarboxylation of either *cis* **18** or *trans* **19** 4-t-butylcyclohexanecarboxylic acids leads to the same mixture containing preponderantly³¹ the axial acetate **20**. A carbonium ion **21** was assumed as an intermediate. Treatment of *cis* **22** and *trans* **23** 1-methyl-4-t-butyl-cyclohexanols, of 1-methyl-4-t-butyl-cyclohexene and of 1-methylene-4-t-butylcyclohexane with hydrochloric acid yields again predominantly the product **24** of an axial attack on the intermediate tertiary carbonium ion **25**.

Cyclohexyl radicals are also electron-deficient and should react to complete their octets from the axial direction. Indeed, bromodecarboxylation,^{33,3} chlorodecarboxylation,³⁵ decomposition of substituted cyclohexanecarbonyl peroxides³⁶ in carbonyl tetrachloride or irradiation of dimethyl-(4-t-butylcyclohexyl)-carbinyl hypochlorite³⁷ yield predominantly products with axial halogens.

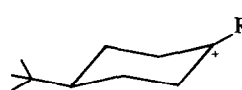
Stabilized carbonium ions could be formed from 2-alkoxy-1,3-dioxans. Some of the reactions of these compounds seem to proceed via these intermediates.³⁸ It was found by Eliel,³⁸ that **26** undergoes a reaction with alkylmagnesium halides to give **27**, whereas the isomer **28** is inert under similar conditions. The simplest explanation of



16: Z = Br
17: Z = NHCOCH₃

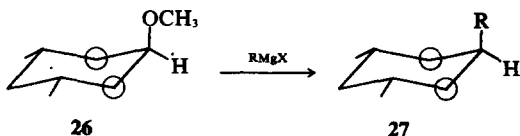


18: R = H; Z = COOH;
19: R = COOH; Z = H
20: R = H; Z = OAc



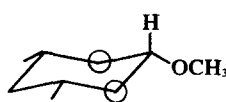
21: R = H
25: R = CH₃

22: R = CH₃; Z = OH
23: R = OH; Z = CH₃
24: R = CH₃; Z = Cl



26

27



28



29



30

these results is the stereoelectronic control of the reactions of the intermediate stabilized carbonium ion **29**. The formation and the reaction of **29** proceeds preferentially by departure and attack respectively of an anion from the axial direction as expected. Eliel³⁹ has also found that the reduction of **26** and **28** with lithium aluminium deuteride proceeded with inversion (S_N2 reaction), but that the reduction of either **26** or **28** with dichloro-deuteroalane gave **30**. This last reaction involved the formation of the positive ion **29** and the reaction of **29** with the hydride proceeded again from the axial side. The explanation of Eliel^{38,39} involving the rule of anti-parallel attack is not in contradiction with the present one. It stresses the conformational aspect of the process, i.e. chair-like *vs* boat-like transition state, whereas our explanation attributes at least part of the effect of axial attack on the carbonium ion to electronic factors. The presence of heteroatoms should not change the $\sigma-\pi$ interaction as seen from the similar structure of cyclohexyl and dithianyl lithium derivatives.

Addition of hydrobromic acid to 1-chloro-4-phenylcyclohexene **21** yields predominantly **33** with an axial bromine atom.⁴⁰ There is no need to assume hydrogen participation to explain this steric course of the reaction. Attack of the intermediate carbonium ion **32** should proceed from the axial side.

Heteroatoms in six-membered ring behave simi-

larly to a trigonal carbon. Electrophilic reactions on the sulfur on thianes, such as direct oxidation, or attack by a chloronium ion proceeds from the equatorial side^{41,42} as in **34**. Alkylation⁴³ yielded also more of the equatorial product **35** relative to the axial **36** than in the equilibrium.

Finally, our rule can be applied to cyclic compounds containing nitrogen since the lone pair on this atom has a p contribution. The stereochemistry of attack on piperidines was studied and discussed extensively, but the prevailing view was, that in non-deformed piperidines the alkylation is preferentially⁴⁴⁻⁴⁷ axial. The question is complicated by the equilibrium between two conformers **37** and **38** due to inversion of the pyramidal nitrogen. However, a recent publication⁴⁸ analysed the course of the electrophilic attack of substituted piperidines by benzyl halides in forms of the equilibrium contribution *K* and the rate constants of the individual conformers. It was is higher than that for the axial one k_a . Here again, the more advanced the transition state on the reaction coordinate the larger the ratio as evidenced by the influence of the substituents on this ratio $NO_2 > H > OCH_3$.

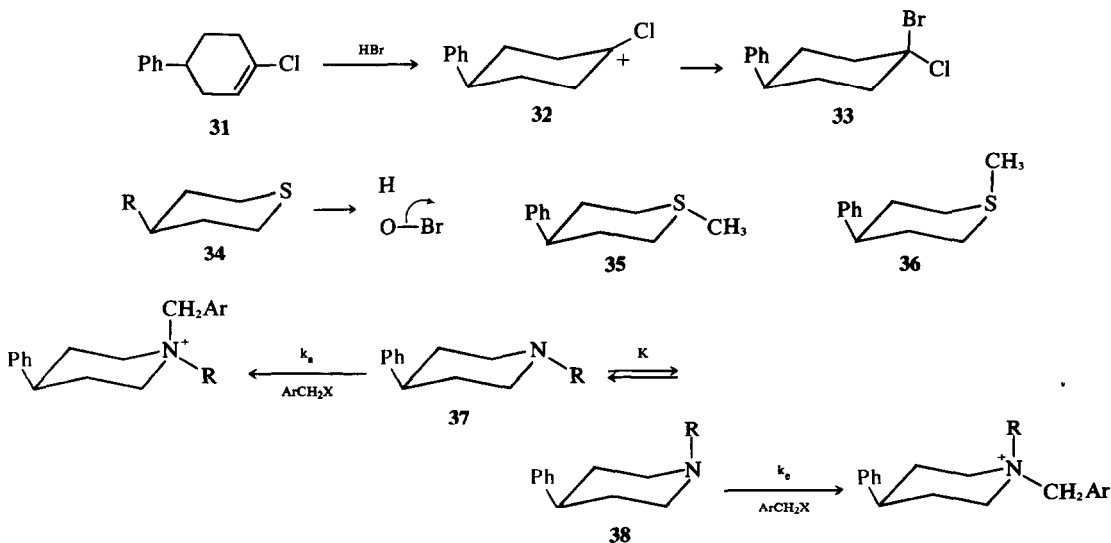
Not all the facts known are accommodated by our simple rule. The most striking exception is the epoxidation of methylenecyclohexanes, which give preponderantly the product derived by axial attack.⁴⁹ Reasons of solvation* and steric hindrance due to bulk of the reagent could be invoked in this case. Polar effects of groups in the molecule certainly play also a role which might be larger or smaller depending on the reaction.

*An example of a solvation effect reversing the steric course of an attack on substitut-*tert* cyclohexanones is the change from an 80-90% equatorial attack by

$[RCH=C(CH_3)_2] MgY$ $Y = Br$ or Cl (higher solvation) to that of 40-50% by the similar reagent with $Y = CH(CH_3)_2$ despite the large bulk of $CH(CH_3)_2$ relative to Cl .⁵⁰

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