

Perspective

Stereoselectivity and vertical polarity hypothesis for carbonyl addition

Fumiaki Uchiyama^{1,2*}

1. Institute of Preventive and Medicinal Dietetics, Nakamura Gakuen University

2. Department of nutritional sciences, Nakamura Gakuen University Graduate School

(Accepted March 5, 2019)

Key words

theoretical hypothesis, carbonyl, transition state of boat form, steric effect, valence shell electron pair repulsion theory, 4-t-butylcyclohexanone, lithium aluminum hydride, 1,4-flagpole interaction, Cram's rule

Abstract

The polarity of π bond of carbonyl groups always occurs horizontally to carbonyl plane. This polarity is used as “horizontal polarity” in this paper. The horizontal polarity determines the reactivity to nucleophilic addition of carbonyl groups and is indicated as LUMO in molecular orbital method. I assume that the vertical shift of π electron density of carbonyl groups, named “vertical polarity”, occurs perpendicular to the plane of carbonyl groups by electron repulsion under the constant geometry of carbonyl atoms. The π electron density in the vertical polarity changes perpendicular to the plane of carbonyl molecules. I propose that the big lobe caused by the vertical polarity stabilizes the overlapping with the nucleophilic electron pair in the transition state and determines the stereoselectivity in the nucleophilic addition of carbonyl groups. I show that the concept of the vertical polarity is verified from the stereoselective reduction of 4-t-butylcyclohexanone and the chiral induction at acyclic carbonyl carbons during nucleophilic additions.

Introduction

Scientists have discussed on organic chemistry issues that theoretical interpretation has not gathered over half a century. One of them is axial attack with stereoselective priority in the nucleophilic addition to cyclohexanones.

Experimentally, sodium borohydride and lithium aluminum hydride reduce 4-t-butylcyclohexanone to give trans-4-tert-butylcyclohexanol stereoselectively (Fig. 1)¹⁾.

Organic chemists have pursued rationality from the stereoselectivity by using the combination of characteristic reagents, reactants, solvents, and experimental conditions.

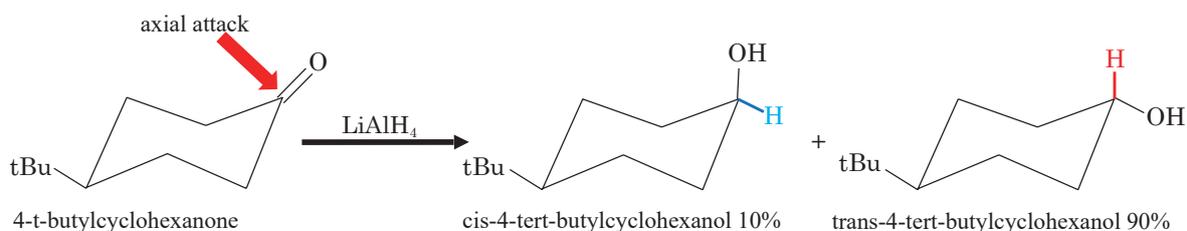


Fig. 1 Stereoselective reduction of 4-t-butylcyclohexanone

* Correspondence Address: Fukuoka, 814-0198, Japan, E-mail: uchiya-f@nakamura-u.ac.jp

These results mainly lead to the advocacy of two models, the Felkin-Anh model²⁾ and the Cieplak model³⁾. Both models are based on the hyperconjugation of electronic effects as well as the steric effect and the torsional strain in the chair form of cyclohexane ring. These models have been reviewed to integrate basic theory on the nucleophilic carbonyl additions^{4,5)}. Unfortunately, we have not reached a consistent idea for stereoselectivity in the nucleophilic addition to carbonyl group on cyclohexanone derivatives. In other words, we have the opportunity to gain insight into steric effects, electronic effects, and molecular orbital theory. The stereoselectivity arises from differences in steric effects and electronic effects in the transition state leading to stereoisomers. Here, I consider the rational interpretation for stereoselectivity in the nucleophilic addition to carbonyl group on cyclohexanones and acyclic carbonyl compounds.

Theoretical hypothesis: from conventional to innovative models

Lithium aluminum hydride reduce 4-*t*-butylcyclohexanone to give *trans*-4-*tert*-butylcyclohexanol and *cis*-4-*tert*-butylcyclohexanol in the yield of 90% and 10%, respectively (Fig. 1)¹⁾. The main product is produced by axial attack in the chair form. Since the steric hindrance of cyclohexane is 1,3-diaxial interaction in chair form, the axial attack is not preferable in respect of the steric effect (Fig. 2a). Even if considering the smallness of hydride, the hydride attack occurs equivalently from equatorial and axial sides in chair form. In order to adhere to chair form, an electronic requirement far beyond its negative 1,3-diaxial interaction is required. That is the only hyperconjugation effect which stabilizes LUMO of the carbonyl group in the transition state by a sigma bond at α -carbon atoms. The hyperconjugation is 10 kcal/mol of stabilizing energy⁶⁾ and weaker than torsional strains in cyclohexane. Therefore, the stereoselectivity of the hydride attack can not fully explain the experimental facts in the chair form. Even if the

hyperconjugation effect is involved, it may not be consistent with some other experimental facts. For an example, the reactivity of nucleophiles to carbonyl group is in the order of formaldehyde > acetone > methyl isopropyl ketone > diisopropyl ketone. This order is exactly the opposite of hyperconjugation effect. This reactivity of carbonyl group shows that the steric effect is more dominant than the hyperconjugation effect. Moreover, the π^* (LUMO) energy of carbonyl is lower than σ^* (LUMO) of donor of the hyperconjugation in the access of lithium aluminum hydride or sodium borohydride. I doubt the nucleophilic addition to carbonyl groups need larger energy for supplementary effect of hyperconjugation than carbonyl LUMO energy. In this way, the stereoselectivity of nucleophilic addition on 4-*t*-butylcyclohexanone may not be explained in both steric effect and electronic effect by the progression of axial attack in the chair form.

On the other hands, the equatorial attack in the boat form, which perfectly occurs on the convex face, can stereoselectively give *trans*-4-*tert*-butylcyclohexanol in the ground state through conformational change and can only explain the experimental facts in the steric hindrance (Fig.2b). Unfortunately, there is no hitherto described article to explain the equatorial attack in the boat form. All nucleophilic attack to cyclohexanones have been explained only on the chair form because the chair form is thermodynamically more stable than the boat form. However, the boat form is about 6.5 kcal mol⁻¹ higher in energy than the chair conformation⁷⁾.

In this way, the stabilizing energy of the conventional effects such as torsional strains and hyperconjugation is not sufficient for determining the stereoselectivity in the transition state.

Here, I propose a theoretical hypothesis including an innovative interpretation. The interpretation is based on acting both a steric effect and an electronic effect cooperatively. The high stereoselectivity of nucleophilic addition on 4-*t*-butylcyclohexanone implies to require a

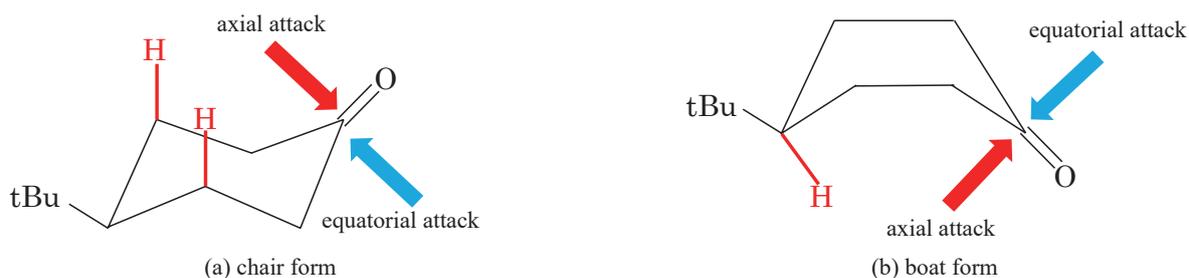


Fig. 2 Hydride attack to 4-*t*-butylcyclohexanone in the chair form (a) and the boat form (b). 1,3-diaxial steric hindrance (a) and 1,4-flagpole steric hindrance (b) are shown in red.

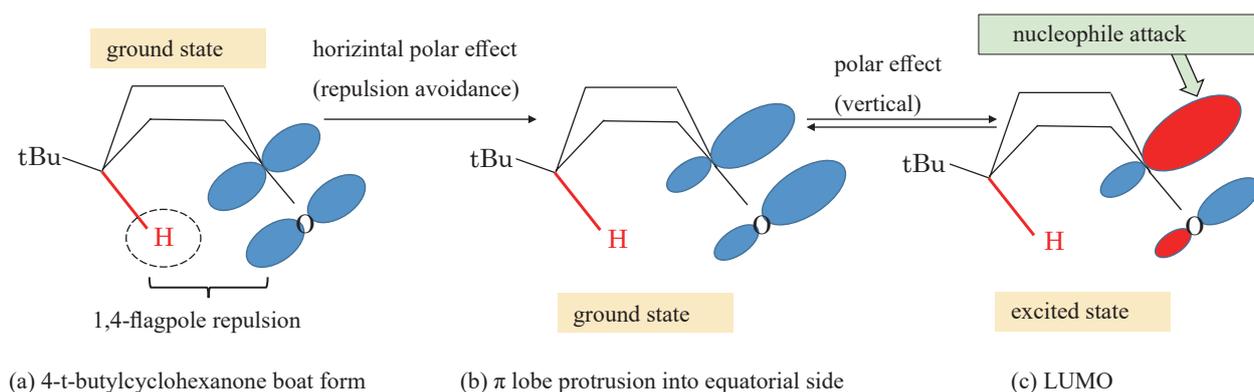


Fig. 3 The mechanism of hydride attack on 4-t-butylcyclohexanone boat form

combination of preferable steric effect and strong electronic effect. The preferable steric effect in 4-t-butylcyclohexanone arises from equatorial attack in the chair form or the boat form to give cis-4-tert-butylcyclohexanol or trans-4-tert-butylcyclohexanol (Fig. 2b). In consideration from the steric effect, only the equatorial attack in the boat form is consistent with the experimental facts. Since the conformation change between chair and boat form is rapid at room temperature by ring flipping, both conformations can exist with sufficient existence probability in the reactions.

Next, strong electronic effects must be considered on the selection of 4-t-butylcyclohexanone boat form. One conformation of 4-t-butylcyclohexanone boat forms is shown in Fig. 3a. The boat form has a steric strain of 1,4-flagpole interaction between hydrogen atom at C6 and π lobe orbital of carbonyl group. Here, valence shell electron pair repulsion (VSEPR) theory is applied to minimize 1,4-flag repulsion. The premise of VSEPR is that the valence electron pairs surrounding an atom tend to repel each other. Usually, an arrangement that minimizes this repulsion changes the molecule's geometry because of strong sigma bonds. On the other hand, π bond electrons can shift without changing the molecule's geometry. Here, I hypothesize that the π lobe of carbonyl group in 4-t-butylcyclohexanone boat forms protrude into the equatorial side on the boat form (Fig. 3b). This means that π orbital is distorted about the carbonyl plane and that the LUMO has a big lobe on the equatorial side of the carbonyl plane in the boat form. We call the π lobe protrusion as π vertical polarity and distinguish it from usual carbonyl polarity (π horizontal polarity). The π lobe protrusion also sustains the molecular symmetry C_{2v} of cyclohexane boat form. The vertical π lobe is a big vacant orbital of the LUMO in the transition state (Fig. 3c) and reduces the activation energy to nucleophilic reactions. As a

result, the π vertical and horizontal vacant orbital suffers the nucleophilic stereoselectivity of cyclohexanone.

Application of vertical polarity to acyclic carbonyl carbons during nucleophilic additions

The concept of carbonyl 1,2 asymmetric induction in acyclic compounds is devised as the Cram's rule of asymmetric induction by Donald J. Cram in 1952. The Cram's rule is based on steric hindrance and indicates that nucleophiles attack the carbonyl group from the least hindered side on the stable conformation⁸⁾.

The horizontal polar effect generates the big lobe of carbonyl carbon that overlap with the nucleophilic electron pair in lower energy of LUMO. Applying the VSEPR theory, the horizontal polar effect correlates positively with the electron repulsion between carbonyl π -electron and the substituent at $C\alpha$. The horizontal polar effect applies to acyclic carbonyl carbons during nucleophilic additions (Fig. 4).

The selection of (a) or (d) pathway is dependent on the bulkiness of R substituent, large or small, respectively. The product of (c) or (f) is the same that from predicted by Cram's rule or Felkin-Anh model. However, in this hypothesis, the driving force is not the concept of Cram's rule or Felkin-Anh model but the formation of big lobes by releasing electron repulsion. In other words, it is enough energy to lower the transition state energy for the formation of one enantiomer over the other.

Discussion

I describe the stereoselective hydride attack to 4-t-butylcyclohexanone by lithium aluminum hydride or sodium borohydride and its mechanism involving π vertical

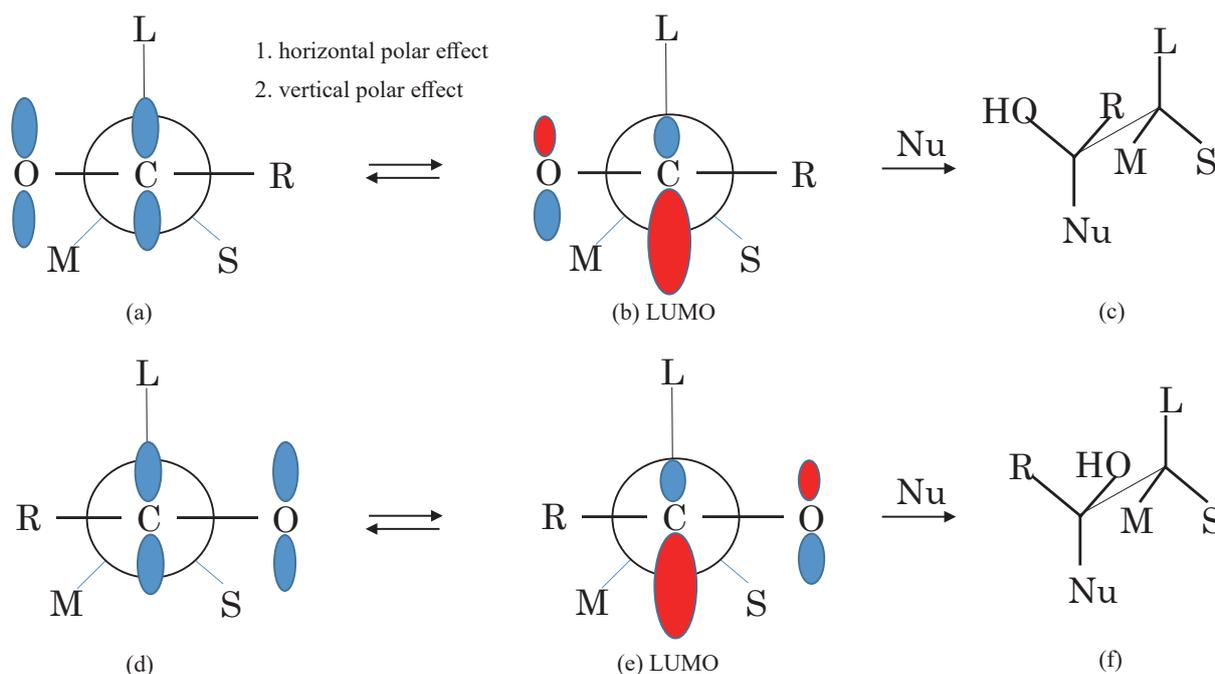


Fig. 4 Newman projection of carbonyl LUMO and Protruded carbonyl vacant orbitals by horizontal polar effect (L=large substituent, M=medium substituent, S=small substituent, R=various substituent). The symbols of (a) and (d) are conventional carbonyl π -electrons. The symbols of (b) and (e) are produced through electron repulsion between L and carbonyl π -electrons. The symbols of (c) and (f) are stereoselective products.

polarity on boat form. Since the reduction mechanism of lithium aluminum hydride or sodium borohydride is in the absence of chelate organization, the stereoselectivity could be explained only by carbonyl characteristics of reactants. Although the various combinations of characteristic reagents, reactants, solvents, and experimental conditions give us useful hints for the mechanism of the stereoselective nucleophile attack to cyclohexanones, there is no guarantee that they will proceed in the same reaction mechanism. For an example, the reduction of 4-*t*-butylcyclohexanone by lithium tri-*sec*-butylborohydride (L-selectride) gives >95% yield of *cis*-4-*tert*-butylcyclohexanol that is minor product by lithium aluminum hydride reduction⁹. L-selectride has different chemical property such as reactant functional groups, regioselectivity, and stereospecificity as well as physical property such as chelating ability, hydride dissociation constant, reaction rate, and rate limiting steps in comparison with lithium aluminum hydride. Some articles have interpreted the stereoselectivity of L-selectride as the steric effect of bulkiness. It is conventional to interpret the stereospecificity to cause all the molecular bulkiness of reagents. Similarly in using reactants of 6-membered cyclic compounds containing heteroatoms, it is rough to argue

the nucleophilic reaction mechanism of stereospecificity by covering all 6-membered cyclic compounds in the reactants.

The vertical polar effect can apply to the nucleophilic additions of acyclic carbonyl carbons.

The conventional theory is that the polar effect of π -electrons has been interpreted to induce only by electronic effect. The innovative hypothesis shows that the vertical polar effect of π -electrons induces by a steric effect.

Reference

- 1) Eliel, E. L. & Rerick, M. N. Reduction with Metal Hydrides. VIII. Reductions of Ketones and Epimerization of Alcohols with Lithium Aluminum Hydride-Aluminum Chloride^{1,2}, *Journal of the American Chemical Society*, **82**, 1367-1372, doi:10.1021/ja01491a021 (1960)
- 2) Chérest, M. & Felkin, H. Torsional strain involving partial bonds. The steric course of the reaction between allyl magnesium bromide and 4-*t*-butyl-cyclohexanone, *Tetrahedron Letters*, **9**, 2205-2208, doi:https://doi.org/10.1016/S0040-4039(00)89720-8 (1968)
- 3) Cieplak, A. S. Stereochemistry of nucleophilic addition to cyclohexanone. The importance of two-electron stabilizing

- interactions, *Journal of the American Chemical Society*, **103**, 4540-4552, doi:10.1021/ja00405a041 (1981)
- 4) Gung, B. W. Structure Distortions in Heteroatom-Substituted Cyclohexanones, Adamantanones, and Adamantanes: Origin of Diastereofacial Selectivity, *Chemical Reviews*, **99**, 1377-1386, doi:10.1021/cr980365q (1999)
- 5) Tomoda, S. The Exterior Frontier Orbital Extension Model, *Chemical Reviews*, **99**, 1243-1264, doi:10.1021/cr980374z (1999)
- 6) Alamiddine, Z. & Humbel, S. Hyperconjugation in Carbocations, a BLW Study with DFT approximation, *Frontiers in Chemistry*, **1**, 37-1-9, doi: 10.3389/fchem.2013.00037 (2014)
- 7) Allinger, N. L. Conformational analysis. 130. MM2. A hydrocarbon force field utilizing V1 and V2 torsional terms, *Journal of the American Chemical Society*, **99**, 8127-8134, doi:10.1021/ja00467a001 (1977)
- 8) Cram, D. J. & Elhafez, F. A. A. Studies in Stereochemistry. X. The Rule of "Steric Control of Asymmetric Induction" in the Syntheses of Acyclic Systems, *Journal of the American Chemical Society*, **74**, 5828-5835, doi:10.1021/ja01143a007 (1952)
- 9) Brown, H. C. & Krishnamurthy, S. Lithium tri-sec-butylborohydride. New reagent for the reduction of cyclic and bicyclic ketones with super stereoselectivity. Remarkably simple and practical procedure for the conversion of ketones to alcohols in exceptionally high stereochemical purity, *Journal of the American Chemical Society*, **94**, 7159-7161, doi:10.1021/ja00775a053 (1972)