Stereoelectronic Effects on π-Facial Selectivity in Addition to 4H-1,3-Dioxin-4-ones

Fumiaki UEHARA, Masayuki SATO,*1) and Chikara KANEKO

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980–77, Japan.
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π-Facial selectivity in catalytic hydrogenation and conjugate addition of a series of 2,2-disubstituted 4H-1,3-dioxin-4-ones was examined. The results indicated that pyramidalization at the reaction center of dioxinones is less important than other stereoelectronic effects and the steric effect as the origin of π-facial selectivity.

Key words asymmetric addition; 4H-1,3-dioxin-4-one; conformation analysis; stereoelectronic effect

The enone carbon-carbon double bond involved in 4H-1,3-dioxin-4-ones with the stereogenic center at the acetal carbon shows excellent π-facial selectivity in a variety of addition reactions, providing highly efficient methods for enantioselective synthesis of potential biologically active compounds.2) It is interesting that conjugate addition and catalytic hydrogenation of 13a) and the 2-methyl analogs3b,4a) occur exclusively from the more hindered top face of the sofa conformation, while cycloadditions4e–g) and fluorine addition4d) to the analogous system occur selectively from the less hindered bottom face. Seebach et al.3d) proposed that top face selectivity is due to pyramidalization of the reaction center C(6) in the top face direction. This hypothesis has been invoked to explain π-facial selectivity in photo[2+2]-cycloaddition of alkenes to dioxinones3h,i) and even to cyclohexenones in which pyramidalization of the reaction center in its excited state is not confirmed.5b) As possible origins of the top face selectivity for 1, polarized π-frontier MO7b) and the Cieplak effect7,8) have been also proposed. To study the relative importance of the pyramidalization and other stereoelectronic effects on the π-facial selectivity of dioxinones, we synthesized a series of 2,2-disubstituted substrates 2 and 3 (racemic) and examined the facial selectivity in catalytic hydrogenation and conjugate addition.

Dioxinones 2a, b, e and 3a, b with t-butyl and alkoxycarbonyl groups at the 2-position were synthesized by a previously reported method9) and carbamoyl derivatives 2c, d were prepared through the benzyl ester 2e.5i) MOPAC PM3 calculations on 2a indicated that the pseudoaxial t-butyl conformer A is more stable than the pseudoequatorial t-butyl conformer B by 4.16 kcal/mol.10) The geometry of A is essentially similar to that of dioxinones with pseudoaxial phenyl and pseudoequatorial alkoxycarbonyl groups at the 2-position in X-ray crystallography,a,b) indicating satisfactory reproducibility of this calculation. It is clear that the stability of conformer A arises from the t-butyl group at the 2-position which disfavors the highly congested pseudoequatorial position. In addition, the anomic effect11) of the pseudoequatorial carbonyl group stabilizes conformer A.1,12) Thus it is quite reasonable to assume that 2a—d and 3a, b exist exclusively as pseudoequatorial t-butyl conformers in solution.

Hydrogenation of 2a—d with Rh-alumina catalyst occurred selectively from the top face in all cases except for 2b, which gave a 1:1 diastereomixture of 4b and 5b. In contrast, conjugate addition of MeMgBr-CuI to 3a and 3b at −78 °C occurred highly selectively from the bottom face, resulting in the exclusive formation of dioxanones 4a and 4b, respectively. The stereochemistry of 4 and 5 was assigned by 1H-NMR spectroscopy. Due to the shielding effect by the axial carbonyl group, the C(6)-H in 4a—d appeared at higher fields (δ 3.90—3.96) than those in 5a—d (δ 4.22—4.31). This assignment was supported by NOE (1.4%) between the t-BuO group and the C(6)-H in 4b.

In dioxinones, the trigonal carbon at the 6-position is always pyramidalized toward the top face of the sofa conformation.3,3a) Thus the bottom face selectivity in conjugate addition to 3 indicates that the pyramidalization is not an important factor in the origin of the π-facial discrimination. The result is consistent with our hypothesis that the top face attack in 1 is due to the Cieplak effect. The antibonding orbital of the incipient bond interacts with lone pair electrons.

Fig. 1

Heat of formation: −197.50 kcal/mol

Fig. 2

Heat of formation: −193.34 kcal/mol
of O(1) and this stabilizing interaction facilitates the top face attack (cf. C). This effect becomes less effective in 3 because of the alternative stabilizing interaction of the lone pair electrons with the antibonding orbital of the C(2)–C=O bond (the anomeric effect), resulting in the preferential attack from the less hindered bottom face (cf. D). On the other hand, the top face selectivity in the catalytic hydrogenation of 2 is seemingly consistent with the hypothesis based on pyramidalization. However, this selectivity can be rationalized alternatively in terms of an attractive stacking between the catalyst and p-system of the pseudoaxial substituent (cf. E). The higher diastere excess (de) with the higher p-density of the carbonyl group supports this rationalization; introduction of the electron-donating N,N-dimethylamino group to the carbonyl resulted in the highest de 88%. The nonselectivity in the hydrogenation of 2b is due to the difficult p-stacking by the bulky t-butoxy group.

In summary, catalytic hydrogenation of 2 occurred from the top face of the sofa conformation, and this anomalous selectivity is better explained by attractive stacking between the catalyst and p-system than by pyramidalization. Moreover, conjugate addition to 3 occurred from the bottom face. These results indicate that pyramidalization of the reaction center is less important than other stereoelectronic effects and steric effects in the origin of the p-facial selectivity of dioxinones.

References and Notes
1) Present address: School of Pharmaceutical Sciences, University of Shizuoka, 52–1 Yada, Shizuoka 422–8526, Japan.
9) Hydrogenolysis of 2e with Pd-C catalyst gave the carboxylic acid, treatment of which with p-TsCl and then with amine hydrochlorides in pyridine furnished 2f and 2d, respectively.
10) MOPAC PM3 calculations were done on a Tektronix CAChe work system.