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Role of the Heteroatoms in the Complex Metal Hydride Reduction of 2-*t*-Butyl-1,3-dioxan-5-one and 3-Oxoquinolizidine: Comparison of Their Reactivity and Stereochemistry with Those of the Corresponding Carbocyclic Compounds

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The complex metal hydride reductions of 2-*t*-butyl-1,3-dioxan-5-one (**1**) and 3-oxoquinolizidine (**3**) are faster than those of the corresponding carbocyclic compounds, 4-*t*-butylcyclohexanone (**2**) and *trans*-2-decalone (**4**). The stereoselectivities were similar in the $LiAlH_4$ reduction, but the heteracyclohexanones exhibited higher stereoselectivity with $NaBH_4$. These facts are discussed in terms of the intramolecular orbital interaction.

Stereochemistry in the complex metal hydride reduction of cyclohexanones has long been discussed, and many investigations have been published.[1] Klein was the first to use molecular orbital arguments.[2] Among the chemists to advance theories of orbital overlap control, Cieplak has proposed that the transition state stabilization energy of the hydride approach to the two diastereofaces of unhindered cyclohexanones was explained by the difference between the nonbonding 2pπ–2pπ interactions of the antibonding orbital of the incipient bond ($\sigma^*_{\ddagger}$) and the antiperiplanar vicinal bonds.[3] Recently, Tomoda and Senju have proposed a new idea: that π facial stereoselectivity is based on the relative magnitudes of the exterior frontier orbital extensions of the LUMO above and below the carbonyl plane.[4] We have investigated the effects of a heteroatom in the ring system or in the substituents of six-membered ketones on the reactivity and the stereochemistry of the complex metal hydride reduction.[5,6]

Jochims et al. reported that nucleophiles such as $LiAlH_4$ and Grignard reagents attack 2-phenyl-1,3-dioxan-5-one to give more of the *trans* alcohol than the corresponding cyclohexanone.[7] They suggested that the introduction of oxygen atoms into the cyclohexanone ring causes a ring distortion and a change in the torsional strain of the transition states.

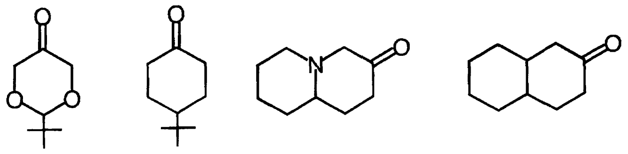
In our continuing interest in the effect of heteroatoms on the stereochemistry of complex metal hydride reduction, we tested 2-*t*-butyl-1,3-dioxan-5-one (**1**) and 3-oxoquinolizidine (**3**), in which the heteroatom/atoms are at the *β*-position to the carbonyl carbon, and the corresponding carbocyclic compounds, 4-*t*-butylcyclohexanone (**2**) and *trans*-2-decalone (**4**) (Fig. 1).

Results and Discussion

The reductions were performed with $LiAlH_4$, $NaBH_4$, and $LiBH_4$ in THF. The $NaBH_4$ and $LiBH_4$ reductions were also carried out in 2-propanol and ethanol. In order for us to examine the effects of the heteroatom on the reactivity of the carbonyl group, an equimolar mixture of **1** and **2** was reduced with $LiAlH_4$, $NaBH_4$, and $LiBH_4$, as was a mixture of **3** and **4**, which was reduced with $LiAlH_4$ and $NaBH_4$ in appropriate solvents. The relative reactivities were determined during the early stages (up to 10%) of the reduction, except in cases in which the difference in reactivity was very large. The relative reactivity of **1** was about 1.3 with $LiAlH_4$ and about 12 with $NaBH_4$ compared with **2** in THF. Similarly, the relative reactivity of **3** was about 1.3 times that of **4** in the $LiAlH_4$ reduction and about 4 times with $NaBH_4$. The differences in relative reactivities decreased with increasing solvent polarity. These results are shown in Table 1.

The high *cis* selectivity observed in the catalytic hydrogenation of 2-*t*-butyl-5-methylene-1,3-dioxane[8] and 2-*t*-butyl-1,3-dioxan-5-one[9] has been interpreted in terms of the electron delocalization by the intramolecular orbital interaction.

Semiempirical MO (AM1) calculations[10] were performed on **1**, **2**, and 2-*t*-butyl-1,3-dioxane. Figure 2 depicts a level diagram correlating n_O, π, π*, and the allylic axial σ_{C-H} and σ^*_{C-H} energies of **1** with those of model compounds **2** and 2-*t*-butyl-1,3-dioxane. It is noted that combining the π and π* orbitals with n_O and the allylic axial σ_{C-H} and σ^*_{C-H} leads to a substantial stabilization of all pertinent levels relative



1 **2** **3** **4**

Fig. 1.

Table 1. Relative Reactivity in the Reduction with Complex Metal Hydride

Complex metal hydride	Solvent	Conversion %	Substrate 1	Substrate 2	Conversion % Relative reactivity	Substrate 3	Substrate 4
			trans alcohol/*cis* alcohol			Equatorial alcohol/Axial alcohol	
$LiAlH_4$	THF	5.0	14/1.7	10/1.2	6.2	13/1.8	10/1.6
$NaBH_4$	THF	8.3	127/4.1	10/0.8	12.5	49/3.7	10/2.9
	2-PrOH	18.4	115/5.6	10/1.0	11.5	21/1.9	10/2.6
	EtOH	8.6	21/1.5	10/2.8	5.2	14/1.7	10/3.1
$LiBH_4$	THF	20.9	247/15	10/0.9			
	2-PrOH	11.3	53/5.2	10/1.0			
	EtOH	8.5	22/2.8	10/2.9			

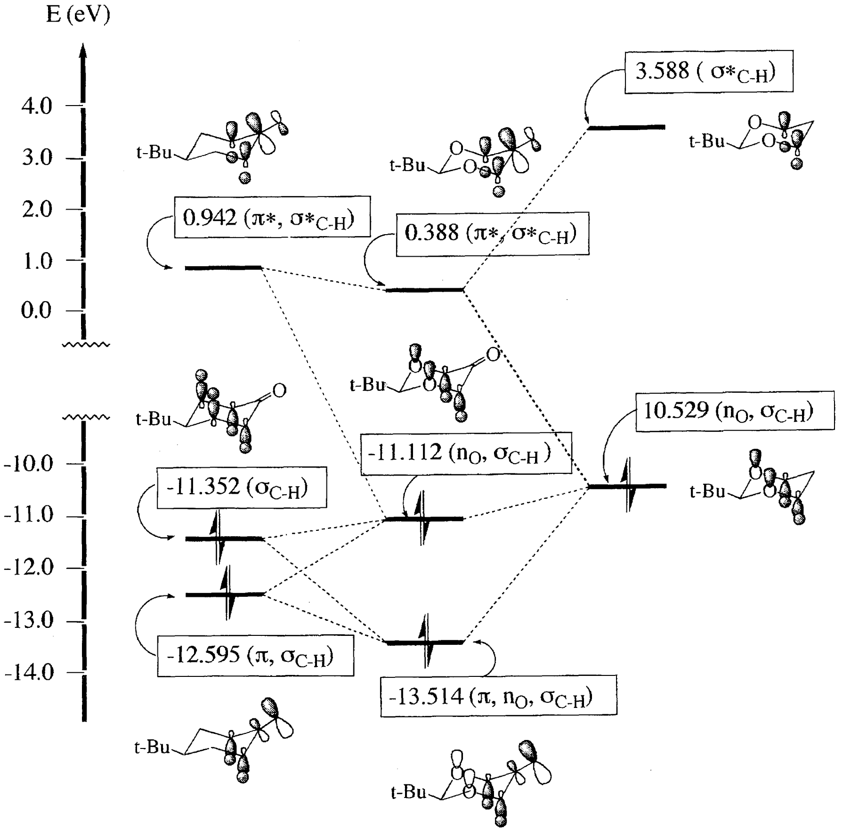


Fig. 2. Interaction diagram correlating n_O, π, π*, and allylic axial σ_{C-H} energies of **1** with those of model compounds.

to their isolated counterparts. The interactions of the n_O orbitals with the allylic axial σ_{C-H} orbitals and the π and π* orbitals are regarded as a through-space interaction.[8] Cyclic voltammetric measurements of **1** and **2** were carried out in THF with 0.1 M $(Bu)_4NClO_4$ as the supporting electrolyte (1 M = 1 mol dm^{-3}). No reduction peak was found for **2** in the measured range (ca. 3.5 V), while a weak anodic wave was observed at −2.9 V for **1**. This voltammetric evidence as well as the theoretical treatment support the conclusion that the energy level of LUMO of the carbonyl group in **1** is lower than that of **2**; the former is more easily reducible than the latter.

In the $NaBH_4$ reduction, the relative reactivity of **1** is significantly higher than that of **2** in THF, but the difference is reduced in protic solvents and becomes about twice as large as that of **2** in ethanol. Such a trend was also observed in the $LiBH_4$ reduction. The competitive reduction of a binary mixture prepared from **3** and **4** also behaved in this manner. This indicates that the relative reactivities of **1** and **3** decrease with increasing Swain's acidity parameter of the solvents.[11] We previously pointed out that the hydrogen bond formation of the n_N orbital with the protic solvent affects the electron donating ability of the allylic σ orbitals in the $NaBH_4$ reduction of 2-azaadamantan-4-one;[6] the same has now been found to be true in the dioxanone system. The presence of the oxygen atom in the cycle stabilizes, in part, the transition states for the reduction of dioxanone in a less polar solvent, but this role is reduced by the gradual increase in the interaction with the solvents, especially by the hydrogen bond formation with the protic solvent. This results in a decrease in the relative reactivity of dioxanone. The energy levels of the LUMO of the carbonyl group for **1** and **2** were computationally estimated by the COSMO method, which has been used to evaluate the solvent effect (Table 2). The energy level for **1** is lower than that for **2** and the energy gap between **1** and **2** is reduced with increasing solvent polarity. This is compatible with the experimental evidence that **1** is more reactive and that the difference in the relative reactivity between **1** and **2** is decreased when one goes from THF to ethanol.

The stereoselectivities in the $LiAlH_4$ reductions of **1** and **3** in THF were similar to those of **2** and **4**. According to Cieplak's proposal, the transition state for the hydride attack from the equatorial direction of the dioxanone is less stabilized by the replacement of the β-position to the carbonyl carbon with the oxygen, since the electron donating ability is in the order C–O < C–C. Such a loss of stabilization of the transition state may be compensated for the intramolecular through-space interaction of the n_O orbital with the antibonding orbital of the incipient bond ($\sigma^*_\ddagger$). On the other hand, the $NaBH_4$ reduction of **1** and **3** exhibited higher stereoselectivity than that of the corresponding carbocyclic ketones, but the ratios of *trans* to *cis* alcohol decrease with increasing solvent polarity in going from THF to ethanol. The $LiBH_4$ reduction reveals similar results to the $NaBH_4$ reduction. These results are shown in Table 3.

Geneste and Lamaty have postulated a four-centered cyclic transition state for the $LiAlH_4$ reduction,[12] while Wigfield and Gowland have found participation of the solvent in the $NaBH_4$ reduction by kinetic measurements; They proposed not the cyclic four-centered transition state but a linear one including the solvent molecules.[13] It is also likely that the ether oxygens and the nitrogen in the cycle play some role in pushing the hydride transfer from the borohydride (tetrahydroborate) reagent to the carbonyl at the transition state.

Table 2. The Energy of the LUMO of $\pi^*_{C=O}$ of Cyclic Ketone (eV)

Condition Compound	Gas phase	in THF	in 2-Propanol	in Ethanol
1	0.942	0.902	0.493	0.483
2	0.388	0.204	0.158	0.154
$\Delta(\mathbf{1}-\mathbf{2})$	0.704	0.752	0.399	0.390

Table 3. Stereoselectivity in the Reduction with Complex Metal Hydrides

Complex metal hydride	Solvent	Substrate			
		1	**2**	**3**	**4**
		Product			
		trans alcohol (%)		Equatorial alcohol (%)	
$LiAlH_4$	THF	89	89	88	86
$NaBH_4$	THF	97	93	93	78
	2-PrOH	95	91	92	79
	EtOH	93	92	89	76
$LiBH_4$	THF	94	92		
	2-PrOH	91	91		
	EtOH	89	78		

We showed that the differences in the relative reactivity and stereoselectivity between **1** and **2** and between **3** and **4** in the complex metal hydride reduction are explained by the intramolecular orbital interaction. Nevertheless, the possibility of an alternative explanation by the steric hindrance still cannot be ruled out. Replacement of the β-position to the carbonyl carbon by the heteroatom/atoms in the cyclohexanone system (i) alters the number of axial hydrogens at this position and (ii) flattens the carbonyl region of the six-membered ring.[14] These two facts may give rise to a change in the steric environment of the two diastereofaces of the carbonyl group and may control the relative reactivity and the stereoselectivity in the complex metal hydride reduction.

Experimental

Materials. 2-*t*-Butyl-1,3-dioxan-5-one (**1**)[15] was prepared from 2-*t*-butyl-5-hydroxymethyl-5-nitro-1,3-dioxane[16] by hydrogenation of the nitro group followed by sodium periodate oxidation. 3-Oxoquinolizidine (**3**)[17] was prepared from ethyl 2-pyridylacetate as the commercially available starting material. The reduction products from **1**[9] and **3**[17] were described earlier.

Reduction with Complex Metal Hydride. $LiAlH_4$, $NaBH_4$, and $LiBH_4$ Reduction. The solution of complex metal hydride (0.02 M, 5 cm^3) in dried solvent was added dropwise to 0.4 mmol of the substrate in 10 cm^3 of the same solvent over a period of 10—15 min at 0 °C, then the mixture was stirred for 60 min. Water and crushed ice were added; then the organic layer was separated, dried over Na_2SO_4, and analyzed by GLC.

Competitive Reduction.[18] The calculated amount (0.023 molar amount) of a hydride solution in the appropriated solvent (0.01 M) was added to a mixture of **1** and **2** or **3** and **4** (0.5 mmol of each) in 3 cm^3 of the same solvent over a period of 10—15 min at 0 °C. The reaction mixture was stirred for 60 min. Water and crushed ice were added; then the organic layer was separated, dried over Na_2SO_4, and analyzed by GLC.

GLC Analyses. Gas chromatographic analyses were performed on a Shimadzu mode GC-8AIF with a carbowax 20M chemical bonded silica capillary column (0.25 mm×25 m) at 120 °C.

Cyclic Voltammetry. Cyclic voltammetry was performed with a three electrode system employing a linear scanning unit (Hokuto Denko Ltd., model HB-104) equipped with a potentiostat (Hokuto Denko Ltd., model HA-310). The electrode system consisted of a glassy-carbon indicator electrode, platinum counter electrode, and a SCE. Measurements were carried out in THF with a substrate concentration of 0.01 and 0.1 M $(Bu)_4NClO_4$ as a supporting electrolyte; the sweep rate was of 50 mV s^{-1}.

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