

Diastereoselectivity in Gas-Phase Hydride Reduction Reactions of Ketones

Alexander Artau,* Yeunghaw Ho,† Hilkka Kenttämä, and Robert R. Squires

Contribution from the The Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

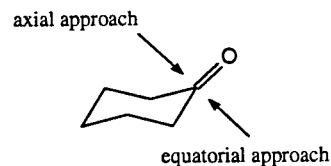
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Abstract: The intrinsic diastereoselectivity of the reduction of a series of cyclic ketones by pentacoordinate silicon hydride ions was investigated in the gas phase with the use of the flowing afterglow–triple quadrupole technique. The percent axial reduction of 4-*tert*-butylcyclohexanone (**1**), 2-methylcyclohexanone (**2**), 3,3,5-trimethylcyclohexanone (**3**), norcamphor (**4**), 2-*tert*-butyl-1,3-dioxan-5-one (**5**), and 2-*tert*-butyl-1,3-dithian-5-one (**6**) was determined by collision-induced dissociation experiments. The results show that axial (exo) reduction dominates for **1**, **2**, and **4**, whereas equatorial reduction is dominant for **3**, **5**, and **6**. The trend observed for the reduction diastereoselectivity of compounds **1–4** and **6** matches their condensed-phase behavior; i.e., the percent axial reduction is reduced when steric hindrance of the ketones is increased (**1**, $99 \pm 3\%$; **2**, $68 \pm 5\%$; **3**, $9 \pm 3\%$). The remarkable consistency of the results obtained in the gas phase and in solution suggests that environmental effects are either unimportant or cancel out and that the reduction diastereoselectivity is a property that can be attributed to the intrinsic nature of the isolated reactants. Qualitatively, the predictions made by Houk et al. regarding the diastereoselectivity of the reduction of **5** and **6** in the gas phase were confirmed, i.e., a preferred equatorial approach of the hydride reducing agent. The preference of compound **5** to undergo equatorial reduction in the gas phase ($33 \pm 4\%$ axial reduction) contrasts with the almost exclusive axial reduction reported in solution (93%). This deviation is likely caused by the strong electrostatic repulsion between the nucleophilic hydride reagent and the ring heteroatoms in **5**. Compound **6** exhibits an even stronger preference for equatorial reduction ($16 \pm 4\%$ axial reduction), in agreement with experimental results obtained by others in the condensed phase. Earlier calculations predict an even stronger preference for equatorial reduction. These results are readily rationalized in terms of competition among steric, torsional, and electrostatic effects.

Introduction

Conversion of a ketone to an alcohol by hydride addition is a key reaction in organic synthesis. Prediction and control of the stereochemical outcome of these reactions are necessary for the synthesis of the desired diastereomer or enantiomer of the product alcohol. This need has inspired numerous qualitative and quantitative models for the prediction of diastereoselectivity in nucleophilic addition reactions.¹ The Felkin–Anh model is the one most commonly used to understand the stereoselectivity of nucleophilic addition to carbonyl compounds. This model invokes contributions from torsional, steric, and electronic effects by stereogenic centers adjacent to the reactive carbonyl group, and it has been supported by several computational investigations.² However, the Felkin–Anh model fails to explain the diastereoselectivity observed in nucleophilic additions to substituted cyclohexanones (the reducing agent prefers to

approach from the more hindered axial face). Cieplak^{3a} rationalizes these results by stereoelectronic control that involves electron donation from the anti-periplanar σ C–H orbitals of the cyclohexane ring into the vacant antibonding σ^* orbital of the incipient bond.



This model successfully explains the observed stereoselectivity in several cyclohexanone-based systems but fails for other carbonyl compounds. Furthermore, the model has been heavily criticized because of the assumption that C–H bonds have greater electron-donating abilities than C–C bonds and the fact that electron donation into the antibonding σ^* orbital, which is a bond-weakening interaction, is used to describe the incipient bond-forming process.²

Several studies have been carried out in order to probe the validity of the assumption made by Cieplak that a C–H bond is a better donor than a C–C bond in hyperconjugative electron release. Rozeboom and Houk⁴ first questioned this idea on the basis of data obtained by photoelectron spectroscopy and by ab initio STO-3G calculations. Results obtained on methylpi-

* Present address: ScinoPharm Taiwan, Ltd., One Ta-Hsueh Rd., Incubator of National Chen Kung University, Tainan, Taiwan 701.

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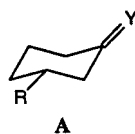
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peridines indicate that axial 2-methyl substituents lower the amine lone pair ionization potential (IP) by ~ 0.26 eV, while equatorial 2-methyl substituents lower the lone pair IP by less than 0.1 eV. This observation suggests that C–C bonds are better donors than C–H, assuming that the vicinal antiperiplanar bonds stabilize the amine radical cation by hyperconjugative electron release. These results were interpreted by Cieplak as the consequence of ring distortion. This distortion is evident in 2,2,6,6-tetramethylpiperidine, wherein the syn-diaxial interaction of the methyl groups effectively increases the size of the six-membered ring.^{3b} The lowering of the ionization potential of cyclic amines and ethers by an increase in ring size is a well-known fact.⁵ Moreover, recent studies on the hydrochlorination and fluorination of 5-substituted adamantan-2-ols⁶ and conformational studies of Lewis acid complexed α,β -unsaturated esters⁷ seem to confirm the greater electron-donating capability of C–H bonds over C–C bonds.

The work carried out by le Noble on hydride reductions of 5-substituted 2-adamantanones further supports the Cieplak model.⁸ These molecules show stereoselectivity opposite to what would be predicted by the widely accepted Felkin–Anh model. Moreover, studies of nucleophilic additions to 3-substituted cyclohexanones (A, Y = O) and electrophilic additions to 3-substituted methylenecyclohexanes (A, Y = CH₂)^{3b} also



provide results that are in full accord with the Cieplak model. The presence of an equatorial electron-donating group at C3 was found to decrease the percentage of axial attack, while an increase occurs for electron-withdrawing substituents. This is consistent with the Cieplak description of the nucleophile's approach in a direction that is anti-periplanar to the best electron-donating bond in the ring. The interpretation of these results, however, has been challenged by Houk,^{2c} who has offered an alternative explanation in terms of electrostatic effects. An electron-withdrawing group at C3 would induce a partial positive charge at that atom, thus making the axial approach of a negatively charged nucleophile more favorable. The contribution of electrostatic control to the diastereoselectivity of hydride additions to carbonyl compounds is also evident in the π -facial selectivity observed in 1,2-addition reactions of organometallic reagents to 4,4-disubstituted dienones.⁹ The results, according to Wipf and Kim, can be readily explained by the Felkin–Anh model and not by Cieplak. Interestingly, a linear correlation was observed between the calculated (AM1) dipole moment of some dienones and their characteristic α -face selectivity. This finding indicates a significant contribution from electrostatic control to the stereochemical outcome of polar additions to sterically unhindered carbonyl groups. However, certain differences in the π -facial selectivity between monocyclic and spirocyclic systems cannot be fully explained on the sole basis of electrostatic control.

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Both the Felkin–Anh and Cieplak models, as well as other models (classical¹⁰ and modern molecular orbital based^{6,11}) that have been proposed to describe stereoselectivity in nucleophilic additions of carbonyl compounds, can be classified as “gas-phase” models. In other words, they refer to isolated reactants and focus entirely on the intrinsic structural and electronic features of the substrate, despite the fact that the stereochemical outcome of the reactions of interest often exhibits a marked sensitivity to the solvent and the type of counterion employed with ionic and polar reducing agents.¹²

The intrinsic effects that determine the stereochemistry of ketone reduction reactions can be examined experimentally in the gas phase, where extrinsic solvent and counterion effects are absent. We introduced in a recent communication an experimental method for distinguishing the diastereomeric products of gas-phase hydride reduction reactions and presented preliminary results on the quantitative determination of the intrinsic diastereoselectivity of reductions of a few alkyl-substituted cyclohexanones.¹³ The stereochemical outcome of gas-phase hydride reduction reactions of 4-*tert*-butylcyclohexanone, 2-methylcyclohexanone, and 3,3,5-trimethylcyclohexanone by pentacoordinate silicon hydride ions was found to be remarkably similar to that reported for these substrates toward common reducing agents in solution^{3,12} and also in agreement with the diastereoselectivities predicted by MO calculations for

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reduction by LiH in the gas phase.^{2a} In this paper, we present a full description of the method as applied to the study of gas-phase hydride reduction reactions of several cyclohexanone derivatives. These results are contrasted to those obtained for cyclic ketones with ring heteroatoms, whose gas-phase hydride reduction diastereoselectivity has been predicted to be opposite to that observed in solution.²⁷

Experimental Section

All of the gas-phase experiments described in this paper were performed at room temperature in a flowing afterglow-triple quadrupole apparatus that has been described in detail previously.¹⁴ The total pressure and flow rate of the helium buffer gas in the $1\text{ m} \times 7.3\text{ cm}$ flow reactor were 0.4 Torr and 200 STP cm^3/s , respectively, with a bulk flow velocity of 9700 cm/s. Hydroxide ions were generated in the ion source region of the flow reactor by electron ionization of a $\text{N}_2\text{O}/\text{CH}_4$ mixture. Fluoride ions were generated by electron ionization of NF_3 . Reagent ions formed in the source region were transported by the flowing helium through the reactor, where they were allowed to react with the gaseous neutral reagents introduced via leak valves. The alkoxide ions were formed by deprotonation of the corresponding alcohols by HO^- . Those arising from *cis*- and *trans*-2-*tert*-butyl-1,3-dithian-5-ol were generated by deprotonation with F^- . The alkoxide ions were used in the formation of monoalkoxysilicate ions by addition to a neutral silane in the flow reactor. Subsequent addition of a ketone formed the dialkoxysilicates. Proton-bound clusters were formed by addition of the alkoxides to alcohols that were introduced downstream. The ions were thermalized to ambient temperature by ca. 10^5 collisions with the helium buffer gas. Negative ions were extracted from the flow reactor through a 0.5 mm orifice in a nose cone and then focused into an EXTREL triple quadrupole analyzer for mass spectrometric analysis.

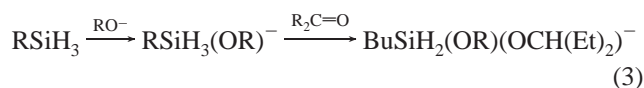
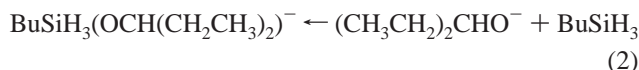
Collision-induced dissociation experiments were performed in the triple quadrupole mass analyzer using argon as the target gas. The target pressure in the central, gas tight quadrupole collision chamber (Q2) was maintained in the 0.08–0.25 mTorr range, which corresponds to multiple collision conditions.¹⁵ Collision energies were in the 15–20 eV range (laboratory frame). Mass-analyzed ions were detected with an electron multiplier. The voltage bias of the third quadrupole (Q3) was adjusted to optimize product ion collection, and the Q3 mass resolution and other tuning conditions of the triple quadrupole analyzer were adjusted to achieve maximum reproducibility ($\pm 10\%$ absolute) in the quantitative measurements of the CID product yield ratios. All intensities were recorded using a digital counter operating at a 10 s gate time. The ion intensity measurements, which follow a Poisson distribution, represent at least 10 replicate measurements. Therefore, the uncertainty in each counter measurement was calculated by taking the square root of the intensity. Uncertainties in the yield ratios were determined by using standard error propagation procedures.¹⁶

All dioxanone and dithianone derivatives were synthesized using literature methods.¹⁷ The compounds were purified according to standard procedures. All other reagents were obtained from commercial sources and used as supplied except for degassing of liquid samples prior to use. Gas purities were as follows: He (99.995%), SiH_4 (99.995%), N_2O (99%), CH_4 (99%), NF_3 (99%).

Results

The generation of pentacoordinate silicon hydride ions in a flowing afterglow instrument by addition of hydride to alkyl-

silanes has been reported previously (eq 1).^{13,18} These species are reactive reducing agents, capable of transferring hydride to transition metal carbonyls, CO_2 , boranes, and SiH_4 .^{5,19,20} Aldehydes and ketones are reduced by net addition of Si–H bond across the carbonyl group, producing an alkoxysilicate ion. An example of this process is given in eq 2. The structural assignment of the product of eq 2 was made by direct comparison of the collision-induced dissociation (CID) spectrum of the adduct obtained from the reaction of BuSiH_4^- with 3-pentanone to that of an authentic $\text{BuSiH}_3(\text{OCH}(\text{CH}_2\text{CH}_3)_2)^-$ ion produced by direct addition of $(\text{CH}_3\text{CH}_2)_2\text{CHO}^-$ to BuSiH_3 .¹³



Monoalkoxysilicate ions, formed either by addition of an alkoxide to a neutral silane or by reduction of an aldehyde or ketone by a pentacoordinate silicon hydride, can further reduce aldehydes and ketones, producing a pentacoordinate silicate ion bearing two alkoxy groups (dialkoxysilicates, e.g., eq 3). In fact, we have observed up to three consecutive reductions by RSiH_4^- to produce a trialkoxysilicate, $(\text{RO})_3\text{SiHR}^-$. Dialkoxysilicate ions formed by the process shown in eq 3 provide the key to determine the diastereoselectivity of the reduction of ketones in the gas phase. Upon collisional activation, dialkoxysilicates undergo competitive dissociation reactions involving loss of either of the alkoxide ligands. The relative yield of the alkoxide fragments appears to be a sensitive function of their relative basicities. This general behavior is analogous to that of proton-bound alkoxide clusters, $(\text{RO}^-)(\text{R}'\text{O}^-)\text{H}^+$, which can also undergo competitive alkoxide cleavages with yields reflecting the relative proton affinities of the alkoxide fragments.²¹ However, the decomposition of dialkoxysilicates also appears to reflect their structures and not just their relative basicities. A good example of this sensitivity is the dialkoxysilicate ion $\text{BuSiH}_2(\text{OCHMe}_2)(\text{OBu})^-$, formed by the direct addition of Me_2CHO^- to BuSiH_3 , followed by addition to butanal. CID of this ion with an argon target at a collision energy of 12 eV (lab frame) yields the alkoxide fragments $\text{Me}_2\text{CHO}^-/\text{BuO}^-$ in the ratio 1.51 ± 0.15 . Under similar conditions, CID of the corresponding proton-bound dimer $(\text{Me}_2\text{CHO}^-)(\text{BuO}^-)\text{H}^+$ gives the alkoxide fragments in essentially identical yields ($\text{Me}_2\text{CHO}^-/\text{BuO}^- = 1.00 \pm 0.01$), a result that reflects their identical Brønsted basicities.²² Thus, the secondary alkoxide is preferentially cleaved from the silicate ion, presumably because of steric repulsion effects that weaken the Si–OCHMe₂ bond. This behavior is what enabled us to distinguish isomeric alkoxide ions with similar basicities.

Dialkoxysilicate ions are presumed to exhibit a trigonal-bipyramidal geometry.²³ The ligands undergo facile positional exchange either in the long-lived ions or during collisional

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Scheme 1

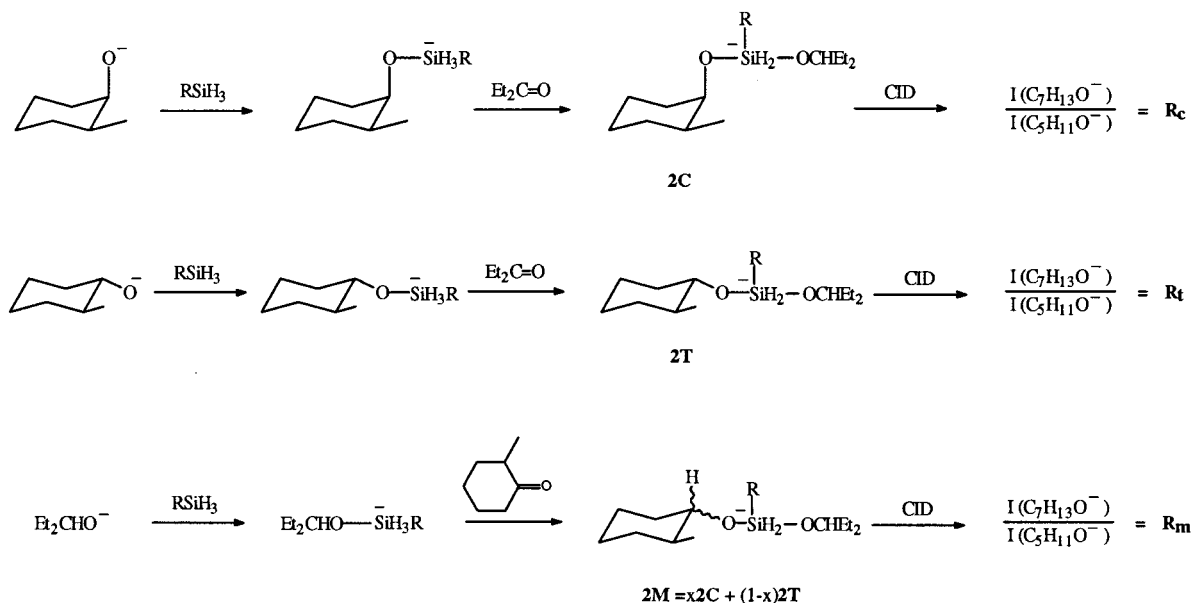


Table 1. Diastereomer Yield Ratios in Gas-Phase Hydride Reduction Reactions of Cyclic Ketones (Obtained by CID of the Dialkoxy siliconates)

ketone	CID product ratio, RO ⁻ /R'O ⁻ ^a			% axial (exo) reduction		
	cis (exo)	trans (endo)	ketone reduction product	this work (gas phase)	lit. (solution) ^b	theory ^c
1 4- <i>tert</i> -butylcyclohexanone	7.0 ± 0.3	1.43 ± 0.02	1.45 ± 0.02	99 ± 3	92, 85	88
2 2-methylcyclohexanone	3.21 ± 0.02	1.44 ± 0.05	1.82 ± 0.03	68 ± 5	76, 70	82
3 3,3,5-trimethylcyclohexanone	1.39 ± 0.02	11.1 ± 0.8	7.8 ± 0.4	9 ± 3	21, 42	30
4 norcamphor	0.42 ± 0.03	0.26 ± 0.01	0.27 ± 0.01	93 ± 7	91, 86	
5 2- <i>tert</i> -butyl-1,3-dioxan-5-one	1.76 ± 0.05	0.35 ± 0.03	0.87 ± 0.04	46 ± 3	93, 94	3

^a Measured yield ratio of alkoxy ion fragments from CID of C₆H₁₃SiH₂(OR)(OR')⁻ ions; R'O⁻ = 3-pentoxide for ketones **1–3**, 4-fluorophenethoxide for ketone **5**. For cis: RO⁻ = pure cis isomer of reduced ketone (**1–5**). For trans: RO⁻ = pure trans isomer of reduced ketone (**1–5**). Ketone reduction product: RO⁻ formed by reduction of ketone (**1–5**) by C₆H₁₃SiH₂(OR')⁻. ^b Reported yield of axial reduction product formed with LiAlH₄ in tetrahydrofuran and NaBH₄ in 2-propanol (**1–4**, ref 12), LiAlH₄ in ether, and NaBH₄ in 2-propanol (**5**, ref 29). ^c Predicted yield of axial reduction product formed with LiH (**1–4**) and SiH₅⁻ (**5**) based on ab initio (MP2/6-31G**/3-21G) molecular orbital calculations (refs 2 and 27).

activation. This is demonstrated by the equivalence of the CID spectra obtained for dialkoxy siliconate ions produced by the two complementary alkoxy addition/ketone reduction sequences (eq 2). For instance, attachment of the cyclohexyl-alkoxide ion to RSiH₃ (R = *n*-hexyl) followed by reduction of 3-pentanone gives a dialkoxy siliconate ion that yields a CID spectrum *identical* to that obtained for the ion formed by addition of the 3-pentoxide ion to RSiH₃ followed by reduction of cyclohexanone. Thus, the two reaction sequences yield dialkoxy siliconate ions with a common structure or mixture of structures, presumably via rapid Berry pseudorotation of the fluxional pentacoordinate silicon ion,²⁴ *regardless of the order in which the alkoxy ligands become attached*.

Given these general characteristics of the bimolecular and unimolecular reactions of pentacoordinate silicon hydride ions, we recently¹³ reported the following strategy for determining the stereochemical outcome of the gas-phase reduction of 4-*tert*-butylcyclohexanone (**1**), 2-methylcyclohexanone (**2**), and 3,3,5-trimethylcyclohexanone (**3**), substrates commonly examined in condensed-phase studies of carbonyl reduction stereochemistry.^{10–12} An illustration of the experimental protocol is given in Scheme 1. 3-Pentoxyl was selected as the auxiliary

alkoxide group for this particular set of experiments after extensive screening of alkoxy/ketone pairs for a system that gave measurable and reliable fragment ion yield ratios. Generation of 3-pentoxide by proton abstraction, followed by attachment to RSiH₃ and subsequent reduction of 2-methylcyclohexanone with this adduct, produces the dialkoxy siliconate whose stereochemical structure was to be determined (**2M**). CID of **2M** by using an argon target (0.10 mTorr) and 20 eV collision energy (lab frame) yields the two alkoxy ions in a ratio (C₇H₁₃O⁻/C₅H₁₁O⁻) of 1.82 ± 0.03. Subsequently, calibration experiments were carried out in which diastereomerically pure *cis*- and *trans*-2-methylcyclohexyl alkoxy ions were generated in the flow reactor by proton abstraction from the pure alcohols. Addition of RSiH₃ (R = *n*-hexyl) to form the monoalkoxy siliconate, followed by reduction of 3-pentanone with this ion, yields the dialkoxy siliconate ions **2C** and **2T**. CID of mass-selected **2C** and **2T** under the same conditions used for the experiments with **2M** gives the two alkoxy ion fragments in yield ratios (C₇H₁₃O⁻/C₅H₁₁O⁻) of 3.21 ± 0.02 for **2C** and 1.44 ± 0.05 for **2T** (Table 1).²⁵ Deconvolution of the diastereomeric mixture ratio from these data was then carried out using the algebraic expression shown in Scheme 1. The final percentages are 68 ± 5% trans and 32 ± 5% cis (±1 standard deviation). Thus,

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(25) The absolute total cross sections for the decomposition of **2C**, **2T**, and **2M** were found to be essentially identical at 12 ± 3 Å.

Table 2. Diastereomer Yield Ratios in Gas-Phase Hydride Reduction Reactions of Cyclic Ketones (Obtained by CID of the Proton-Bound Clusters)

ketone	CID product ratio, R ₁ O ⁻ /R ₂ O ⁻ ^a			% axial reduction		
	cis	trans	ketone reduction product	this work (gas phase)	lit. (solution)	theory ^b
5 2- <i>tert</i> -butyl-1,3-dioxan-5-one	0.43 ± 0.06	8.3 ± 0.2	0.98 ± 0.04	33 ± 4	93, 94 ^c	3
6 2- <i>tert</i> -butyl-1,3-dithian-5-one	0.28 ± 0.04	2.6 ± 0.1	0.43 ± 0.03	16 ± 4	15 ^d	0

^a Measured yield ratio of alkoxide ion fragments from CID of [R₁O⁻...H⁺...OR₂] ions. R₁O⁻ = 2,2-difluoroethanol for **5**, 2,2,2-trifluoroethanol for **6**. For cis: R₂O⁻ = pure cis isomer of reduced ketone. For trans: R₂O⁻ = pure trans isomer of reduced ketone. Ketone reduction product: R₂O⁻ formed by reduction of ketone by C₆H₁₃SiH₄⁻. ^b Predicted yield of axial reduction product formed with SiH₅⁻ based on ab initio molecular orbital calculations (MP2/6-31G*/3-21G) (ref 27). ^c Reported yield of axial reduction product formed by LiAlH₄ in ether and NaBH₄ in 2-propanol (ref 29). ^d Reported yield of axial reduction of 1,3-dithian-2-phenyl-5-one by LiAlH₄ in ether (ref 29).

reduction of 2-methylcyclohexanone by a pentacoordinate silicon hydride ion in the gas phase occurs mainly from the axial direction to give the more stable trans product.

Use of analogous procedures with the same 3-pentoxide/3-pentanone auxiliaries for **1**, **3**, and **4** leads to the results shown in Table 1. Reduction occurs almost entirely from the axial direction for compound **1**, a rigid substrate representing a relatively unhindered chair cyclohexanone. In contrast, nearly exclusive equatorial reduction occurs for ketone **3**, wherein the axial face of the carbonyl group is effectively blocked by the axial methyl at C-3. The complete inversion in the preferred mode of attack between **1** and **3** illustrates the intrinsic preference for axial addition to unhindered cyclohexanones, even by a relatively bulky reducing agent such as an alkoxysiliconate ion.²⁶ The relatively greater yield of cis product for **2** compared to **1** is believed to be due, in part, to axial reduction of the higher energy conformer with the methyl group in the axial position. Ketone **4**, containing a rigid bicyclic structure with well-defined hindered (endo) and unhindered (exo) faces, undergoes a hydride reduction primarily from the exo direction, producing the less stable endo isomer of the product. The results obtained for ketones **1–3** (Table 1) are in good agreement with theory.² No theoretical predictions have been published on the diastereoselectivity of the hydride reduction of **4**.

The success of the method depends critically on two factors: (1) the auxiliary alkoxide RO⁻ fragment and the other alkoxide fragment must be observable upon CID so that the ratios can be reliably measured; (2) the CID fragment ion ratios measured for the two pure diastereomers in the calibration experiments must be as different as possible in order to minimize quantitative uncertainty in the mixture analysis; (3) the absolute cross sections for the decomposition of the diastereomeric dialkoxysiliconates, e.g., **2C** and **2T**, have to be similar. These requirements actually became an obstacle in the studies involving 2-*tert*-butyl-1,3-dithian-5-one (**6**), as discussed below.

Recently, Houk et al. made some provocative predictions regarding the preferred mode of hydride delivery by SiH₅⁻ to 1,3-dioxan-5-one and 1,3-dithian-5-one in the gas phase. An almost exclusive equatorial approach of the reducing agent was calculated for these substrates.²⁷ This result contrasts with the behavior observed in solution, where 94% of the reduction by LiAlH₄ in ether occurs from the axial direction (Table 2).^{12a,28,29} To probe the intrinsic reactivity, we determined the diastereoselectivity of the gas-phase hydride reduction of 2-*tert*-butyl-

1,3-dioxan-5-one (**5**) and 2-*tert*-butyl-1,3-dithian-5-one (**6**). The *tert*-butyl group at C-2 makes the ring structures of **5** and **6** rigid, a property that is essential for distinguishing the products resulting from axial reduction from those arising from equatorial approach of the reducing agent. However, the results of these experiments can be applied to 1,3-dioxan-5-one and 1,3-dithian-5-one because the *tert*-butyl group is too removed to exert any steric influence at the reaction center. In addition, its inductive and field effects should be minimal.

In contrast to all of the experiments discussed above, 3-pentoxyl cannot be used as the auxiliary group (R'O) for the dioxanone system because the gas-phase basicity of 3-pentoxide is greater than that of the cis and trans alkoxide ions corresponding to **5**. Survey experiments with several different systems eventually pointed to CH₃CH(Ar)O⁻ (Ar = 4-fluorophenyl) as a suitable partner alkoxide. The corresponding ketone, 4-fluoroacetophenone, has enantiotopic faces. This means that a racemic mixture of monoalkoxysiliconates is formed upon reduction of the dioxanone. However, since the carbonyl carbon in the substrate is not prochiral, only one pair of diastereomeric products is generated. Hence, the values obtained for R_c and R_t reflect only the differences in the structures of the alkoxides that correspond to the ketone of interest and are not dependent on the chirality of the partner alkoxide CH₃CH(Ar)O⁻. The final percentage obtained for the reduction of **5** (46 ± 3% axial reduction, Table 1) is in disagreement with the theoretical prediction (97% equatorial reduction). However, the results reflect a trend predicted by theory, i.e., less axial reduction than that observed for reduction of 4-*tert*-butylcyclohexanone.

A problem was encountered when examining ketone **6**: the CID spectra obtained in the calibration experiments (Scheme 1) did not yield significantly different values for R_c and R_t. In other words, the relative yields of the two alkoxide fragments are not sensitive to the differences in the structure of the two diastereomeric pentacoordinate silicon ions. To enhance stereodifferentiation in the CID process, a series of different alkylsilanes (*n*-hexylsilane, diethylsilane, *tert*-butylsilane) were examined. An increase in the steric bulk around the pentacoordinate silicon bridge was expected to promote the dissociation of the alkoxy ligands to different extents for the two diastereomers. However, these values remained essentially the same for all alkylsilanes used. Therefore, the dialkoxysiliconate approach, while successful for the dioxanone system, did not seem to work for the analysis of the reduction of **6** and had to be abandoned.

In the course of these studies, however, it became evident that **6** has a sufficiently high hydride affinity to react with monoalkylsilicon hydride ions through an overall (bimolecular) hydride transfer to produce the free alkoxide (eq 4). This observation, which was also noted in earlier studies,³⁰ im-

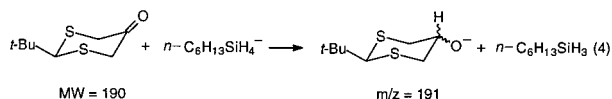
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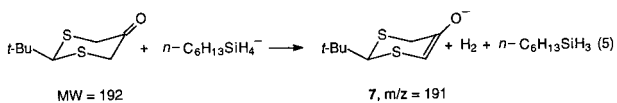
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mediately suggested a solution to the lack of stereodifferentiation of CID of dialkoxysiliconates: the use of proton-bound clusters. Proton-bound clusters²¹ ($R_1O^- \cdots H^+ \cdots -OR_2$) are readily generated in the flow reactor by the (termolecular) addition of an alkoxide R_1O^- to an alcohol R_2OH . Examination of CID of these clusters allows the stereochemical analysis to be carried out as described above. For these experiments, 2,2,2-trifluoroethanol was chosen as the auxiliary alcohol, since its proton-bound clusters synthesized in the flow reactor exhibited excellent stereodifferentiation upon CID ($R_c = 0.28 \pm 0.04$, $R_t = 2.6 \pm 0.1$) [the gas-phase acidity (ΔH_{acid}) of *trans*-2-*tert*-butyl-1,3-dithian-5-ol is about 6 kcal/mol lower than that of *cis*-2-*tert*-butyl-1,3-dithian-5-ol³¹].

This new approach seemed to effectively solve the obstacles encountered in the calibration experiments described above for pure *cis*- and *trans*-2-*tert*-butyl-1,3-dithian-5-ol. However, it introduced a new problem. In addition to overall hydride transfer, protolytic cleavage of an α -proton occurs with the dithianone (**6**) upon reaction of the pentacoordinate silicon hydride ions to produce an enolate, **7** (eq 5), instead of the



desired free alkoxide. This product has a mass-to-charge ratio that is two units less than that of the corresponding alkoxide. The enolate (**7**) forms a proton-bound cluster with 2,2,2-trifluoroethanol, just like the desired alkoxide produced by reduction of **6** (eq 4). Furthermore, the proton-bound cluster containing the enolate moiety (with a ³⁴S atom, ~4% natural abundance) produces fragment ions at the same mass-to-charge value as the proton-bound cluster containing the alkoxide moiety (with two ³²S atoms), thus introducing an error in the value obtained for R_m (Scheme 1). This problem was addressed by determining the percentage of enolate-containing proton-bound clusters that undergo CID along with the alkoxide-containing proton-bound clusters (by making use of the ³⁴S natural abundance and monitoring the intensity of enolate-containing proton-bound clusters in the flow reactor with two ³²S atoms) and by independently measuring the absolute collision cross section of the enolate-containing proton-bound cluster. After making the appropriate subtraction to the fragment ion intensities in the CID spectra, we obtained a value of $16 \pm 4\%$ for axial reduction of **6** by $n-C_6H_{13}SiH_4^-$. This result agrees well with theory²⁹ (Table 2).

To make a direct comparison between the dithianone and dioxanone systems, it was necessary to reanalyze the dioxanone system by using the proton-bound cluster approach. This comparison exposes any possible biasing of the final results due to the use of different reducing agents [alkylsilicon hydride (eq 5) vs monoalkoxysiliconate (eq 4)] or different types of parent ions in the diastereomeric mixture analysis (dialkoxysiliconates vs proton-bound clusters). 2,2-Difluoroethanol was chosen as the auxiliary alcohol for the reexamination of the reduction of **5**. CID of the proton-bound clusters of this alcohol produced measurable ion yield ratios with excellent stereodifferentiation (Figure 1). To eliminate the contribution of the enolate-containing proton-bound clusters with an ¹⁸O atom

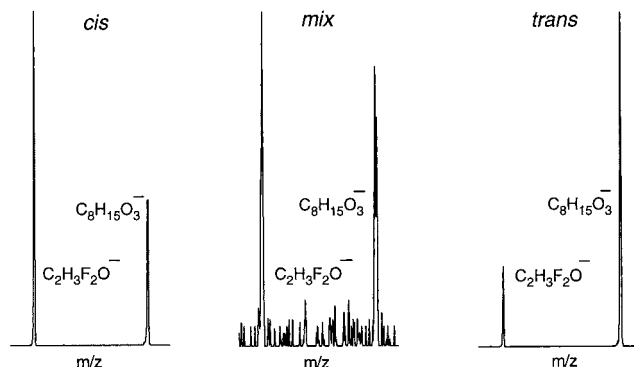


Figure 1. Partial CID spectra for $(C_2H_3F_2O^-)(cis-C_8H_{15}O_3^-)H^+$, $(C_2H_3F_2O^-)(trans-C_8H_{15}O_3^-)H^+$, and $(C_2H_3F_2O^-)(mix-C_8H_{15}O_3^-)H^+$.

(~0.2% natural abundance) generated from the protolytic cleavage of α -protons of **5** to the total intensity of the parent ion selected for CID, the correction made for the analysis of the reduction of **6** was also employed for this system. The final percentage obtained was $33 \pm 4\%$ for axial reduction of **5** (Table 2), a value that is well above the theoretical prediction. However, this result demonstrates a dramatic reversal of the behavior observed in solution, in agreement with theory.

Discussion

Among the alkyl-substituted cyclohexanones studied, **1** is of particular interest, since it has the least flexible ring structure and the least hindered axial face for hydride addition to the carbonyl group. The *tert*-butyl group is locked in an equatorial position and is spatially removed from the reaction center. Therefore, the gas-phase diastereoselectivity of **1** should effectively represent the ratio of axial and equatorial attack on the chair conformation of cyclohexanone in the absence of solvent, i.e., the intrinsic diastereoselectivity. The $99 \pm 3\%$ value obtained for the axial reduction of **1**, corresponding to formation of the more stable *trans* isomer of the product, is in excellent agreement with the behavior observed for this compound in solution and consistent with the theoretical prediction of a preferred axial reduction in the gas phase (Table 1). Torsional strain has been proposed to be the dominant factor in the strong preference for axial attack observed for **1** in solution.^{32,33}

The diastereoselectivity observed for the reduction of **2** in the gas phase ($68 \pm 5\%$ axial reduction) is also consistent with the reported condensed-phase behavior of this compound toward the common reducing agents $LiAlH_4$ and $NaBH_4$. However, theory predicts a somewhat greater amount of axial reduction for LiH in the gas phase (82%, Table 1) than what was measured in our experiments. We believe that this difference is due, in part, to the fact that only the conformer with the methyl group in the equatorial position was considered in the theoretical study (Table 1). At ambient temperature, **2** is reported to exist as a mixture of conformers composed of 5% of the high-energy conformer with the methyl group in the axial position and 95% of the low-energy conformer with the methyl group in the equatorial position.³⁴ The diastereoselectivity observed for the reaction of *cis*-4-*tert*-butyl-2-methylcyclohexanone (in which the 2-methyl group is fixed in an equatorial position) and $LiAlH_4$ in tetrahydrofuran (83% axial reduction) supports this hypothesis.¹²

Electronic, torsional, and steric effects have been proposed to explain the stereoselectivity in the hydride reduction of cyclic

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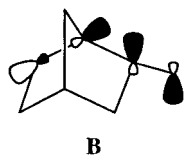
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ketones.¹¹ The torsional component is believed to overwhelm the steric component as a control factor in systems in which axial hydride addition dominates, such as in **1** and **2**. However, hydride addition to alkyl-substituted cyclohexanones from the equatorial direction becomes favorable if a large steric hindrance exists for axial attack. Ketone **3**, in which the axial face of the carbonyl group is effectively blocked by the axial methyl group at C-3, is ideal for investigating this effect. Experimental results obtained in solution as well as theoretical predictions for the gas phase indicate that hydride addition to **3** occurs from the equatorial rather than the axial direction. The 9% axial reduction observed for **3** in the gas phase, which represents a complete inversion in the preferred mode of attack when compared to **1**, verifies that the measured diastereomer ratios are kinetically determined in these experiments (*cis*-3,3,5-trimethylcyclohexanol is more stable than the *trans* isomer by ca. 1.5 kcal/mol, and an even larger energy difference is expected for the dialkoxysiliconate ion reduction products of **3**).³⁹ The preference for the axial reduction of **3** observed in this study is, however, somewhat less than that predicted by theory (Table 1). This inconsistency can be explained by differences in the steric effects considered in the theoretical studies and those present in the real system. LiH is the reducing agent in the theoretical study, a species that is much smaller than the monoalkoxysiliconate C₆H₁₃SiH₃(OCH₂)₂⁻.

Norcamphor (**4**), which contains a rigid bicyclic structure, is another example of a ketone with well-defined hindered and unhindered faces. However, reduction of **4** with LiAlH₄ in ether is highly selective in solution. Reduction (91%) occurs from the exo direction in solution (Table 1), which is less sterically hindered. No theoretical predictions have been published on the diastereoselectivity of the hydride reduction of **4**. The gas-phase results (93 ± 7% *exo* reduction) are consistent with the reduction of **4** by LiAlH₄ in tetrahydrofuran (Table 2). Compound **4** exhibits a behavior similar to that of **3**; i.e., the hydride approaches **4** from the least hindered direction. Steric effects,³⁵ torsional interaction,³⁶ and frontier orbital interactions³⁷ have been used to rationalize the outcome of the hydride reduction of **4**. It appears that steric effects overwhelm the torsional effects as a control factor in the reduction of **4** by a monoalkoxysiliconate ion in the gas phase (DePuy et al. experimentally determined that there is no difference in the intrinsic thermodynamic stability of its reduction products, gaseous *exo*-norborneol and *endo*-norborneol³⁸). The steric repulsion results from the interaction between the reducing agent and the *endo* hydrogens at C-5 and C-6. Alternatively, examination of the LUMO arising from hyperconjugation of the β C-C σ* orbital with the carbonyl π* orbital (**B**) reveals a distortion of the vacant



π* orbital that favors *exo* attack of the hydride reducing agent, in agreement with our results in the gas phase and the observed diastereoselectivity of hydride reductions in solution (Table 1).

The gas-phase stereochemical results obtained for ketones **1–4** are generally consistent with the reported behavior of these

substrates in solution toward common reducing agents in, for example, LiAlH₄ and NaBH₄, and with the diastereoselectivities predicted by MO calculations for reduction by LiH in the gas phase (Table 1). The observation of the same diastereoselectivity in the gas phase and in solution implies that extrinsic factors, such as specific solvation, ion-pairing, and/or metal ion coordination effects, need not necessarily be invoked; i.e., that diastereoselectivity of these ketones is a property ascribed to intrinsic characteristics of the isolated reactants.

Wu and Houk predicted a strong departure in the stereochemical outcome between the gas phase and solution for the hydride reduction of 1,3-dioxan-5-one by SiH₅⁻.²⁷ The basis for this prediction is the calculated strong electrostatic repulsion upon attack of the hydride reducing agent from the axial face of the dioxanone. The intrinsic controlling factor in this reduction is repulsion between the nucleophilic hydride and the ring heteroatoms, which overwhelms the torsional effect associated with equatorial attack (in solution, this repulsion is attenuated by the presence of solvent). Furthermore, owing to the short C–O bonds in the ring, the six-membered ring of the dioxanone is flatter than that of cyclohexanone, increasing the torsional strain associated with equatorial attack of the hydride nucleophile relative to cyclohexanone. Hence, the diastereoselectivity observed for reduction of 1,3-dioxan-5-one by LiAlH₄ in solution is one in which axial attack occurs to a greater extent than in cyclohexanone.²⁹ In the gas phase, however, the electrostatic repulsion between the nucleophilic hydride and the ring heteroatoms overwhelms the torsional effect, and the reduction is predicted to occur almost exclusively (97%) from the equatorial direction. The 46 ± 3% axial reduction obtained here for the gas-phase reduction of the *tert*-butyl derivative (**5**) is inconsistent with the theoretical prediction. This inconsistency may arise from the different reducing agent employed in the two studies (SiH₅⁻ vs C₆H₁₃SiH₃OC₈H₈F⁻). The monoalkoxysiliconate ion has an electron-withdrawing group attached to the Si atom, which may result in less electron density on the hydrides compared to SiH₅⁻. Therefore, less electrostatic repulsion between the monoalkoxysiliconate ion and the ring oxygens may be present than for SiH₅⁻. This expectation is supported by the results obtained in the gas-phase experiments involving proton-bound clusters as the substrates for CID (Table 2), which reflect a decrease of 13% in axial reduction compared to the systems in which monoalkoxysiliconates are used as reducing agents (Table 1). In the proton-bound clusters, the Si atom in the reducing agent does not contain an electron-withdrawing group. Therefore, the electron density on the hydrides may be greater than in monoalkoxysiliconates, resulting in an increased electrostatic repulsion between the reducing agent and the ring oxygen atoms and, therefore, a reduced percent axial reduction. Finally, Houk's prediction does not include any interactions between the Si atom and the carbonyl group oxygen. In the real system, a net addition of an Si–H bond occurs across the carbonyl group. The carbonyl oxygen may slightly stabilize the transition state for axial attack by interacting with the electropositive Si atom. The change in selectivity relative to **1**, however, is in the predicted direction.

The preferred mode for hydride addition to 1,3-dithian-5-one is predicted to occur from the equatorial direction.²⁷ As in the case of 1,3-dioxan-5-one, this preference can be explained by electrostatic repulsion between the incoming negative hydride nucleophile and the lone pairs of the two sulfur atoms in the ring. However, the dithianone should exhibit an even larger preference for equatorial reduction than the dioxanone due to torsional effects. The long C–S bonds and small C–S–C angles

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cause the ring to be significantly puckered relative to cyclohexanone, favoring equatorial addition.²⁷ This trend is indeed what was observed in the gas phase. Interestingly, the gas-phase stereochemical results are in excellent agreement with the observed diastereoselectivity for reduction by LiAlH_4 in solution (Table 2). Hence, it appears that, in the case of axial attack, the electrostatic repulsion between the incoming reducing agent and the ring sulfur lone pairs is so large that it is not effectively muted by the solvent molecules. This proposition is supported by theory.²⁷ The energy calculated for the equatorial transition state in the reaction with SiH_5^- (MP2/6-31G* SCRF//HF/3-21G) is 2.9 kcal/mol lower than that of the axial transition state, which gives a selectivity of 99:1 in favor of equatorial attack. The equivalent energy difference predicted for the dioxanone system is 2.8 kcal/mol. This leads to a selectivity of 1:99 in favor of axial attack, which is in agreement with the reported selectivity in solution.

Conclusions

An experimental method for distinguishing the diastereomeric products of gas-phase hydride reduction reactions has been developed and applied to the determination of the intrinsic diastereoselectivity of reduction of cyclic ketones commonly used as substrates in solution studies. The results obtained for alkyl-substituted cyclohexanones (axial attack of the hydride reducing agent to sterically unhindered ketones and equatorial attack to ketones with a sterically hindered axial face) and norcamphor (exo attack) are in excellent agreement with the behavior reported for the same substrates in solution toward common reducing agents, such as NaBH_4 and LiAlH_4 ,^{3,12} and are consistent with the diastereoselectivities predicted by molecular orbital calculations for reduction by LiH and SiH_5^- in the gas phase.^{2,27} The similarity between the condensed-phase and gas-phase behavior implies that environmental effects, such as solvation, ion-pairing effects, and metal ion coordination, are either canceling or unimportant and that reduction diastereoselectivities are the result of the intrinsic properties of the isolated reactants.

The differences observed for the reduction diastereoselectivities among the alkyl-substituted ketones [% axial (exo) attack

= 99 ± 3 , 68 ± 5 , 9 ± 3 , and 93 ± 7 for **1**, **2**, **3**, and **4**, respectively] are readily rationalized in terms of competition between steric and torsional effects. Hence, concepts of hyperconjugative electron donation from the anti-periplanar $\sigma\text{C-H}$ orbitals of the cyclohexane ring into the vacant antibonding σ^* orbital of the incipient bond need not be invoked. The preference for hydride attack from the axial direction in unhindered cyclohexanones (**1** and **2**) arises from a torsional barrier for the equatorial attack. This is true even for a relatively bulky reducing agent such as a monoalkoxysiliconate ion.²⁶ The extent of axial attack is reduced when steric hindrance is introduced. Equatorial attack becomes the preferred mode of addition when steric effects overcome torsional strain (as in the case of **3** and **4**).

Houk's predicted trend of a preferred equatorial attack of the reducing agent in the gas-phase hydride reduction of 2-*tert*-butyl-1,3-dioxan-5-one (**5**),²⁷ in sharp contrast to the behavior observed in solution, was experimentally confirmed. This observation is readily rationalized by electrostatic effects. Although the gas-phase results obtained for **5** do not exactly match the theoretical prediction, the lower percent axial reduction observed in **5** relative to **1** is in agreement with the computed trends. Houk's theoretical prediction²⁷ of a larger preference for equatorial attack in the gaseous dithianone compared to the dioxanone system was also verified. The diastereoselectivity observed for hydride reduction of 2-*tert*-butyl-1,3-dithian-5-one (**6**), i.e., almost exclusive equatorial approach of the reducing agent, is also in good accord with the behavior observed for the 2-phenyl-substituted dithianone system in solution.²⁹ Experiments are in progress to distinguish *enantiomeric* products of gas-phase hydride reduction reactions of prochiral ketones by using the same stereochemical protocol.

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