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Supplementary Material Available: Details of structure determination including tables of crystal and data collection parameters, bond distances and angles with estimated standard deviations, atomic coordinates, anisotropic displacement coefficients, and H-atom coordinates and isotropic displacement coefficients (12 pages); listing of observed and calculated structure factors (16 pages). Ordering information is given on any current masthead page.

Development of a Gas-Phase Stereochemical Protocol. Intrinsic Diastereoselectivity in Hydride Reductions of Cyclohexanones

Yeunghaw Ho and Robert R. Squires*

Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

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A common feature of classical, intuitive models[1] and modern molecular orbital-based theories[2] for diastereoselectivity in ketone reduction reactions is an emphasis on the structural and electronic properties of the *substrate*, despite the fact that the stereochemical outcome of these reactions often displays marked sensitivity to the solvent and the type of counter-ion employed with ionic and polar reducing agents.[3] One way to separate intrinsic and extrinsic effects on the stereochemistry of ketone reduction reactions is to examine them in the gas phase, where solvent and counterion effects are absent. We describe here an experimental method for distinguishing the *diastereomeric* products of gas-phase hydride reduction reactions, and its application in determining the intrinsic diastereoselectivity involved in reductions of alkyl-substituted cyclohexanones.[4]

Some time ago we reported the generation of pentacoordinate silicon hydride ions in a flowing afterglow instrument from addition of hydride to alkylsilanes (eq 1).[5] These species were found to

$$H^- + RSiH_3 \rightarrow RSiH_4^- \qquad (1)$$

be reactive reducing agents, transferring hydride to CO_2, transition metal carbonyls, boranes, and even to SiH_4.[5-7] With simple aldehydes and ketones, reduction occurs by the net *addition* of an Si–H bond across the carbonyl group to produce an alkoxysiliconate ion (eq 2). The occurrence of C=O reduction is clearly shown by comparing the collision-induced dissociation (CID)

$$BuSiH_4^- + Me_2C{=}O \rightarrow BuSiH_3(OCHMe_2)^- \leftarrow Me_2CHO^- + BuSiH_3 \qquad (2)$$

spectrum[4] of the adduct obtained from reaction of $BuSiH_4^-$ with acetone to that obtained from an authentic $BuSiH_3(OCHMe_2)^-$ ion produced by direct addition of Me_2CHO^- to $BuSiH_3$. The spectra measured under similar conditions are indistinguishable,[8] thereby verifying the structural assignment shown for the product of eq 2. Analogous experiments with other alkoxide/carbonyl compound pairs and different alkylsilanes show this behavior to be general.

An alternative approach to siliconate ion reducing agents is the direct addition of a preformed alkoxide ion to a primary, secondary, or tertiary alkylsilane. Reduction of an aldehyde or ketone by the resulting alkoxysiliconate ion then produces a pentacoordinate silicon ion bearing two alkoxy groups (e.g., eq 3). The

$$BuSiH_3 \xrightarrow{RO^-} BuSiH_3(OR)^- \xrightarrow{Me_2C=O} BuSiH_2(OR)(OCHMe_2)^- \qquad (3)$$

dialkoxysiliconate ions formed in this way provide the keys to determining the diastereoselectivity of the gas-phase reductions. Upon collisional activation, these ions undergo competitive dissociation reactions by loss of the alkoxide ligands. Moreover, the relative yield of the two alkoxides appears to be an extremely sensitive function of their structures and relative basicities. In this sense, dialkoxysiliconate ions are analogous to proton-bound alkoxide dimers $(RO^-)(R'O^-)H^+$, which also undergo competitive alkoxide cleavages with yields reflecting their relative proton affinities.[9] However, the decomposition of dialkoxysiliconate ions appears to be somewhat more sensitive to the *structures* rather than just the basicities of the alkoxy ligands. For example, addition of Me_2CHO^- to $BuSiH_3$ followed by reaction of the adduct with butanal produces the dialkoxysiliconate ion $BuSiH_2(OCHMe_2)(OBu)^-$. CID of this ion with argon target at 12 eV (lab frame) yields the alkoxide fragments in the ratio $Me_2CHO^-/BuO^- = 1.51 \pm 0.15$. For comparison, CID of the corresponding proton-bound dimer $(Me_2CHO^-)(BuO^-)H^+$ under similar conditions gives the alkoxides in essentially identical yields: $Me_2CHO^-/BuO^- = 1.00 \pm 0.01$—a result reflecting their identical Brønsted basicities.[10] Thus, the secondary alkoxide is preferentially cleaved from the siliconate ion, presumably due to steric repulsion effects that weaken the $Si{-}OCHMe_2$ bond.

The attached ligands in the presumably trigonal–bipyramidal dialkoxysiliconate ions[11] can undergo facile positional exchange, either in the long-lived ions or during CID. This is shown by the equivalence of the CID spectra obtained from the dialkoxy-

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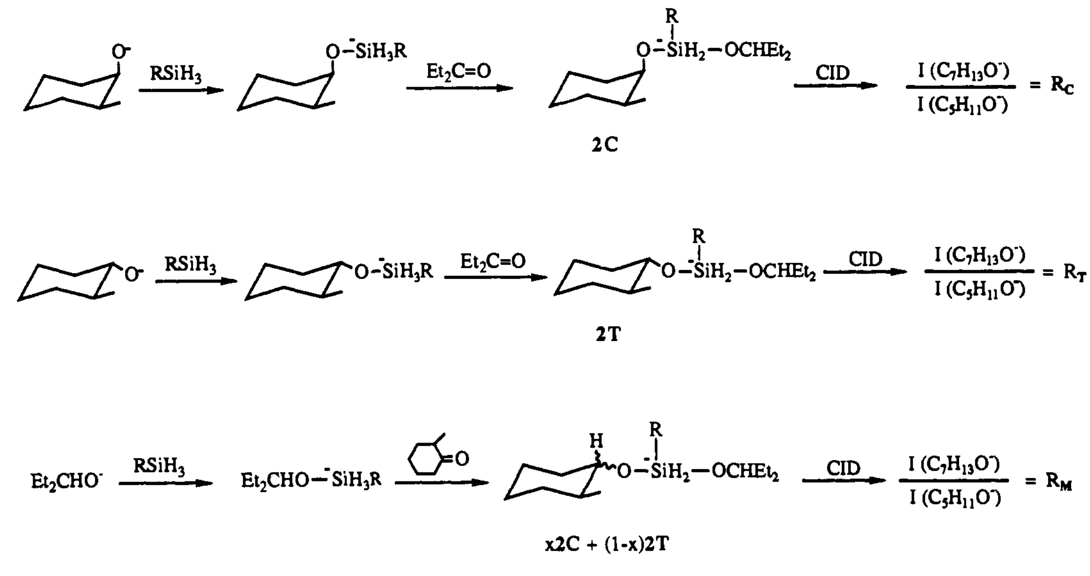
Scheme I



$$\% \text{ cis product} = x = \frac{(R_M - R_T)(1 + R_C)}{(R_C - R_T)(1 + R_M)} \cdot 100$$

Table I. Diastereomer Yield Ratios in Gas-Phase Hydride Reduction Reactions of Substituted Cyclohexanones

		dialkoxysiliconate CID ratio, $RO^-/C_5H_{11}O^-$ [a]			% axial reduction		
	ketone	cis	trans	ketone reduction product	this work (gas phase)	lit. (solution)[b]	theory[c]
1	4-*tert*-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

[a] Measured yield ratio of alkoxide ion fragments from CID of $C_6H_{13}SiH_2(OR)(OC_5H_{11})^-$ ions. cis: RO = pure *cis*-cyclohexylalkoxide isomer; trans: RO = pure *trans*-cyclohexylalkoxide isomer; ketone reduction product: RO formed by reduction of the substituted cyclohexanone by $C_6H_{13}SiH_3(OC_5H_{11})^-$. [b] Reported yield of axial reduction product formed with $LiAlH_4$ in tetrahydrofuran and $NaBH_4$ in 2-propanol (ref 3a). [c] Predicted yield of axial reduction product formed with LiH based on ab initio molecular orbital calculations (ref 2i).

siliconate ions produced by the two complementary alkoxide-addition/ketone-reduction sequences. For instance, attachment of cyclohexylalkoxide ion to $RSiH_3$ (R = *n*-hexyl) followed by reduction of 3-pentanone gives a dialkoxysiliconate ion that exhibits a CID spectrum *identical* to that obtained from the ion formed by addition of 3-pentoxide ion to $RSiH_3$ followed by reduction of cyclohexanone. Thus, a common structure or mixture of structures is formed, presumably by rapid Berry pseudorotation of the fluxional pentacoordinate silicon ion,[12] *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 formulated 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**)—prototype substrates commonly examined in solution-phase studies of carbonyl reduction stereochemistry.[1-3] An illustration of the experimental protocol for **2** is given in Scheme I. Diastereomerically pure *cis*- and *trans*-2-methylcyclohexylalkoxide ions were generated in the flow tube by proton abstraction from the pure alcohols. Addition of $RSiH_3$ (R = *n*-hexyl) to form the monoalkoxysiliconates followed by reduction of 3-pentanone yields the dialkoxysiliconate ions **2C** and **2T**. 3-Pentoxyl was selected as the auxiliary alkoxide group for these studies after extensive screening of alkoxide/ketone pairs for a system that gave easily measured fragment ratios. CID of mass-selected **2C** and **2T** using an argon target (0.10 mTorr) and a 20 eV (lab) collision energy gives the two alkoxide ion fragments in yield ratiois ($C_7H_{13}O^-/C_5H_{11}O^-$) of 3.21 ± 0.02 for **2C** and 1.44 ± 0.05 for **2T** (Table I). In the final step, attachment of 3-pentoxide to $RSiH_3$ followed by reduction of 2-methylcyclohexanone with this adduct produces the dialkoxysiliconate **2M** with an unknown diastereomeric composition. CID of **2M** under the same conditions used for the control experiments yields the two alkoxides in a ratio ($C_7H_{13}O^-/C_5H_{11}O^-$) = 1.82 ± 0.03.[13] Deconvolution of the diastereomer mixture ratio from these data was then carried out using the algebraic expression shown in Scheme I. The final percentages are 68 ± 5% trans and 32 ± 5% cis (±1 standard deviation). Thus, 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 for **1** and **3** along with the same 3-pentoxide/3-pentanone auxiliaries leads to the results shown in Table I. Reduction occurs almost entirely from the axial direction with compound **1**, a rigid model substrate representing a relatively unhindered chair cyclohexanone. In contrast, nearly exclusive equatorial reduction occurs with ketone **3**, in which 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** verifies that the measured diastereomer ratios are *kinetically* determined in these experiments[14] and illustrates the intrinsic preference for axial addition to unhindered

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

(14) *cis*-3,3,5-Trimethylcyclohexanol is more stable than the trans isomer by ca. 1.5 kcal/mol, see: Eliel, E. L.; Gilbert, E. C. *J. Am. Chem. Soc.* **1969**, *91*, 5487. An even larger energy difference is expected for the dialkoxysiliconate ion reduction products from **3**.

cyclohexanones—even by a relatively bulky reducing agent such as an alkoxysiliconate ion.[15] The relatively greater yield of cis product from **2** compared to **1** is believed to be due, in part, to axial reduction of the small amount of the higher energy substrate conformer with the methyl group in an axial position.[3a]

The gas-phase stereochemical results for ketones **1–3** are generally consistent with the reported behavior of these substrates toward common reducing agents in solution such as $LiAlH_4$ and $NaBH_4$[1-3] and with the predicted diastereoselectivities for reduction by LiH obtained from MO calculations[2i] (Table I). The occurrence of this same diastereoselectivity in the gas phase implies that extrinsic factors such as specific solvation, ion-pairing, and/or metal ion coordination effects need not necessarily be invoked, i.e., that it is properly ascribed to intrinsic properties of the isolated reactants. Experiments with other cyclic, bicyclic, and acyclic ketones and ketones bearing polar substituents are in progress.

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(15) Extremely bulky reducing agents in solution, such as the trialkylborohydrides display a preference for equatorial attack with **1**, cf.: Smith, K.; Pelter, A.; Norbury, A. *Tetrahedron Lett.* **1991**, *32*, 6243.

Electron-Transfer Communication between Redox-Functionalized Polymers and the Active Center of the Enzyme Glutathione Reductase

Itamar Willner,* Ron Kasher, Eran Zahavy, and Noa Lapidot

Institute of Chemistry and the Farkas Center for Light Induced Processes, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

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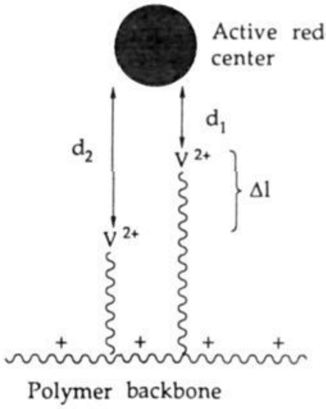
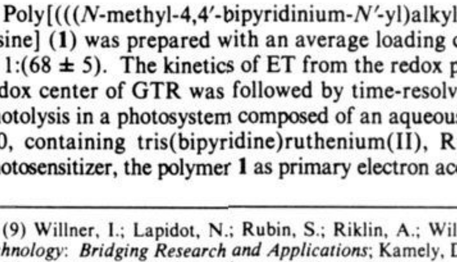
Electron-transfer (ET) processes in protein assemblies are a subject of extensive experimental[1,2] and theoretical research.[3,4] The distance,[5] stereochemical dynamics,[6] and nature of chemical bonds[7] of donor–acceptor pairs in proteins have been found to affect intra- and interprotein electron-transfer rates. ET processes between protein redox centers and their macroscopic environments are also of practical importance.[8] ET communication between proteins and electrodes is the basis for amperometric biosensors,[8] and electrical interactions between proteins and an excited species provide routes for photosynthetic transformations.[9] Recent experiments by Heller and co-workers have revealed that electrical communication between the enzyme glucose oxidase and electrodes is maintained by chemical modification of the protein with electron relay components[10] or by its interaction with redox-functionalized polymers.[11] In the latter system, electrical communication is improved as the chain anchoring the relay component to the polymer is lengthened. This has been attributed to the capability of longer chain relay components to attain closer distances to the protein active site and consequently enhance electron-transfer communication. Recent studies have revealed that the enzyme glutathione reductase, GTR, does not electrically communicate with a short-chain bipyridinium–acrylamide polymer,[12] but effective electrical wiring of the protein is accomplished by its chemical modification with bipyridinium relay components.[13] Here we wish to report on the ET processes occurring in assemblies composed of glutathione reductase with *N*-methyl-*N'*-(carboxyalkyl)-4,4'-bipyridinium-modified poly(L-lysine) (**1**). We reveal that the effectiveness of ET from the redox polymer to the protein active site is controlled by the alkyl chain length anchoring the bipyridinium salt to the polymer backbone and correlates ET rate constants with the average distance between the relay site and protein redox center.

Scheme I. Schematic Model for Spatial Orientation of Redox Functionalized Poly(L-lysine) in Respect to the Redox Site of the Enzyme





(**1**)

Poly[(((*N*-methyl-4,4'-bipyridinium-*N'*-yl)alkyl)carbonyl)-L-lysine] (**1**) was prepared with an average loading corresponding to 1:(68 ± 5). The kinetics of ET from the redox polymer to the redox center of GTR was followed by time-resolved laser flash photolysis in a photosystem composed of an aqueous solution, pH 7.0, containing tris(bipyridine)ruthenium(II), $Ru(bpy)_3^{2+}$, as photosensitizer, the polymer **1** as primary electron acceptor, EDTA

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