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The Importance of Entropy in Stereoselection. Reduction of *tert*-Butylcyclohexanone by Lithium Aluminum Hydride

Robert E. Rosenberg* and Jonathan S. Vilardo

Department of Chemistry, SUNY, College at Geneseo, Geneseo, NY 14454

Abstract: In the title reaction, the differences in both the enthalpy and the entropy of activation between the *cis* and *trans* diastereomers were measured ($\Delta\Delta H^{\neq}$ = -793 (56) cal/mol and $\Delta\Delta S^{\neq}$ = 2.00 (0.20) e.u.). The experimentally determined $\Delta\Delta H^{\neq}$ is shown to be consistent with both the Felkin torsional strain model and *ab initio* calculations. While past comparisons have been based on $\Delta\Delta G^{\neq}$, it is argued that the use of $\Delta\Delta H^{\neq}$ is more appropriate.

Stereoselectivity can be achieved by many factors, including steric, electronic, and chelation control. Stereodifferentiation can be further improved by judicious choice of solvent and reaction temperature. Though entropy surely plays a role in this optimization process, it is rare for entropic control to be explicitly cited as a means of achieving this stereoselectivity. Yet small entropic differences between two pathways can change the diastereomeric excess (de) significantly. Consider a reaction which leads to two diastereomeric products run between 200-350 K. The effect on the de of varying $\Delta\Delta S^{\neq}$ from -1 to 0 to 1 e.u. while keeping $\Delta\Delta H^{\neq}$ at 1 kcal/mol is shown in Figure 1, below.

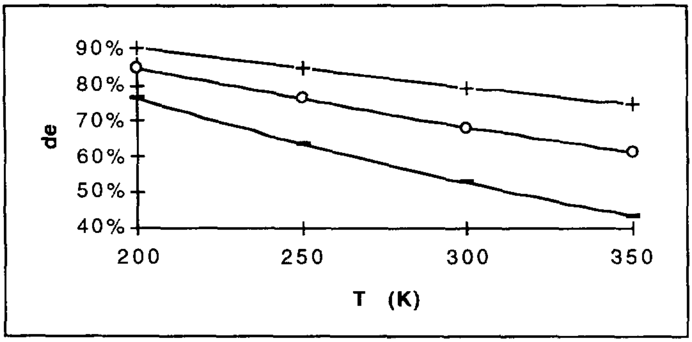
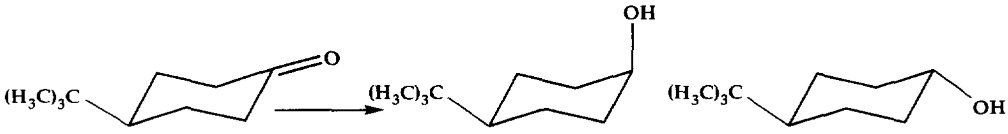


Figure 1. Diastereomeric excesses (de) for a hypothetical reaction as a function of temperature. The "+"s indicate a favorable entropy component, the open circles a neutral entropy component, and the "-"s an unfavorable entropy contribution.

In general, de decreases as temperature increases, even when $\Delta\Delta S^{\neq}$ is 0 e.u. At a given temperature, nonzero values of $\Delta\Delta S^{\neq}$ can dramatically affect de, with the greatest changes occurring at higher temperatures or for reactions with modest enthalpic differences. The relative effects of entropy and enthalpy on the de for the title reaction are determined below.



(1) cis-(**2**) *trans*-(**2**)

Figure 2. Reduction of 4-*tert*-butylcyclohexanone (**1**).

Since the discovery nearly 40 years ago that the $LiAlH_4$ reduction of 4-*tert*-butylcyclohexanone (**1**) gives predominately the *trans* product,[1] chemists have strived to identify how experimental factors affect the diastereomeric product ratio. Given that "diastereomer ratios in hydride reductions are quite temperature dependent",[2] it is surprising that this area has received so little attention. In the $LiAlH_4$ reduction of **1** in THF, Lansbury and Macleay reported de's at three temperatures (-40° C, 0° C, and 27° C)[3] and in the $NaBH_4$ reduction of **1** in isopropanol, Wigfield and Phelps obtained enthalpic and entropic data over a narrow temperature range (0° C- 25° C).[4] We have made two improvements to these studies: 1) data were taken over a wider temperature range (-84° C to 60° C) and 2) the potential for mechanistic complexity due to the presence of multiple reducing agents was minimized.[5,6]

Table 1. Percentage of *trans*-**2** for the Reduction of **1** in THF by $LiAlH_4$ at Various Temperatures[a]

T(K)	% *trans*-**2**			
	Run#1	Run#2	Run#3	Run#4
189	95.0	94.4	95.5	
210	93.3			
232	93.0			
273	90.5	90.3	91.6	91.4
300	89.4			
313	90.1			
333	89.1	89.5	88.5	

[a]Percentages were determined by GC.

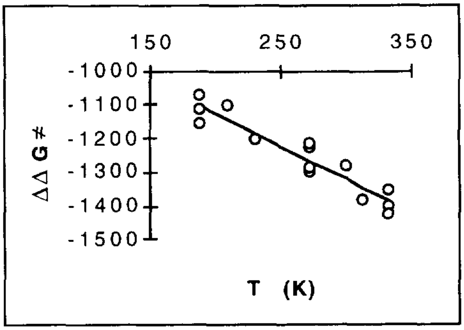


Figure 3. Plot of $\Delta\Delta G^{\neq}$ versus temperature using data from Table 1.

1) $\Delta\Delta G^{\neq} = -RT\ln K$ where $K = [trans\text{-}\mathbf{2}]/[cis\text{-}\mathbf{2}]$,

2) $\Delta\Delta G^{\neq} = \Delta\Delta H^{\neq} - T\,\Delta\Delta S^{\neq}$ $\Delta\Delta(\text{symbol})^{\neq} = \Delta(\text{symbol})^{\neq}$ for *trans*-**2** - $\Delta(\text{symbol})^{\neq}$ for *cis*-**2**,

and T = temperature.

A $\Delta\Delta H^{\neq}$ of -793 (56) cal/mol and a $\Delta\Delta S^{\neq}$ of 2.00 (0.20) e.u. were found using the relations above and a plot of $\Delta\Delta G^{\neq}$ versus T. The standard errors are given in parentheses. Interestingly, under different conditions, Wigfield and Phelps obtained a $\Delta\Delta H^{\neq}$ of -0.7 kcal/mol and $\Delta\Delta S^{\neq}$ of 1.4 e.u.[4] While standard organic texts correctly note that reduction of **1** at 0° C gives a de of 82% or a $\Delta\Delta G^{\neq}$ of 1.3 kcal/mol, there is little or no discussion of the relative importance of entropy and enthalpy. From this work it is seen that only 0.8 of the 1.3 kcal/mol are due to $\Delta\Delta H^{\neq}$, the remainder are due to $\Delta\Delta S^{\neq}$. Furthermore, $\Delta\Delta S^{\neq}$ leads to a higher de than would be obtained solely through enthalpic control. The mechanistic implications of these data are discussed below.

Though there is still no universally accepted mechanism for the stereoselectivity seen in the reduction of **1**,[7] perhaps the most widely used explanation is due to Felkin.[8] In this model, equatorial attack is disfavored by eclipsing interactions between the axial C-H bonds at C_2 and C_6 and the hydride-carbonyl carbon bond. These interactions are absent in axial attack, as shown in Figure 4. Since the Felkin model describes enthalpic differences, predictions of this theory should be compared to the enthalpic component of the experimental stereoselectivity, which is $\Delta\Delta H^{\neq} = 0.79$ kcal/mol. A reasonable upper limit for the theoretical energy difference is 2 kcal/mol, twice the value of a C-H, C-H eclipsing interaction in ethane. The experimental value, which is significantly less than the upper limit, is consistent with the idea that the cyclohexanone ring distorts in order to reduce the torsional strain of the incoming hydride in equatorial attack. This torsional strain model has received strong support from *ab initio* studies.[9]

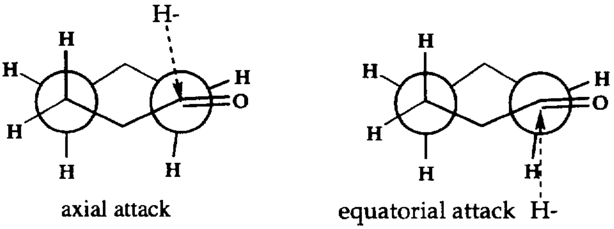


Figure 4. Axial and equatorial attack of **1** by hydride ion, Newman projections

Clearly, it is of interest to compare *ab initio* data with experimental work for the title reaction. In order to reduce the complexity of the computational problem, two simplifications have often been employed. First, a smaller reducing agent such as LiH is substituted for $LiAlH_4$. Second, calculations are performed at 0 K in the gas phase. Since under these conditions no attempt is made to model entropy, the resulting data should be compared to the $\Delta\Delta H^{\neq}$ of 0.79 kcal/mol determined above. Four previously developed methodologies have been extended to higher levels of theory for this comparison. As can be seen in Table 2, the agreement is quite good for all models used.

In conclusion, the well known reduction of **1** into *cis* and *trans* **2** by $LiAlH_4$ in THF is shown to have a $\Delta\Delta H^{\neq}$ of 0.79 kcal/mol and a $\Delta\Delta S^{\neq}$ of 2.0 e.u. These values should be used in the evaluation of mechanistic and computational models of hydride reductions. We are currently measuring the difference in activation parameters for reductions where either the reducing agent or solvent is varied.

Table 2. Values of $\Delta\Delta H^{\neq}$ for the Reduction of **1** using Different Computational Reducing Agents.[a]

Basis Set[10]	LiH	NaH[b]	AlH_3	SiH_5^-
3-21G//3-21G	0.93[b]	0.70	1.14[c]	1.44[d]
6-31G*//6-31G*	1.84	1.53	1.91	1.81
6-311++G**/6-31G*	1.68	1.51	1.83	2.11
MP2/6-31G*//6-31G*	1.29	0.83	1.26	1.86

[a] $\Delta H^{\neq}_{cis\text{-}2} - \Delta H^{\neq}_{trans\text{-}2}$ in kcal/mol. Unless otherwise noted values are from this work. [b] Ref. 9b. [c] Ref. 9c. [d] Ref. 9d.

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5. When powdered $LiAlH_4$ is added to a solution of **1** as in ref. 3, multiple aluminum reducing agents, $Al(OR)_mH_n$, are formed. Ashby, E. C.; Boone, J. R. *J. Org. Chem.* **1976**, *41*, 2890-2903. and also ref. 2. However, when a carbonyl compound is added to a normal excess of $LiAlH_4$, as in this study, $LiAlH_4$ is the predominant reducing reagent. As mentioned in ref. 4, $NaBH_4$ is also known to form reducing agents of the form $B(OR)_mH_n$ during the course of the reaction.
6. A 0.1M solution of **1** in THF was added dropwise to a 0.1M solution of $LiAlH_4$ (4 equivs.) in THF under inert atmosphere conditions. A control experiment showed that the rate of addition had no effect on the product ratio. THF solutions of both **1** and $LiAlH_4$ were pre-equilibrated at the reaction temperature for 0.5 h before addition. Cold solutions (< 0° C) were achieved through the appropriate solvent/N_2(l) slurry. Warm solutions (>27° C) were achieved by immersing the entire apparatus in a constant temperature water bath (Haake). Reactions were run to completion. The product ratio is independent of the extent of reaction under the conditions used (ref. 5). A standard workup was used (quench with water or MeOH, dissolve the aluminum salts with 10% H_2SO_4, extract with ether, etc.). Control experiments on a mixture of *cis* and *trans*-**2** showed no change in the *cis/trans* ratio under the reaction and workup conditions. Product ratios were monitored by peak area on a Varian Aerograph Series 1700 Gas Chromatograph. The reported value is the average of three GC runs for each experiment.
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10. Ab initio calculations were performed using Gaussian 92. The initial guess for each transition state was made from using data from ref. 9. Transition state geometries were optimized at either the HF/3-21G or HF/6-31G* level of theory. The presence of a single imaginary frequency, which is characteristic of a transition state, was confirmed by analytical frequencey calculations. Standard notation is employed, e. g. MP2/6-31G*//6-31G* denotes an MP2/6-31G* single point calculation performed at the HF/6-31G* optimized geometry. Gaussian 92, Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, G.; Schlegel, H. B.; Robb, M. A.; Repogle, E. S.; Gomperts, R.; Andres, J. L.; Ragavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc. Pittsburgh, PA 1992

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