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CIS/TRANS RATIOS IN CLAISEN AND COPE REARRANGEMENTS

Charles L. Perrin (1) and D. John Faulkner (2)
University of California, San Diego, La Jolla, California 92037

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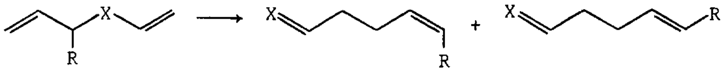
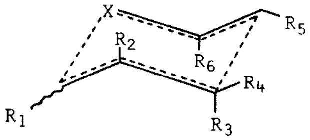
We wish to present a simple method for quantitatively predicting *cis/trans* product ratios in Claisen and Cope rearrangements.



For some time it has been known (3) that these rearrangements give predominantly *trans*-substituted olefins, but only recently have such *cis/trans* ratios been determined quantitatively (4). Since the transition state (I) is known (4i) to resemble the chair conformation of cyclohexane,



I

these results have been explained (3bde,4,5) qualitatively on the basis of the preference of a substituent for equatorial positions. This analogy does not seem to have been pursued further. However, we have noted surprisingly close quantitative agreement between the observed *cis/trans* ratios and the observed axial/equatorial ratios in cyclohexanes, notwithstanding the obvious fact that the transition states for these rearrangements are not identical with cyclohexanes.

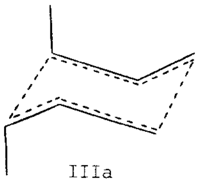
Table I lists observed values of RT ln($k_{\underline{trans}}/k_{\underline{cis}}$) = $\Delta\Delta G^{\ddagger}$. For comparison, the most recently recommended (6) values of ΔG^{o} are also listed. These represent the free-energy change for the conversion of a substituent from the equatorial to the axial position of a cyclohexane.(7) The first four entries (A-D) demonstrate that a remarkable agreement exists for these uncomplicated examples. The next two entries (E,F) show that the interaction with an axial methyl group (R_3) is so large as to prevent formation of a detectable amount of *cis* product, but that the

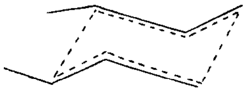
Table I

	R_1	R_2	R_3	R_4	R_5	R_6	X	$\Delta\Delta G^{\ddagger}$, Kcal	ΔG^{o}, Kcal (6)
A	Me	H	H	H	H	H	CH_2	1.5 (4a)	1.7
B	Me	H	H	H	ϕ,Me[*]	H	Nϕ	1.7 (4b)	1.7
C	Et	Me	H	H	H	H	O	1.6_5 (4c)	1.75
D	*i*Pr	Me	H	H	H	H	O	2.1 (4d)	2.15
E	Me	H	Me	H	- benzo	-	O	$\geqslant$3.6 (4e)	3.7[†]
F	Me	H	H	Me	- benzo	-	O	1.9 (4e)	1.7
G	*i*Hex,Me[*]	H	H	H	H	H	O	0.3 (4f)	0.05[#]
H	*i*Hex,Me[*]	H	H	H	H	Me	O	0.3-0.4 (4f)	0.05[#]
I	ϕ,Me[*]	H	H	H	H	Me	O	0.35 (4f)	1.3[§]
J	ϕ,Me[*]	H	H	Me	H	H	CH_2	2.0 (4g)	1.3[§]
K	ϕ,Me[*]	H	H	H	Ac	OH	O	2.1 (4h)	1.3[§]

[*] *Gem*-disubstituted. [†] *Syn*-axial methyl-methyl interaction (8). [#] $\Delta G^{o}_{Et} - \Delta G^{o}_{Me}$. [§] $\Delta G^{o}_{\phi} - \Delta G^{o}_{Me}$.

interaction with an almost axial benzo group (R_6, on the opposite allylic moiety) does not dictate the stereochemistry of the product (9). Likewise, comparison of the next two entries (G,H) suggests that an almost axial methyl group (R_6) may also have no appreciable effect on the product ratio (11). Furthermore, we note that in general the product ratios seem to be insensitive to the nature of substituents R_2, R_4, and R_5, as expected for cyclohexanes. However, the quantitative agreement for the last five entries (G-K) is poorer, presumably because *gem*-substitution cannot be treated in this simple fashion. Finally, the $\Delta\Delta G^{\ddagger}$ of 1.9 Kcal (4i) between transition states IIIa and IIIb is quite close to twice ΔG^{o}_{Me}, corrected for the additional

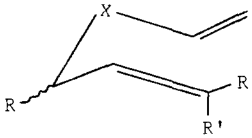

IIIa


IIIb

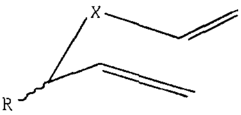
cis-butane interaction in IIIb.

Thus we conclude that the quantitative methods of conformational analysis may be applied to these six-atomic transition states, and that the vast body of data on conformational preferences in cyclohexanes may be used to predict *cis*/*trans* ratios in such reactions. Such predictions are helpful in connection with the problems of stereospecific synthesis (12) of natural products by Cope rearrangements, not only for estimating the stereospecificity of a proposed route, but also for suggesting alternative approaches that will increase the stereospecificity. In particular, [1] the selectivity is greater at lower temperature (4cd), [2] a trisubstituted double bond should be constructed in such fashion that R_2 in I is not the hydrogen, and [3] suitable bulky substituents, possibly removable, should be placed at R_3 and perhaps R_6.

Furthermore, this system may provide a simple method for estimating *syn*-axial interactions in cyclohexanes, which are not readily obtained. For example, the *cis*/*trans* product ratio from IV, relative to that from V, would give the *syn*-axial R-R' interaction. Indeed, this method



IV



V

should be applicable to interactions that are so large as to force a cyclohexane into a flexible (boat) conformation, since the flexible conformation of the transition state for these rearrangements, which is destabilized not only by the usual torsional strains but also by π-electron antibonding effects (13), may not be readily accessible.

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7. Here we must compare relative rates determined at elevated temperatures with conformational free energies determined near room temperature. From the temperature dependence (4c) of the product ratio in case C, we have concluded that $\Delta\Delta S^{\ddagger}$ is negligible. We also assume that ΔS° is negligible for the conformational equilibria under consideration. Therefore we have compared $\Delta\Delta G^{\ddagger}$ directly with ΔG°, without trying to separate entropy and enthalpy effects.

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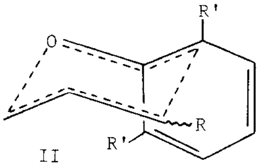
9. We may also note that a comparable result is obtained in the kinetics (10) of the Claisen rearrangement leading to transition state II: When R=Me and R'=H or Me, the trans ether reacts more rapidly by a factor of ca. 2 at 200°C. Even when $R=\phi$, the rate ratio is less than 5. To the extent that the axial → equatorial ΔG in the transition states cancels the cis → trans ΔG of the reactants, this ratio reflects only the interaction of the axial substituent with the benzo group.



II

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11. Nevertheless, the effect of substituents R_6 warrants further investigation. It is understandable that such a substituent does not behave as a genuine axial substituent, since it is "tipped back" from the axial position. However, we expected that a sufficiently large substituent should interact to an appreciable extent with an axial substituent R_1. Indeed, with $R_6 = Me_2N$ and $R_1 = Et$, the product olefin is almost exclusively trans (4c).

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