Substituent effects on the Cope rearrangement neither centaurs nor chameleons can characterize them

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Dedicated to Prof. Dionis Sunko on his 80th anniversary

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Abstract

Phenyl and cyano substituent effects on the activation free energy of thermoneutral Cope rearrangements of 1,5-dienes are analyzed in terms of the activation free energies for formation of the two non-concerted mechanistic alternatives, cyclohexane-1,4-diyl and two allylic radicals. The experimental data, adjusted upwards in the case of 2-phenyl-1,5-hexadiene, is reasonably correlated utilizing the harmonic mean values of the activation free energies and not some simple average of them or either one independently depending on which is lower. The latter two approaches appear to represent Centauric and Chameleonic models, respectively, as proposed by Doering. The harmonic mean is derived from consideration of the saddle point surface represented by a More O'Ferrall-Jencks diagram which appears to characterize the transition state structure and energetics of the Cope rearrangement. The conclusion from the correlation is that substitution of radical stabilizing groups alters the nature and stability of the transition state in accord with the position of substitution, and further substitution has an even greater effect if the position of substitution reinforces the change induced by the original substitution. If the position of substitution is opposed to the original substitution, the increase in stability of the transition state is attenuated.

Keywords: Cope rearrangement, substituent effects, 1,5-dienes, More O’Ferrall-Jencks diagrams

Introduction

Recent years have witnessed a resurgence of concern regarding characterization of substituent rate effects in the pericyclic 3,3-shift or Cope rearrangement. The Cope rearrangement involves pairwise interchange of C-1 with C-3 and C-6 with C-4 in the pyrolysis of 1,5-dienes, fig 1.[1] Doering determined the activation parameters for the parent compound using deuterium labels[2] while ignoring secondary deuterium kinetic isotope effects which could amount to 10% as shown by Humski, Molojcic, Borcic, and Sunko in 1970.[3] The entropy of activation is strongly negative consistent with a concerted reaction.

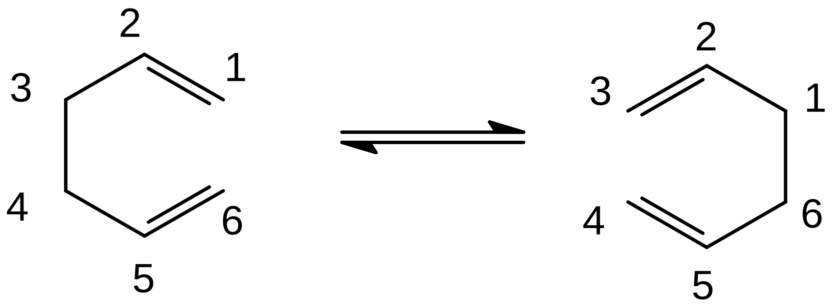
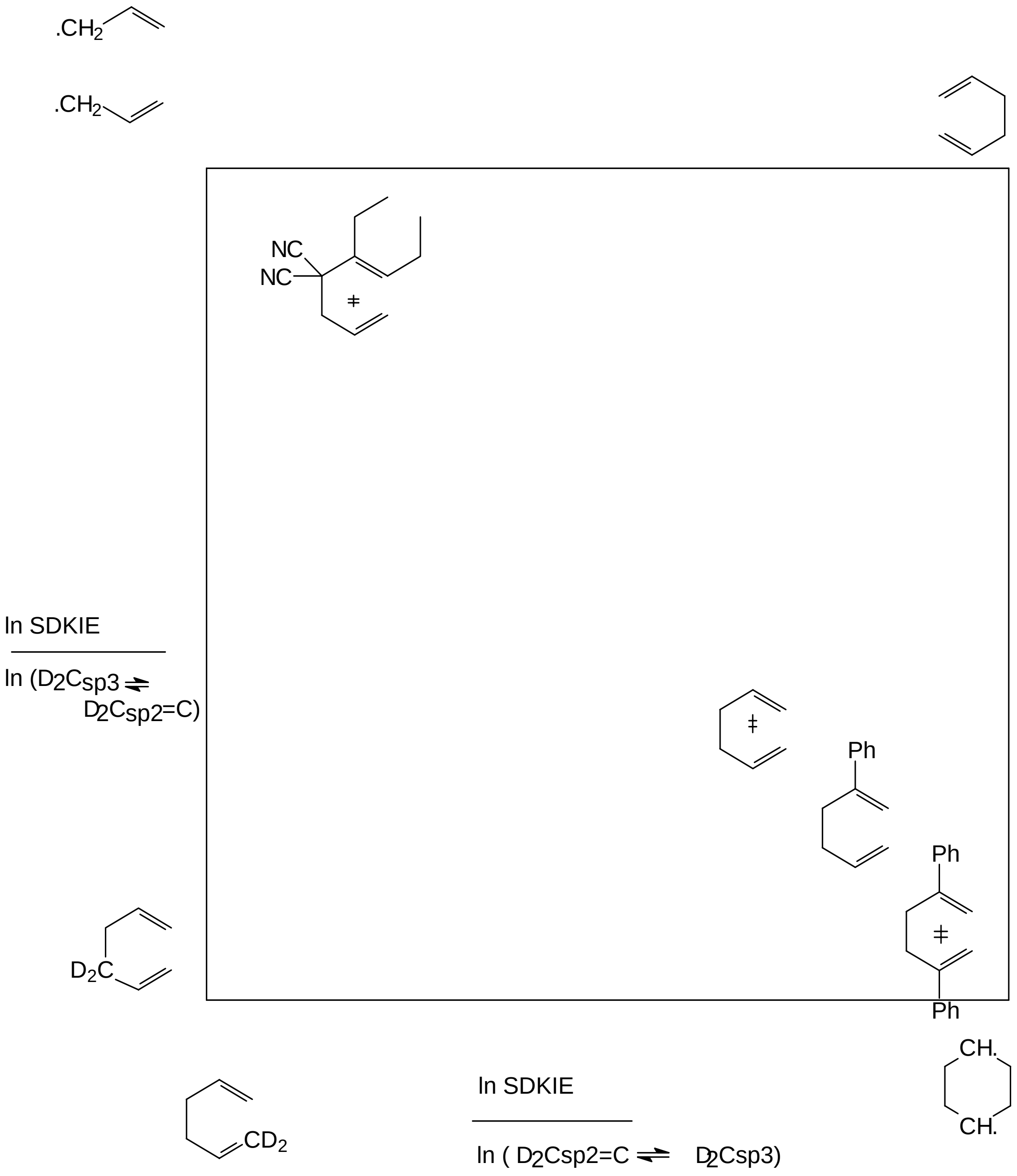


Figure 1. The Cope rearrangement.

Work in the 1970's and 80's, both experimental[4,5] and theoretical[6] indicated that the transition state could be intermediate between two extreme structures, either two allyl radicals or a 1,4-cyclohexane diyl. Indeed, kinetic isotope effects suggested that the transition state could vary between these two extremes depending on the placement and nature of the substituents.[3,5] That is, radical stabilizing groups at C-3 and C-4 promoted a transition state that was more like two allyl radicals, and radical stabilizing substituents at C-2 and C-5 would make the transition state more diyl-like. A More O'Ferrall-Jencks diagram utilizing two reaction coordinates, C-3, C-4 bond breaking and C-1,C-6 bond making, provides a pictorial basis to understand the transition state variation (Scheme 1).[7] Here the reactant and product are potential energy minima, and the two transition state extremes are potential energy maxima. The actual transition state is a saddle point between these extremes. In the parent case, the isotope effects and the MO calculations indicate that the transition state for the chair-like[8] Cope rearrangement is more diyl-like than resembling two-allyl radicals. However, for the boat transition state[8], the transition structure is more like two allyl radicals judging from entropies of activation.[9]



Scheme 1. More O'Ferrall-Jencks diagram representing the Cope rearrrangement.

Understanding, let alone prediction, of substituent effects on the Cope rearrangement has been a continuing challenge. The fact that the transition state changes with substitution in different ways depending on the position of substitution renders useless standard one parameter Linear Free Energy relationships like Hammett treatments. Long ago we addressed this problem utilizing as a model, the simplest equation that could describe the hyperbolic paraboloid energy surface represented by the More O'Ferrall-Jencks diagram.[10] Our approach was not new as references in theoriginal paper will attest. However, it did seem to reproduce some of the data available at the time. For thermoneutral Cope rearrangements, the equation reveals that the free energy of activation is a function of the harmonic mean of the free energy of activation to produce the two allyl radicals and that to produce the cyclohexane diyl, eq. 1.

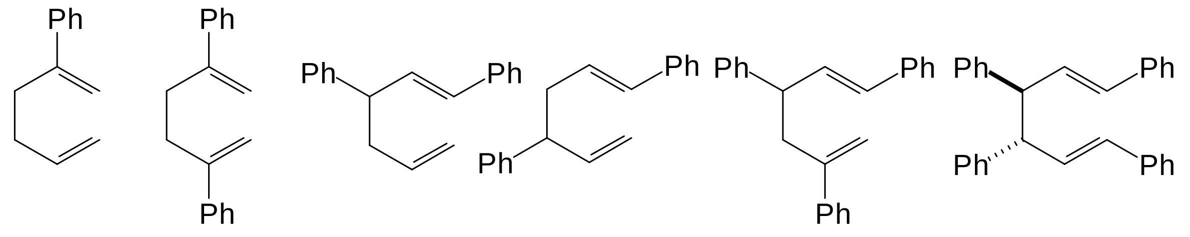
$$\Delta G^{\ddagger} \; \alpha \; \frac{\Delta G^{\ddagger}(\text{diyl}) * \Delta G^{\ddagger}\,(\text{two allyl radicals})}{\Delta G^{\ddagger}(\text{diyl}) + \Delta G^{\ddagger}\,(\text{two allyl radicals})} \qquad (1)$$

Further, the reaction free energy entered into the denominator as a subtraction, eq. 2.

$$\Delta G^{\ddagger} \; \alpha \; \frac{\Delta G^{\ddagger}(\text{diyl}) * \Delta G^{\ddagger}\,(\text{two allyl radicals})}{\Delta G^{\ddagger}(\text{diyl}) + \Delta G^{\ddagger}\,(\text{two allyl radicals}) - \Delta G\text{rxn}} \qquad (2)$$

In the cases examined, the proportionality constant was 1.5. Further, eq. 2 worked well for the Claisen rearrangement of allyl vinyl ether substituted with cyano groups at various positions. The major concern, however, was establishing the values for the activation free energies for the formation of the allyl radicals and the cyclohexanediyl. Group additivity and radical resonance energies were crudely, but reasonably, estimated with not-unreasonable results.

In recent years, Doering has addressed the stabilizing effect of phenyl substitution on 1,5-dienes and their effect on the rate of the Cope rearrangement.[11] The compounds, which undergo thermoneutral 3,3-shifts (in order to avoid complications due to thermodynamic effects) are given in fig 2. Doering then used these to examine two different models for the Cope rearrangement which were termed the "Centauric" and the "Chameleonic" models.



2-phenyl **2,5-diphenyl** **1,3-diphenyl** **1,4-diphenyl** **1,3,5-triphenyl** **1,3,4,6-tetraphenyl**

Figure 2. Symmetrically (w/ respect to the cope rearrangement) phenyl substituted 1,5-dienes.

In a Centauric transition state, Doering conjectured that there is independent action of substituents making conflicting, but full, electronic demands on the two halves of the transition region. In the Chameleonic model the substituent groups in positions of opposing demands are no more effective than the stronger of them. If one were to quantify the models proposed, it would appear that eqs 3 and 4, respectively, were being proposed although Doering cast the analysis in terms of enthalpies to avoid consideration of temperature differences.

"Centauric": $$\Delta G \ddagger \ \alpha \ \ \Delta G\ddagger(\text{diyl}) + \Delta G\ddagger\ (\text{two allyl radicals}) \qquad (3)$$

"Chameleonic": $$\Delta G \ddagger \ \alpha \ \ \Delta G\ddagger(\text{diyl})^{*}\ a + \Delta G\ddagger\ (\text{two allyl radicals}) \ {*}\ b \qquad (4)$$

where $a + b = 1$, but either a or $b = 0$

To make the comparisons, Doering carefully analyzed the effect of phenyl in stabilizing double bonds in the ground state in order to assess the effect of this substituent on the rate of the Cope rearrangement. Thus, adding a phenyl group to an alkyl substituted double bond stabilizes the double bond by 2.6 kcal/mol, but a phenyl group added to the terminal carbon of a vinyl group stabilizes the double bond by 5.1 kcal/mol .

Doering found that the effect of phenyl substituents on the enthalpies of activation, once corrected for ground state stabilization, fell into neither category, Centauric or Chameleonic. To illustrate the point, the most striking comparison in examining the corrected activation enthapies for the dienes of Table 1 is that of placing a 5-phenyl group on the 2-phenyl material relative to placing it on the 1,3-diphenyl material. In the former case, the second phenyl (of 2,5-diphenyl) lowers the activation enthalpy by 10.6 kcal/mol which is more than the effect of the original 2-phenyl substitution, namely, 6.8 kcal/mol. However, a 2-phenyl (really 5-phenyl) group also lowers the activation enthalpy of the 1,3-diphenyl material but by a lesser amount, namely, 5.4 kcal/mol. These results are not consistent with either of Doering's models.

Given the uncertainty in the Doering analysis, we sought a more general explanation for the rate effects of Table 1 and related materials. Previous experimental efforts in our laboratory to characterize the structure of the transition state in the Cope rearrangement and substituent effects on it utilized secondary deuterium kinetic isotope effects as a metric for the extent of bond breaking and bond making.[5] Further, as indicated above empirical models, eqs. 1 and 2, were utililized to describe the behavior of the energy of the transition state in response to substituents. These models do not have the character of either the Centauric or Chameleonic models proposed by Doering despite his assertion that they Chameleonic.[11] We here show

how our harmonic mean model rationalizes the energetics described in Table 1 and other 3,3-sigmatropic shift rate data.

Table 1. Activation parameters for various cope rearrangements

1,5-Hexadiene	$\Delta H^{\ddagger}$	$\Delta\Delta H^{\ddagger}$ corr.[a]	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$ at 127 °C	$\Delta\Delta G^{\ddagger}$ corr.[a]
Parent	33.5	0	-13.8	39.0	0
2-Phenyl	29.3	-6.8	-9.9	33.3	-8.3
2,5-Diphenyl	21.3	-17.4	-20.8	29.6	-14.6
1,3-Diphenyl	30.5	-8.1	-14.6	36.4	-7.2
1,4-Diphenyl	29.9	-8.7	-15.0	35.9	-7.7
1,3,5-Triphenyl	27.7	-13.5	-15.4	33.8	-12.9
1,3,4,6-Tetrapheny	21.3	-22.4	-13.2	26.6	-22.6

[a] $\Delta H^{\ddagger}$ is corrected for the ground state stabilization of the double bond(s) by phenyl then it is subtracted from the value for the parent (ref 11).

Results and Discussion

Type your text H While enthalpies of activation can be obtained with reasonable accuracy and while these are modestly independent of temperature, it is free energy that controls rate processes. One might feel comfortable comparing activation enthalpies if the activation entropies were the same for all compounds considered by Doering. However, examination of the data of Table 1 reveals large variations in the entropies of activation for the various Cope rearrangements. This might be interpreted in terms of compensatory changes or experimental error. It would appear prudent to consider the former alternative and focus on activation free energies at a common temperature. Experimental error, however, cannot be ruled out. For instance, e.g. 3.6 e.u. is the cited deviation in the activation entropy for the 2-phenyl case leading to a deviation of 1.5 kcal/mol in its contribution to the activation free energy. More distressing is the fact that the reported4 rate constant of the 2-phenyl material at 170 °C is a factor of three higher than that of the 3-methyl-2-phenyl derivative in its formation of an E diene at 175 °C.[5] The extra methyl and the higher temperature would suggest that the activation free energy for the 2-phenyl derivative itself might be as much as 2 kcal/mol higher! The difficulty with this value will be recognized from the discussion below.

Utilization of the relative free energies of activation once corrected for ground state stabilization by the substituents (Table 1) reveals different behavior than that described for the corrected activation enthalpies. Thus, placing a 5-phenyl group on the 2-phenyl material reduces the activation free energy by a smaller amount than the original 2-phenyl substitution, namely, 6.3 vs. 8.3 kcal/mol. Further, placing the 2-phenyl group on the 1,3-diphenyl material reduces the activation energy by an amount, 5.7 kcal/mol, which is almost the same as placing the 5-phenyl group on the 2-phenyl derivative (6.3 kcal/mol). However, the activation parameters for the 2-phenyl material are problematic given their high standard deviation, the substantially less negative entropy of activation relative to the other compounds in the series, and a anomously higher rate constant compared with what should be a more reactive 2-phenyl derivative at a higher temperature.[5] If, the activation free energy for the 2-phenyl material were 1.7 kcal/mol higher, then the behavior of the system described by Doering based on an erroneous activation energy for the the 2-phenyl compound is nearly realized. Thus, the addition of a 5-phenyl group to an existing 2-phenyl compound lowers the activation free energy by 8.0 kcal/mol which is more than the effect of the 2-phenyl substitution, namely 6.6 kcal/mol, and placing a 5-phenyl group on the 1,3-diphenyl substituted compound lowers the activation free energy by 5.7 kcal/mol which is less than the effect of a 5-phenyl group on a 2-phenyl substituted material .

If the "adjustment" in the activation free energy for the 2-phenyl case described above would be primarily in the enthalpy term, the relative effects of 5-phenyl on the 2-phenyl and and 1,3-diphenyl cases would still be in the sense of the original values. Therefore Doering would still have difficulty in reconciling the data to either the Centauric or the Chameleonic models. However, the adjusted value for the 2-phenyl derivative along with the other activation free energies of Table 1 lead to the idea that the transition state free energy is lowered to a greater extent when the substitution reinforces the effect of the previous substitution, and the transition state free energy is lowered to a lesser extent when the substitution stabilizes the opposite moiety, diyl or two-allyl radicals, from that favored by the original substitution. This is consistent with transition state structure variation in response to substitution as described in our original papers.[5,10]

We here analyze the effect of phenyl substituents on the Cope rearrangment using the simplest mathematical model for a three dimensional saddle surface based on the MOFJ diagram of Scheme 1 where the free energy as a function of each of the two structural coordinates varies in a linear way (linear edge potentials) but becomes a saddle-like surface as a result of the coupling of the two structural coordinates. The saddle point on this surface is obtained by setting the first derivatives of the surface equation to zero and identifying the corners with starting material, product, diyl, and two-allyl radicals. Equation 1 describes the behavior of the free energy of that saddle point as a function of the energies of the diyl and the two-allyl radicals for a thermoneutral reaction.10

Because the simplest hyperbolid-paraboloid surface equation provides no means for adjusting the energy of the saddle point for the parent compound, the proportionality constant of equation 1, which is like a ρ value, functions in that manner. Thus the "sigma values" are the harmonic means of free energy changes for complete bond making and breaking resulting from the nature and position of each substituent. To estimate the quantities which should appear in eq. 1 for each compound we estimated[10] that the free energy of activation for bond making and bond breaking in the parent compound is 53 kcal/mol and 57 kcal/mol, respectively. We now assume that the benzyl radical resonance energy is 13.2 kcal/mol and the effect of a phenyl at the each end of an allyl radical stabilize it by 9.8 kcal/mol, and further recognize that these values must be modified by the conjugative stabilization of the phenyl groups in the ground state which is lost upon becoming either the 1,4-diyl or two allyl radicals. The latter modifications are exactly those determined by Doering, namely, 2.6 kcal/mol per phenyl at the center of a propenyl group and 5.1 kcal per phenyl at the terminal end of a propenyl group. This then leads to the activation free energies for generation of the diyl and two-allyl radicals given in Table 2. Table 2 also lists the calculated activation free energies as the result of a least squares analysis using the original activation free energies of Table 1. The "ρ"value from the correlation is 1.56 with a standard deviation of 0.20, and the correlation coefficient is 0.962. The standard deviation of the calculated from the experimental free energies of activation is 1.1 kcal/mol

The correlation utilizing eq. 1 and reported in Table 2 is not bad, and examination of the calculated relative free energies of activation reveal that placement of a 5-phenyl group on a molecule with 1,3-diphenyl substitution lowers the activation free energy by less (2.4 kcal/mol) than 5-phenyl substitution on a molecule with 2-phenyl substitution (6.1 kcal/mol). Further, the 5-phenyl substitution on the 2-phenyl material produces a bigger decrease (10.5 kcal/mol) than twice that of the first substitution (4.4 kcal/mol) relative to the parent. The same is true of the tetraphenyl (11.8 kcal/mol) vs the 1,3-diphenyl (4.3 kcal/mol) substitutions. This is a unique characteristic of eq.1 which sets it apart from the Centauric and Chameleonic models. All of this is because the transition state responds more when it more resembles the species, 1,4-diyl or two allyl radicals, which is being most affected by the substituent.

Table 2. Calculated (from eq. 1) cree energies of activation for phenyl-substituted 1,5-dienes

1,5-Hexadiene	ΔG‡127^{o}C	ΔG‡(calc)	ΔG‡diff	ΔG‡rel(calc)	ΔG‡bm	ΔG‡bb
Parent	39.0	39.5	-0.5	0.	53.	57.
2-Phenyl	33.3	35.1	-1.8	-4.4	42.	59.6
2,5-Diphenyl	29.6	29.0	0.6	-10.5	31.	62.2
1,3-Diphenyl	36.4	35.2	1.2	-4.3	58.1	43.0
1,4-Diphenyl	35.9	35.2	0.7	-4.3	58.1	43.0
1,3,5-Triphenyl	33.8	32.8	1.0	-6.7	47.1	45.6
1,3,4,6-Tetraphenyl	26.6	27.7	-1.1	-11.6	63.2	29.0

The correlation and deviations in the calculated vs experimental activation free energies listed in Table 2 are not ideal, and examination of the results suggest that the largest deviation occurs with the 2-phenyl material whose data is questionable as described above. However, this data point cannot be removed because it is the lynchpin upon which all comparisons are made. If the "adjusted" value of 35.0 kcal/mol is taken as the experimental value for the activation free energy for the 2-phenyl material then the correlation is much better, Table 3.

Table 3. Calculated (from eq. 1) free energies of activation for phenyl-substituted 1,5-dienesa

1,5-hexadiene	ΔG‡127^{o}C	ΔG‡calc	ΔG‡diff	ΔG‡rel calc	ΔG‡bm	ΔG‡bb
Parent	39.0	39.9	-0.5	0.	53.	57.
2-Phenyl	35.0[a]	35.4	-0.4	-4.5	42.	59.6
2,5-Diphenyl	29.6	29.1	0.5	-10.8	31.	62.2
1,3-Diphenyl	36.4	35.5	0.9	-4.4	58.1	43.0
1,4-Diphenyl	35.9	35.5	0.4	-4.4	58.1	43.0
1,3,5-Triphenyl	33.8	33.1	0.7	-6.8	47.1	45.6
1,3,4,6-Tetraphenyl	26.6	27.8	-1.2	-12.1	63.2	29.0

[a] The activation free energy for the 2-phenyl compound is adjusted upwards by 1.7 kcal/mol. See text for justification.

Now the slope, ρ, of the correlation is 1.60 with an SD of 0.14, and the correlation coefficient is 0.981. The standard deviation in the calculated vs experimental values is 0.8 kcal/mol Further, the data of Table 3 reveals the same characteristics described for the entries in Table 2, but the uncertainty in the values is less .

The analysis presented here is subject to the criticisms that a crude geometric model is applied to an energy surface with complex edge potentials and that its reasonable agreement with experiment is the result of redefining a crucial experimental value. The fact that Conrad's kinetic data on 2,5-diphenyl-1,5-hexadiene5 matches that of Dewar and Wade4 that is utilized through this work should raise some concern about the value reported for the 2-phenyl material. Further, the equilibrium constant reported for the 2-phenyl material substituted with deuterium to allow the analysis is not consistent with the usual expectation that deuterium stabilizes carbons with stiffer bonds, that is, sp^3 carbon over sp^2 carbon. In general, higher vibrational frequencies, particularly the bending frequencies, associated with an atom and their attendant zero point energies are lowered to a greater extent than those associated with lower frequencies. Another point of difference is that the original experimental determinations were conducted in dichlorobenzene solvent4 while Conrad's kinetics were performed on reactions in the gas phase using base washed tubes.[5] Finally, it should be noted that substantial computational efforts have reproduced the experimental activation enthalpy data of Table 1 including that of the 2-phenyl material.[12] Why this is the case is not clear .

Doering also examined the effect of 5-phenyl substitution on the rate of 3,3-shift of a 1,3-dicyano compound with the result that the activation enthalpy was lowered by 4.6 kcal/mol after correction for ground state stabilization. This value is less than that (10.6 kcal/mol) for lowering the activation enthalpy by substitution of a 5-phenyl group on a 2-phenyl material. If the comparisons are made on a free energy of activation basis, the results are very similar because the activation entropies do not vary substantially. Thus 5-phenyl substitution on a 1,3-dicyano compound lowers the activation free energy by 4.0 kcal/mol; in contrast the activation free energy for the Cope rearrangement is lowered by 6.3 (or 8.3 when adjusted-Table 3) when placing the phenyl group at C-5 of 2-phenyl-1,5-hexadiene. It hardly seems worthwhile to utilize equation 1 in the cyano substituted cases, but it is worthy of note that cyano substituents at the ends of an allylic radical appear equally effective in stabilizing the radical and the double bonds in the precursor as do phenyl groups (-8. kcal/mol vs. -8.1 kcal/mol).

Table 4. Activation energies for cyano substituted Cope rearrangements

1,5-Hexadiene	ΔH╪	ΔΔH╪ corr.[a]	ΔS╪	ΔG╪ at 127 °C	ΔG╪ corr.	ΔΔG╪ corr.a
Parent	33.5	0	-13.8	39.0	39.0	0
1,3-Dicyano	28.8	-8.0	-15.1	34.9	31.6	-7.4
1,3-Dicyano-5-phenyl	26.8	-12.6	-16.7	33.5	27.6	-11.4

[a] ΔH╪ is corrected for the ground state stabilization of the double bond(s) by phenyl and cyano.

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