

Table I. Rotational Data for Determination of Stereospecificity of Insertion

entry	2		7		8		
	$[\alpha]_D$, deg	% ee ^a	$[\alpha]_D$	% ee ^b	$[\alpha]_D$	% ee ^c	% ret
1	-53.25 ^d	91.9	+112.7 ^e	86.7			94.3
2	-53.25 ^d	91.9	+113.6 ^f	87.4			95.1
3	-53.25 ^d	91.9	+111.8 ^g	86.0			93.6
4	+13.29 ^h	22.9			+31.98 ⁱ	21.8	95.2
5	+13.29 ^h	22.9			+32.95 ^j	22.1	96.3

^a Based on $[\alpha]_D$ (max) 57.95° (3.04, C₆H₆).^{eb} ^b Based on $[\alpha]_D$ (max) 130°.¹⁰ ^c Based on $[\alpha]_D$ (max) 147°.¹⁰ ^d c = 15.6, C₆H₆. ^e c 1.3, EtOH. ^f c 3.1, EtOH. ^g c 2.0, EtOH. ^h c 18.5, C₆H₆. ⁱ c 1.6, EtOH. ^j c 2.7, THF.

Table II. Data from 200-MHz ¹H NMR Spectrum of 10 and Chiral Shift Reagent

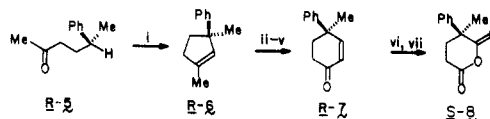
compd	o-Ar H ^a		% ee	vinylic H ^a		% ee	CCH ₃ ^a		% ee	=CCH ₃ ^a		% ee
	S	R		S	R		R	S		S	R	
<i>rac</i> -10	58.5	60.0		49.5	50.5		61.0	61.0		65.0	64.5	
(<i>R</i>)-(+)-10 ^b	29.5	109.5	57.5	24.0	86.0	56.4	107.0	32.0	54.0	35.5	131.5	57.4
(<i>R</i>)-(+)-10 ^c			54.8			56.2			54.6			54.2

^a Relative area of downfield to upfield peak(s) of each diastereomeric pair. ^b Percent enantiomeric excess based on electronic integration of 200 MHz PMR spectrum. ^c Percent enantiomeric excess based on "cut and weigh" method with compensation being made for overlapping of baselines of peaks in the 200-MHz ¹H NMR spectrum.

phenyl-2-hexanone (5), available from 3-phenylbutanoic acid (2),⁵ by the sequence shown in Scheme I. The acid 2 is resolvable through its *l*-menthol ester, and the maximum rotation⁶ and absolute configuration⁷ of the acid are well-defined. Other workers had earlier demonstrated that conversion of 2 to the bromide 4 by way of the alcohol 3 occurs with little, if any, loss of enantiomeric purity,⁸ and it was expected that the subsequent steps required to produce 5 would not be attended by racemization. Consequently, the sequence of Scheme I should produce 5-phenyl-2-hexanone (5) of known absolute configuration and enantiomeric purity.

Exploratory studies demonstrated that *rac*-5 is converted to 1,3-dimethyl-3-phenylcyclopentene (6) upon base-promoted reaction with DAMP and that 6 in turn could be transformed to the known⁹ *rac*-4-methyl-4-phenyl-2-cyclohexenone (7), and thence to anhydride 8,¹⁰ by the steps set forth in Scheme II. This latter reaction sequence serves to augment the spectroscopic data (see Experimental Section) supporting assignment of structure to the previously unknown cyclopentene 6. Moreover, because none of the steps in it are conducive to stereorandomization, it also provides the key to determining the stereochemical outcome of the insertion reaction that produced this cyclopentene, since there already are data available on the absolute configurations of the optical antipodes of 7 and 8 as well as on the maximum specific rotation of these entities.¹⁰

A sample of (*R*)-(-)-2, of 91.9% enantiomeric excess (ee), was converted into bromide 4 of 91.5% ee. Conversion of the bromide through 5 (Scheme I) to the cyclopentene 6, followed by transformation of this alkene according to the sequence of Scheme II, afforded enone 7 having a specific rotation, $[\alpha]_D$ (max) +112.7° (Table I, entry 1). That the sign of rotation was positive means that the enantiomer of 7 produced from (*R*)-(-)-2 is also of the *R* configuration,

Scheme II. Conversion of 5-Phenyl-2-hexanone to Enone 7 and Anhydride 8^a

^a i, DAMP/KOBUt (73%); ii, O₃/MeOH/HCl; iii, Me₂S; iv, AcOH; v, K₂CO₃ (60% for ii-v); vi, KMnO₄; vii, Ac₂O (23% for vi and vii).

given the unambiguous configurational assignments reported for this enone.¹⁰ This permits the definitive conclusion that the intramolecular 1,5 C-H insertion reaction of the alkylidenecarbene derived from 5 to produce 6 occurs with *retention* of configuration, as shown by the configurations of the structures given in Scheme II.

Otani and Yamado¹⁰ have estimated that the maximum rotation of 4-methyl-4-phenyl-2-cyclohexenone (7) is about 130° and that of the anhydride 8 as 147°, although the justification for such estimates is ill-defined. In any event, accepting this value for 7 leads to the conclusions that the enone produced in our sequence is of 86.7% ee and that the insertion reaction has occurred with 94.3% retention of configuration. Two replications of the insertion reaction starting with (*R*)-(-)-2 gave samples of 7 having specific rotations corresponding to 94 ± 1% retention of configuration (Table I, entries 2 and 3). Conversion of two samples of (*S*)-(-)-6 derived from (*S*)-(+)-2 of 22.9% ee to 8 produced material consistent with the cyclopentene 6 having been formed with greater than 95% retention of configuration, assuming a maximum rotation for 8 of 147° (Table I, entries 4 and 5).

Although these data bespeak high specificity in the insertion reaction of alkylidenecarbenes 1 to give cyclopentenes (eq 1), they generate uncertainty from the standpoint of mechanistic interpretation: Is there operating a mechanism that accommodates a racemizing pathway and leads to a diminution of the enantiomeric purity of 6 relative to its parent ketone 5 or is the reliance upon the estimated maximum rotations of 7 and 8 at fault for falsely denoting such diminution? To resolve this uncertainty, an alternate method for assessing the enantiomeric purity of 7 was sought.

Preliminary studies showed that reaction of *rac*-7 with methylolithium to give the tertiary alcohol 9, followed by oxidation of 9 with pyridinium chlorochromate, cleanly

(4) Colonge, J.; Pichat, L. *Bull. Soc. Chim. Fr.* 1949, 853.

(5) Marvel, C. S.; Dec, J.; Cooke, H. C. *J. Am. Chem. Soc.* 1940, 62, 3501.

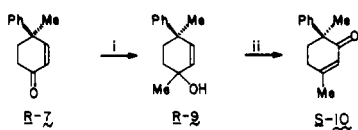
(6) (a) Cram, D. J. *J. Am. Chem. Soc.* 1952, 74, 2137. (b) Hoffman, T. D.; Cram, D. J. *Ibid.* 1969, 91, 1000.

(7) Brewster, J. H.; Kline, M. W. *J. Am. Chem. Soc.* 1952, 74, 5179. Mills, J. A.; Klyne, W. *Prog. Stereochem.* 1954, 1, 177.

(8) Lardicci, L.; Salvadori, P.; Caporusso, A. M.; Menicagli, R.; Belgodere, E. *Gazz. Chim. Ital.* 1972, 102, 64.

(9) Flaugh, M. E.; Crowell, T. A.; Farlow, D. S. *J. Org. Chem.* 1980, 45, 5399.

(10) Otani, G.; Yamado, S.-I. *Chem. Pharm. Bull.* 1973, 21, 2119.

Scheme III. Conversion of Enone 7 to Enone 10^a

^a i, MeLi; ii, PCC (62% overall).

Table III. Maximum Rotations Based on 2 and on the Assumption of Complete Stereospecificity of Reactions

compd ^a	$[\alpha]_D$ (max)	compd ^a	$[\alpha]_D$ (max)
5	20.2	8	141.5
6	22.4	10 ^b	301.5
7	122.5		

^a Concentration and solvent as given in Table I, unless otherwise noted. ^b c 2.01, EtOH.

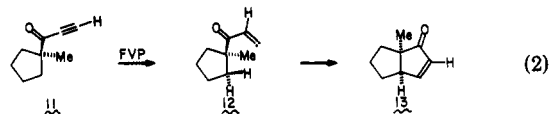
afforded 3,6-dimethyl-6-phenyl-2-cyclohexenone (10, Scheme III).¹¹ Examination of the 200-MHz ¹H NMR spectrum of a solution in chloroform-*d* of 10 and the chiral lanthanide shift reagent Eu(hfc)₃¹² in a molar ratio of ca. 1.5:1 revealed clean resolution of four sets of diastereomeric protons in the complex formed between 10 and the shift reagent. In order of increasing field strength, these sets were assigned as the ortho aromatic, the vinylic, the aliphatic methyl, and the allylic methyl protons present in 10. The relative integrated areas of the sets of peaks, in the same order, were 5.85:6.00, 4.95:5.05, 6.10:6.10, and 6.50:6.45 (Table II), respectively, within experimental error of those expected for racemic 7.

The results of applying this analytical technique to a sample of 10 derived from (*S*)-(-)-3-phenylbutanoic acid (2) of 55.4% ee are shown in Table II. The data from electronic integration of the peak areas are within experimental error of the value anticipated if all transformations originating with 2 are stereospecific, with the average % ee being 56.3. Reanalysis of the ¹H NMR data by the "cut and weigh" method, with an effort being made to compensate for overlapping of peaks, gave an average value of 55.0% ee. The same type of analysis was repeated on a sample of 10 derived from (*R*)-(+)-2 of 97.6% ee. The result confirmed that the insertion reaction producing 6 had occurred with high stereospecificity as resonances due to the *S* antipode were not detectable; doping experiments indicated that were there as little as 2.0% of this enantiomer present, it would have been detected.¹³ Since 1.2% of it was present in the sample of (*R*)-(+)-2 used, the result with the *R* enantiomer of 10 suggests that the insertion reaction has proceeded with a stereospecificity of at least 99%. On the basis of both sets of results, it seems safe to conclude that the intramolecular insertion of alkylidenecarbenes into carbon-hydrogen bonds at C-5 occurs with a retention of configuration that is complete or nearly so.

It would appear from our results that the predicted¹⁰ maximum rotations for 4-methyl-4-phenyl-2-cyclohexenone (7) and 2-methyl-2-phenylglutaric anhydride (8) should be revised downward. Estimated maximum rotations for these two substances, as well as for 5, 6, and 10, based on the present results are given in Table III. Note that these rotations rely on the maximum rotation of 57.95° reported

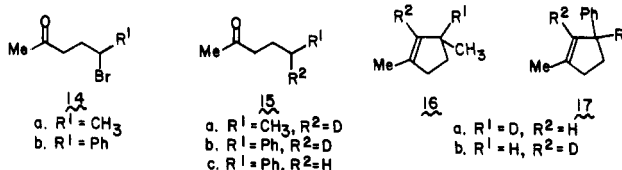
for 2^{6b} and on the assumption that all subsequent reactions of 2 are stereospecific.

The stereochemical conclusions drawn here are consistent with those recently reported by Dreiding et al. for the flash vacuum pyrolysis of 11 (eq 2), in which the major product 13 is formed by carbon-hydrogen insertion of the presumed alkylidenecarbene 12 with retention of configuration.¹⁴ Of course, this system is geometrically biased



toward retention, so that the present work provides the first unambiguous demonstration that alkylidenecarbenes insert into a carbon-hydrogen bond of an unconstrained system with essentially complete retention of configuration.

To test for the existence of a kinetic isotope effect in the 1,5-insertion reaction of alkylidenecarbenes 1, 5-deuterio-2-hexanone (15a), and 5-deuterio-5-phenyl-2-pentanone (15b) were selected as substrates so as to probe this phenomenon at both a secondary alkyl and a secondary benzylic position. Compound 15a was prepared by heating 5-bromo-2-hexanone (14a)¹⁵ in 1,2-dimethoxyethane (DME) at reflux in the presence of a large excess of D₂O and zinc dust.¹⁶ The ketone 15b was generated in a similar manner from 5-bromo-5-phenyl-2-pentanone (14b), which was in turn prepared by the free radical bromination of 5-phenyl-2-pentanone (15c).¹⁸



Spectroscopic analysis of 15a obtained by this method showed it to be identical in all respects with the protio material¹⁹ with the exception of variations resulting from introduction of deuterium at C-5. Stirring a sample of 15a with aqueous potassium hydroxide for 12 h left the deuterium content unchanged, as measured by both ¹H NMR and MS techniques, thereby demonstrating that the synthetic method had not resulted in incorporation of deuterium α to the ketone function. The integrated ¹H NMR and ¹³C NMR spectra both indicated that 15a was 100% monodeuterated at C-5, whereas MS analysis showed the level of deuteriation to be 96.3%; the latter value was used in calculating the deuterium isotope effect.

Similarly, the ketone 15b prepared by reduction of 14b had spectra identical with those reported²⁰ except for differences associated with the presence of deuterium at C-5. Exposure of 15b to aqueous sodium carbonate solution at reflux for 4 h produced no change in the deuterium content, as shown by ¹H NMR and MS analyses, proving

(14) Karpf, M.; Huguet, J.; Dreiding, A. S. *Helv. Chem. Acta* 1982, 65, 13.

(15) Mihailovic, M. L.; Gookovic, S.; Konstantinovic, S. *Tetrahedron* 1973, 29, 3675.

(16) Minton, M.; Whitesell, J. K., unpublished results. We thank Dr. Minton for providing details of their experimental procedure which is a modification of one previously used for reduction of tosylates.¹⁷

(17) Kocovsky, P.; Cerny, V. *Collect. Czech. Chem. Commun.* 1979, 44, 246.

(18) Heilbron, I. M.; Heslop, R. N.; Irving, F.; Wilson, J. S. *J. Chem. Soc.* 1931, 1336.

(19) Doering, W. v. E.; Sachdev, K. *J. Am. Chem. Soc.* 1975, 97, 5512.

(20) Dalton, J. C.; Chan, H. G. *Tetrahedron Lett.* 1973, 3145. Thies, R. W.; Meshgini, M.; Chiarello, R. H.; Seitz, E. P. *J. Org. Chem.* 1980, 45, 185.

(11) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* 1977, 42, 682.

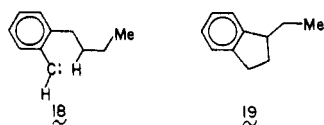
(12) Fraser, R. R.; Petit, M. A.; Saunders, J. K. *J. Chem. Soc., Chem. Commun.* 1971, 1450. Goering, H. L.; Eikenberry, J. N.; Koerner, G. S. *J. Am. Chem. Soc.* 1971, 93, 5913.

(13) A similar level of sensitivity of this method for determination of enantiomeric excesses has been noted by others: Doering, W. V. E.; Robertson, L. R.; Ewing, E. E. *J. Org. Chem.* 1984, 48, 4280.

that no deuterium had been incorporated α to the carbonyl group. The integrated ^1H NMR spectrum was consistent with a level of deuteration at C-5 of $82 \pm 4\%$, whereas the mass spectrum gave a deuterium content of 83.5%. As before, the latter value was used for determination of the deuterium isotope effect.²¹

Reaction of either **15a** or **15b** with DAMP at -78°C afforded the cyclopentenones **16** and **17**, respectively. Both of these products were identified by comparison of their IR and ^1H NMR spectra with those reported for their protio analogues.^{19,22} Mass spectrometric analysis of recovered starting ketone and of the product confirmed that no deuterium had been lost in the course of the reaction. On the basis of the supposition that the relative yields of carbene-derived products are proportional to their relative rates of formation,²³ the intramolecular deuterium isotope effect is simply the ratio of **16a** to **16b** for **15a** and of **17a** to **17b** for **15b**, with appropriate correction factors being applied to compensate for the presence in **14a** and **14b** of undeuterated material (see Experimental Section). Determination of the necessary ratios was accomplished by multiple integrations of the resonances of the vinylic and tertiary allylic protons of the cyclopentenones **16** and **17** obtained from two different runs on each ketone.

The kinetic isotope effects that resulted are 3.5 (0.2)²⁴ and 2.0 (0.1) for formation of **16** and **17**, respectively. The greater isotope effect found in the case of the conversion of **15a** to **16** is consistent with the proposition that although the transition state for the insertion reaction is expected to be "early" with both substrates, owing to the exothermicity of the process, that involving **15a** should be the later of the two, given the relative strengths of secondary aliphatic vs. secondary benzylic C-H bonds. The value obtained with the aliphatic system is comparable to that of 3.25 ± 0.15 observed in the 1,5-insertion of the arylcarbene **18** to produce **19**.²⁵

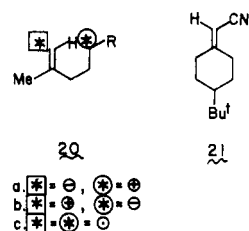


The above discussion interprets the data on isotope effects in terms of an activation barrier for the C-H insertion of an alkylidene carbene, although theoretical treatments of such insertion reactions of carbenes are in disagreement regarding the presence of a barrier. Unfortunately, no calculations exist that describe the intramolecular 1,5 C-H insertion reaction of any carbene, much less an alkylidene carbene.

There have been several reports concerning the reaction path for intermolecular insertion reactions of singlet methylene into both hydrogen-hydrogen and carbon-hydrogen bonds. With respect to the former reaction, some calculations predict an activation barrier, ranging from 5^{26a}

to 14^{26b} kcal/mol, for the process, whereas others do not.²⁷ There has been less effort with regard to the latter type of insertion, which is more closely related to our system, but again both the presence²⁸ and the absence²⁹ of an activation barrier along the reaction path have been predicted; the value for the barrier, if it exists, is calculated to be about 8 kcal/mol.²⁸ From the experimental standpoint, it is difficult to reconcile the theoretically predicted absence of an activation barrier for C-H insertion of methylene with data such as those provided by Halberstadt and Crump that show that methylene itself discriminates among the various types of C-H bonds in simple hydrocarbons, with insertion occurring preferentially into the weaker bonds.³⁰ A similar trend in selectivity is also found with alkylidene carbenes.^{2,14} Moreover, the existence of isotope effects, as found here and also by others^{25,31} is also difficult to rationalize in terms of an activationless process.

The simplest mechanistic constructs that fit the stereochemical and kinetic isotope effect data obtained for the intramolecular 1,5-insertion reaction of alkylidene carbenes are those of a concerted reaction or of a stepwise pathway not involving any long-lived intermediates. The key entity in the latter option would presumably be **20**, a species having substantial zwitterionic or diradical character. To account for the stereospecificity of the insertion reaction, **20** would be required to undergo inversion at the vinylic center and collapse to the cyclopentene faster than it would suffer stereorandomization. Assessing the likelihood of this is not easy, as can be seen from the following discussion.



If **20** is a zwitterionic species, the charge distribution should be that shown in **20a** rather than **20b**. Such an entity would undergo stereorandomization if the barrier to rotation about the C-4-C-5 bond is less than the barrier to inversion at the vinylic position. An estimate of ca. 31 kcal/mol can be assigned to the latter on the basis of the relative rates of H-D exchange and racemization of **21** in methanolic sodium methoxide.³² However, interpretation of such data in terms of a true inversion barrier for vinyl anions is made difficult owing to the substantial role that solvation phenomena can play in prototropic reactions.³³

(21) The level of deuteration obtained by this sequence was variable, with values ranging from less than 40% to greater than 80% being observed. This variability is ascribed to the presence of unchanged **15c** in the crude **14b** that was reduced.

(22) Wolinsky, J.; Clark, T. W.; Thorstenson, P. C. *J. Org. Chem.* 1976, 41, 745.

(23) Kirmse, W.; von Scholz, H.-D.; Arnold, H. *Justus Liebigs Ann. Chem.* 1958, 614, 19.

(24) The value in parentheses for this and all other isotope effects measured by us represents one standard deviation.

(25) (a) Gutsche, C. D.; Bachman, G. L.; Coffey, R. S. *Tetrahedron* 1968, 24, 617. (b) Baer, T. A.; Gutsche, C. D. *J. Am. Chem. Soc.* 1971, 93, 5180.

(26) (a) Bauschlicher, C. W., Jr.; Schaefer, H. F., III; Bender, C. F. *J. Am. Chem. Soc.* 1976, 98, 1653. (b) Khalil, S. M.; Shanshal, M. Z. *Naturforsch., A* 1978, 334, 722. (c) Kollmar, H. *Tetrahedron* 1972, 28, 5893.

(27) (a) Murrell, J. N.; Redley, J. B.; Durmaz, S. *J. Chem. Soc., Faraday Trans. 2* 1973, 1370. (b) Cremaschi, P.; Simonetta, M. *J. Ibid.* 1974, 1801. (c) Bauschlicher, C. W., Jr.; Haber, K.; Schaefer, H. F., III; Bender, C. F. *J. Am. Chem. Soc.* 1977, 99, 3610. (d) Jeziorek, D.; Zurawski, B. *Int. J. Quantum Chem.* 1979, 16, 277.

(28) (a) Dobson, R. C.; Hayes, D. M.; Hoffmann, R. *J. Am. Chem. Soc.* 1971, 93, 6188. (b) Jug, K.; Mishra, P. C. *Int. J. Quantum Chem.* 1983, 23, 887.

(29) Bodor, N.; Dewar, M. J. S.; Wasson, J. S. *J. Am. Chem. Soc.* 1972, 94, 9095.

(30) Halberstadt, M.; Crump, J. *J. Photochem.* 1972/73, 1, 295. Kollmar, H. *J. Am. Chem. Soc.* 1978, 100, 2660.

(31) Simons, J. W.; Rabinovitch, B. S. *J. Am. Chem. Soc.* 1963, 85, 1023. Goldstein, M. J.; Baum, S. J. *Ibid.* 1963, 85, 1885. Chesick, J. P.; Willcott, M. R., III *J. Phys. Chem.* 1963, 67, 2850. Simons, J. W.; Rabinovitch, B. S. *Ibid.* 1964, 68, 1322. Placzek, D. W.; Ring, D. F.; Rabinovitch, B. S. *Ibid.* 1965, 69, 1782. Ring, D. F.; Rabinovitch, B. S. *Can. J. Chem.* 1968, 46, 2435.

(32) Walborsky, H. M.; Turner, L. M. *J. Am. Chem. Soc.* 1972, 94, 2273.

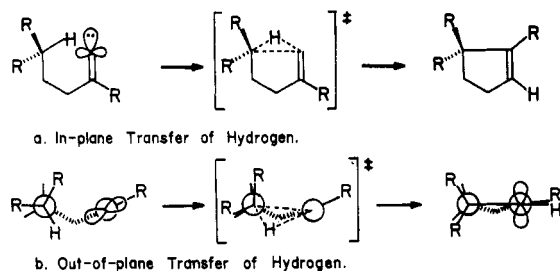
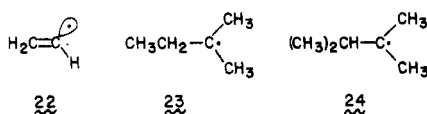


Figure 1. Trajectories for the 1,5 C-H insertion reaction.

It might be argued that even if the actual barrier for inversion of a "naked" vinyl anion were only one-tenth of the estimated value, stereorandomization should still occur, given that the barrier to rotation about the designated single bond is predicted to be less than that in the corresponding hydrocarbon.³⁴ However, this argument neglects the possibly crucial role associated with electrostatic factors present in 20a, but absent in the models on which the estimated barriers are based. These factors would be expected to lower the barrier for inversion and to raise the barrier to rotation, with the consequence that stereorandomization of 20a would be suppressed.

Should 20 be a diradical, 20c, ignoring interactions between the two radical centers would lead to a prediction of stereorandomization in the stepwise reaction pathway. This conclusion is based on the knowledge that the barrier to inversion of the vinyl radical 22 is 1.4 kcal/mol³⁵ whereas the barriers to rotation of the alkyl radicals 23 and 24 are 0.6 and 1.2 kcal/mol, respectively.³⁶ As with 20a, however, use of these barriers as models for the barriers in the diradical 20c is flawed by the lack of information regarding the possibility that the inversion barrier may be lowered and the rotation barrier raised in the diradical relative to the monoradicals.



Within the context of either a concerted or a stepwise process, it is of interest to consider the geometrical details of the transition state involving transfer of the hydrogen atom to the carbenic center, the stage of the reaction responsible for the observed isotope effect. Reference to the two detailed calculations of the reaction trajectories for the reaction of methylene with methane that have been reported will serve as the theoretical basis for our analysis.^{28a,29} Both of the calculations are similar in their prediction that the trajectory at the initial stages of the reaction (Figure 1) involves approach of the carbene generally along the axis of the C-H bond undergoing attack. However, there is substantial disagreement with respect to subsequent events; one calculation predicts that the new carbon-hydrogen bond forms much faster than does the new carbon-carbon bond,^{28a} whereas the other²⁹ is more in line with development of the triangular relationship that has been proposed for the insertion reaction on largely stereoelectronic grounds.³⁷ For our purposes, these two

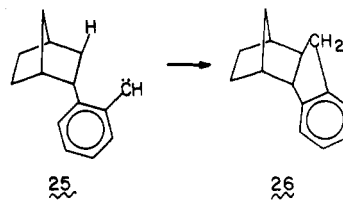
trajectories fundamentally differ in whether there is a linear or a nonlinear relationship between the carbenic carbon atom and the C-H bond at the stage of the reaction in which substantial formation of the new C-H bond is occurring.³⁸

Kwart has proposed that the geometries of transition states involving transfer of hydrogen can be analyzed by determination of the temperature dependence of the kinetic deuterium isotope effect.⁴⁰ Specifically, he argues that the ratio of A factors in eq 3 will be in the range of 0.75–1.2 for a linear transition state and that $-\left[\Delta E_a\right]_D^H$, where $[\Delta E_a]_D^H = E_a^H - E_a^D$ may be as large as 1.15;

$$k_H/k_D = A_H/A_D \exp(-\Delta E_a/RT) \quad (3)$$

a dependence on temperature of k_H/k_D would therefore be expected. In contrast, Kwart predicts that a nonlinear transition state will be characterized by a ratio of A factors greater than 1.2 and a value of $-\left[\Delta E_a\right]_D^H$ of less than 0.3 kcal/mol. The consequence is the expectation that this geometry would result in a temperature-independent isotope effect of magnitude greater than 1.2. Although this theory is relatively untested and has met controversy,⁴¹ it was thought to have the potential of giving useful insight into the transition state of the present insertion reaction.

Examination of Dreiding models of the molecular geometries possible for the 1,5-insertion of an alkylidene-carbene shows that either a linear or nonlinear array of the carbenic carbon atom and the C-H bond is geometrically accessible. Determination of the isotope effect for secondary benzylic insertion resulting from reaction of 15b with DAMP at 24–28 °C gave a value of k_H/k_D for 1.9 (0.1), which is within experimental error of that obtained at –78 °C. In light of the proposals of Kwart,⁴⁰ this suggests a nonlinear geometry for the transition state of this reaction.⁴² This result is in accord with those of previous workers who have concluded that because of severe structural constraints, as in the conversion of 25 to 26,^{24b} a bent arrangement is required to account for the selectivities observed in intramolecular C-H insertions. The present example appears to be the first in which this question has been probed by use of kinetic isotope effects.



Within the constraints of a nonlinear geometry, additional discussion of the detailed reaction trajectory by which 1,5-insertion of an alkylidenecarbene occurs is

(37) Skell, P. S.; Woodworth, R. C. *J. Am. Chem. Soc.* 1956, 78, 4496. Doering, W. v. E.; Prinzbach, H. *Tetrahedron* 1959, 6, 24.

(38) It is to be noted that experimental investigations involving intramolecular 1,5-insertions of arylcarbenes have been interpreted as supporting the former type of geometry.^{24b,39}

(39) Crow, W. D.; McNab, H. *Aust. J. Chem.* 1979, 32, 89.

(40) Kwart, H. *Acc. Chem. Res.* 1982, 15, 401.

(41) For example, see: (a) Li, M.-Y.; San Filippo, J., Jr. *Organometallics* 1983, 2, 544. (b) Hess, B. A., Jr.; Schaad, L. J. *J. Am. Chem. Soc.* 1983, 105, 7185. (c) Vitole, A. A.; San Filippo, J., Jr. *Ibid.* 1982, 104, 7341.

(42) If the extreme ranges of the error limits are considered, i.e., $k_H/k_D = 2.1$ at –78 °C and $k_H/k_D = 1.9$ at 25 °C, values of A_H/A_D and $[\Delta E_a]_D^H$ may be calculated assuming a linear transition state. The values obtained are 1.6 and 0.12, respectively. Earlier theoretical considerations have indicated that A_H/A_D should not exceed the square root of two for a linear transfer of hydrogen.⁴³

(43) Caldin, E. F. *Chem. Rev.* 1969, 69, 135. Schneider, M. E.; Stern, M. J. *J. Am. Chem. Soc.* 1972, 94, 1517. Bell, R. P. *Chem. Soc. Rev.* 1974, 3, 513.

(33) Cram, D. J. "Fundamentals of Carbanion Chemistry"; Academic Press: New York, 1965.

(34) Radom, L.; Pople, J. A.; Buss, V.; Schleyer, P. v. R. *J. Am. Chem. Soc.* 1970, 92, 6380, 6987.

(35) Krusic, P. J.; Meakin, P.; Jesson, J. P. *J. Phys. Chem.* 1971, 75, 3438.

(36) Hay, J. M. "Reactive Free Radicals"; Academic Press: New York, 1974. Simamura, D. "Topics in Stereochemistry"; Eliel, E. L., Allinger, N. L., Eds.; Wiley-Interscience: New York, 1969; Vol. 4.

worthwhile, given the substantial geometrical changes that attend the transformation. Application of the principle of least motion predicts a trajectory in which the hydrogen atom of interest moves in a plane defined by the carbon atom to which it originally is attached and the doubly bound carbon atoms of the carbene, as illustrated in Figure 1a. However, there are steric problems associated with this proposal in that the migrating hydrogen atom is within about 0.9 Å of the carbenic carbon atom if the five-carbon skeleton of the system is held coplanar and within approximately 1.1 Å if the skeleton is allowed to adopt a puckered conformation. Development of substantial van der Waals repulsion is thus expected for the trajectory of Figure 1a although the destabilization associated with it could be compensated for by partial bonding interactions between the hydrogen and the carbenic carbon atom.

Consideration of other stereoelectronic factors leads to a slightly modified pathway and attenuates the destabilization associated with van der Waals repulsion. If the C-H insertion reaction is viewed as having electrophilic and nucleophilic phases,^{26c,27d} the initial stage of the reaction at hand is presumably formation of a complex between the p-like, empty orbital of the carbenic carbon and the σ electrons of the carbon-hydrogen bond undergoing insertion. The nucleophilic phase of the process then ensues, with interaction of the nonbonding electrons of the carbene occurring with the hydrogen atom, probably concomitant with development of the new carbon-carbon σ bond, although such concert is not a necessity in light of our earlier arguments regarding stereorandomization of a zwitterionic or diradical species, 20. Examination of the molecular models suggests that formation of the complex would be facilitated, and steric interactions would be decreased, if the carbon-hydrogen σ bond were out of the plane defined by carbon atoms C₁-C₂-C₃. Moreover, moving C₅ out of this plane as well would appear to enhance the interaction necessary for formation of the initial complex. A representation of the resulting trajectory is shown in Figure 1b. Note that *two* trajectories of this sort are actually possible, differing only in whether a chairlike or boatlike conformation is invoked.

To summarize, the intramolecular 1,5 C-H insertion reaction of alkylidenecarbenes is stereospecific and, on the basis of its temperature-independent deuterium isotope effect, is believed to occur by way of a nonlinear transition state. Although an unambiguous decision cannot be made regarding the detailed reaction trajectory at this time, the overall process is viewed as a nonplanar transfer of the hydrogen atom that proceeds by formation of a complex between the σ bond and the carbenic carbon followed by development of the new carbon-hydrogen and carbon-carbon bonds in either a stepwise or concerted fashion.

Experimental Section

All IR spectra were recorded on a Beckman IR-5A AccuLab 8 spectrophotometer, and the polystyrene absorption at 1601 cm⁻¹ was used as reference. Samples were run as liquid films between salt plates; only major absorptions are reported.

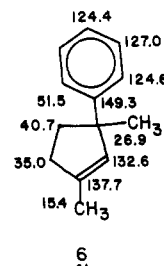
¹H NMR spectra were measured with a Varian Associates A-60 or EM-390 spectrometer, and all quantitative ¹H NMR analyses were repeated on a Nicolet NT-200 instrument. Integrations were the same within 5% in all cases. ¹³C NMR spectra were recorded with either a Varian Associates FT-80A or a Bruker WH-90 spectrometer. Chemical shifts are reported in units of δ downfield of internal Me₄Si. Unless otherwise noted, chloroform-*d* was used as the solvent.

Mass spectra (MS) were obtained with a Du Pont 21-471 double-focusing mass spectrometer operating at 70 eV. High-resolution mass spectrometry for exact mass measurements was conducted with a Du Pont (CEC) 21-110 instrument.

Preparative GC was executed on a Varian A90-P chromatograph equipped with a thermal conductivity detector. Helium was used as the carrier gas and retention times are given relative to air. The following columns were used (column, dimensions): A, 4 m \times 1/4 in. 6% SE-30 on 60/80 mesh silylated Chromosorb P-A; B, 3 m \times 1/4 in. 10% SE-30 on 30/60 mesh Chromosorb P-A; C, 0.6 m \times 1/4 in. 20% SF-96 on 60/80 mesh Chromosorb G; D, 4 m \times 1/4 in. 15% FFAP on 60/80 mesh Chromosorb P-A.

(\pm)-5-Phenyl-2-hexanone (5). The literature procedure afforded the ketone 5 in 67% yield, bp 70–81 °C (0.2 torr) [lit.⁴ bp 125–127 °C (13 torr)].⁴ Purification by GC (column C, 55 °C, 54 mL/min, 500 s) gave a sample for spectroscopic analysis. ¹H NMR 7.2 (m, 5 H), 2.7 (m, 1 H), 2.3 (m, 2 H) 2.0 (s, 3 H), 1.9 (m, 2 H), 1.2 (d, *J* = 7 Hz, 3 H); IR (neat) 1710 cm⁻¹; MS, *m/e* 176 (51, M⁺), 118 (100, M - C₃H₆O), 105 (91); HRMS calcd for C₁₂H₁₆O 176.1201, found 176.1205. A sample of *rac*-5 was prepared in 81% yield by reaction of acetaldehyde with the Grignard reagent from *rac*-1-bromo-3-phenylbutane (4)⁴⁴ and oxidation of the resulting alcohol according to the general procedure reported previously.² Spectroscopic analysis (IR, ¹H NMR, MS) demonstrated that ketone made in this way was identical with authentic material.⁴

(\pm)-1,3-Dimethyl-3-phenylcyclopentene (6). Application to 11.3 mmol of *rac*-15c of the previously reported² general procedure for the synthesis of cyclopentenones afforded 6 in 66% isolated yield. The hydrocarbon was purified by either GC (column B, 180 °C, 53 mL/min, 440 s) or column chromatography over silica gel, using petroleum ether (bp 60–80 °C) as eluent. ¹H NMR 7.2 (m, 5 H), 5.4 (m, 1 H), 2.2 (m, 4 H), 1.74 (s, 3 H), 1.37 (s, 3 H); IR (neat) 1652 cm⁻¹; MS, *m/e* 172 (2, M⁺), 157 (100, M - CH₃); ¹³C NMR (see structure 6); HRMS calcd for C₁₃H₁₆ 172.1252, found 172.1251.



(\pm)-4-Methyl-4-phenyl-2-cyclohexenone (7). A solution of 1.28 g (7.5 mmol) of 6 and 0.5 mL of concentrated hydrochloric acid in 75 mL of methanol was cooled to -78 °C and subjected to ozonolysis until a pale blue color persisted. Excess ozone was purged from the cold solution with nitrogen, and 3 mL of dimethyl sulfide and a magnetic stirring bar were added. The mixture was stirred for a period of 0.5 h each at -78 °C, room temperature, and reflux, after which 25 mL of 50% aqueous acetic acid was added; the resulting mixture was heated at reflux for 1 h. Solvent was then removed by rotary evaporation, the residue was extracted with benzene (2 \times 20 mL), and the organic solution was washed sequentially with water (2 \times 20 mL), 10% aqueous sodium bicarbonate (20 mL), and water (20 mL). Drying (Na₂SO₄) and removal of solvent afforded crude 5-oxo-2-methyl-2-phenylhexanal, as shown by ¹H NMR analysis: 9.3 (s, 1 H), 7.2 (br s, 5 H), 2.15 (br s, 4 H), 1.8 (s, 3 H), 1.3 (s, 3 H).

The residue was dissolved in 20 mL of anhydrous methanol and stirred with 0.75 g of anhydrous potassium carbonate for 36 h at room temperature. Solvent was removed under reduced pressure, the residue was taken up in 50 mL of pentane, and the resulting solution was washed with water (4 \times 25 mL). Drying (Na₂SO₄) and removal of solvent by rotary evaporation afforded crude product, which was purified by GC (column C, 190 °C, 60 mL/min, 168 s) to give 7 as a colorless, low-melting solid in 60% yield. This material had ¹H NMR, IR, and mass spectra identical with those of an authentic specimen prepared by the method of Flaugh et al.⁹

3,6-Dimethyl-6-phenyl-2-cyclohexenone (10). A solution of 0.40 g (2.1 mmol) of 7 in 2 mL of anhydrous diethyl ether was cooled to -78 °C under an atmosphere of nitrogen, and 3.0 mL (4.5 mmol) of methylolithium in hexane was added dropwise to

the magnetically stirred solution. The reaction mixture was then allowed to warm to room temperature and to stir for 1 h. After addition of 2 mL of water, the organic layer was extracted with ether (2 × 5 mL), and the combined extracts were washed with 2 mL of water and dried (MgSO₄). Solvent was removed by rotary evaporation, and the residue was dissolved in 2 mL of CH₂Cl₂ that had been purified by filtration through activated alumina. This solution was added in one portion to a stirred slurry of 0.90 g (4.2 mmol) of pyridinium chlorochromate in 7 mL of purified CH₂Cl₂. The mixture was stirred at room temperature under an atmosphere of nitrogen for 2 h after which 8 mL of ether was added. The organic solution was decanted and the black residue was washed with ether (3 × 4 mL). The combined solutions were washed sequentially with 1 M aqueous NaOH (2 × 20 mL), 2 M HCl (1 × 20 mL), 10% NaHCO₃ (2 × 10 mL), and brine (1 × 10 mL) and then dried (MgSO₄). Following removal of solvent by rotary evaporation, the crude enone was purified by HPLC (5% EtOAc/petroleum ether, 30–60 °C) to give 10 as a colorless oil in 62% yield. Anal. [2,4-DNP, mp 205.0–6.0 °C (uncorr)]. Calcd for C₂₀H₁₇N₄O₄: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.38; H, 5.22; N, 14.55. ¹H NMR (200 MHz) 7.10–7.40 (m, 5 H), 5.94 (q, *J* = 1 Hz, 1 H), 2.40–2.55 (m, 1 H) 1.95–2.25 (m, 3 H), 1.82 (d, *J* = 1 Hz, 3 H), 1.38 (s, 3 H); ¹³C NMR 202.4, 161.2, 142.7, 128.6, 126.7, 126.6, 126.3, 49.0, 35.9, 29.0, 26.6, 23.9; IR (neat) 1680, 1650 cm⁻¹; HRMS calcd for C₁₄H₁₇O 200.1201, found 200.1196.

5-Deuterio-2-hexanone (15a). A slurry of 25 g (0.38 mol) of zinc dust and 3 mL of D₂O was stirred for 10 min at room temperature and filtered by vacuum, and the filter cake was dried at 100 °C (0.2 torr). The zinc was added to a solution of 6.5 g (36 mmol) of 5-bromo-2-hexanone (14a),¹⁵ 8 mL of D₂O, and 75 mL of anhydrous DME, and the resulting slurry was stirred and heated at reflux for 2 h. After being stirred an additional 20 h at room temperature, the slurry was filtered by vacuum through Celite, the filter cake was washed with pentane (2 × 20 mL), and these washes and an additional 50 mL of pentane were added to the filtrate. The organic solution was washed with water (4 × 100 mL) and dried (Na₂SO₄), and the solvent was removed by fractional distillation. ¹H NMR 2.34 (t, *J* = 8 Hz, 2 H), 2.05 (s, 3 H) 1.15–1.70 (m, 3 H), 0.90 (m, 3 H); IR (neat) 2160, 1720 cm⁻¹; MS, *m/e* 101 (16.8, M⁺), 100 (0.6, M - 1), 43 (100, CH₃CO⁺); ¹³C NMR 208.5, 43.51, 29.7, 26.1, 22.09 (t, *J* = 19.1 Hz), 13.78.

5-Bromo-5-phenyl-2-pentanone (14b). A solution of 2.2 g (13.6 mmol) of 5-phenyl-2-pentanone (15c)¹⁸ in 40 mL of CCl₄

was combined with 3.1 g (17.4 mmol) of freshly recrystallized NBS, and the resulting solution was stirred magnetically and irradiated with a 200-W sunlamp for 30 min. The temperature of the reaction mixture was maintained at 20–25 °C. Following the irradiation, succinimide was removed by vacuum filtration, and the filtrate was washed sequentially with water (20 mL), saturated aqueous Na₂CO₃, and water (20 mL), dried (Na₂SO₄), and freed of solvent by rotary evaporation. The crude product was reduced directly. ¹H NMR 7.2 (m, 5 H), 4.8 (br t, 1 H), 2.2 (m, 4 H), 1.9 (s, 3 H).

5-Deuterio-5-phenyl-2-pentanone (15b). Crude 14b was deuterated in the same manner as was 14a and gave 15b in 68% overall yield from 5-phenyl-2-pentanone (15c). It was purified in the same way as 15a. The level of deuteration was determined by ¹H NMR and mass spectral analyses and was found to vary from less than 40% to 82% monodeuteration at C₅. Samples containing less than 40% deuterium were not used.

Analysis of the deuterium content of the samples was accomplished by mass spectrometric techniques and application of the following formula to the data: % D = M - (M - 1)[(M + 1)/M]/[M + (M - 1)[1 - (M + 1)/M]] × 100, where M is the molecular ion due to monodeuterated 15b.

Determination of Kinetic Isotope Effect. The ketone 15 were separately subjected to the general procedure for preparation of cyclopentenones reported previously,² and the products were isolated by GC as before. The reaction was performed at -78 °C with both 15a and 15b and also at room temperature in the case of the latter ketone. Two separate repetitions of each reaction were executed at each temperature.

Acknowledgment. The Robert A. Welch Foundation provided partial financial support for this research. Helpful discussions with Prof. Craig Wilcox regarding the determination of the stereospecificity of the insertion reaction are noted with gratitude.

Registry No. (R)-(-)-2, 772-14-5; (R)-4, 27798-98-7; 5, 96455-76-4; (R)-5, 96553-63-8; 6, 96455-77-5; (R)-6, 96553-64-9; 7, 51020-13-4; (R)-7, 24432-28-8; 8, 51447-25-7; 10, 96455-78-6; 10 (2,4-DNP deriv.), 119-26-6; 10b, 96553-65-0; 14a, 52355-85-8; 14b, 96455-80-0; 15a, 96455-79-7; 15b, 96455-81-1; 15c, 2235-83-8; D₂, 7782-39-0.

Kinetics and Mechanism of the Ivanov Reaction: Reaction of Aldehydes and Ketones with Phenylacetic Acid Magnesium Enediolate^{1,2}

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Received August 14, 1984

Stopped-flow kinetics of the reaction between aldehydes or ketones and the magnesium enediolate of phenylacetic acid in THF are second order at enediolate concentrations <10⁻³ M. At concentrations of 10⁻³–3 × 10⁻² M, the formation of a bis(enediolate) requires a more complex kinetic equation. Second-order rate constants are reported for the reaction of the enediolate with a number of aldehydes and ketones at 25 °C. Entropies of activation for cyclohexanone, benzaldehyde, 2-methylpropanal, and 2,2-dimethylpropanal are positive, and enthalpy–entropy compensation is observed. Effects of cycloalkane ring size and benzaldehyde substituents are small and are ascribable to a transition state with a very small C–C bond order. A two-step mechanism is proposed, with preequilibrium formation of a coordination intermediate which, in some cases, is accompanied by a change in the magnesium coordination number. Effects of alkyl groups on aldehyde and ketone reactivity stem mainly from steric desolvation.

Enediolates of carboxylic acids 1, known as Ivanov reagents, are usually obtained by the action of an or-

ganometallic reagent on carboxylic acids RCH₂COOH.^{3,4a,b} Reactions of Ivanov reagents with electrophiles such as

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(1) Work at the Université de Paris VII and at the Université P. et M. Curie supported in part by grants to M.M. from the Bulgarian Academy of Sciences and from the Centre National de la Recherche Scientifique.