Table I. Relative Yields of Olefins via the Bamford–Stevens Route from Ketones **4b,c**[a]

Starting ketone	Relative yields olefins[b]			Migratory ratio of a/e
	5a	**5b**	**5c**	
4b (D[a])	7.1[c]	41.3	51.6	0.80 (D/H)[e]
4c (D[e])	5.2[d]	25.0	69.8	2.8 (H/D)

[a] Results tabulated are averages of at least two duplicate runs which agreed to better than 5% of the value being determined. [b] The ratio of **5a**/(**5b** + **5c**) was determined mass spectrometrically. The ratio of **5b**/**5c** was determined by ^{1}H NMR (100 MHz); see ref 15. [c] This value corresponds to 5% H/D exchange from **4b.** [d] This value corresponds to 0% H/D exchange from **4c.** [e] This value was obtained in both the absence and presence of 8 equiv of TMEDA in the thermolysis of the lithium salt of the tosyl hydrazone.

11b (~70%) and the other which we suspect to be the bis(tosyl)hydrazone derivative. Rapid chromatography on silica gel (contact time ~5 min) gave the pure tosylhydrazone (70%), but with ~20% H-D exchange. Because of this exchange problem, we carried out the Bamford–Stevens reaction on the above-described mixture by adding a second equivalent of *n*-BuLi at −78 °C. The resulting solution was warmed to room temperature, concentrated, and evacuated at 40 °C (10 μ). The solid residue was suspended in dry, degassed cyclohexane and rapidly heated to 155 °C by immersing a sealed tube containing the mixture in an oil bath. The decomposition was complete in 5 min. A simple aqueous extraction, followed by removal of the cyclohexane and chromatography on alumina (pentane), gave a mixture of **5a–c** in yields of 40–50%. Table I shows the relative yields of the olefins which were arrived at mass spectrometrically and by ^{1}H NMR.[15] A similar sequence of steps starting with **4c** gave the data also shown in Table I.[16]

The data in Table I can now be used to determine the H^a/H^e migratory ratio, assuming that the deuterium isotope effect is the same for both axial and equatorial positions.[17,18] This leads to an isotope effect of 1.9 and a surprisingly small migratory ratio, H^a/H^e of 1.5. To test whether or not equilibration between a chair and twist-boat conformation might be the cause of the low selectivity, we used ketone **4a** as a model for **12.** We established that the ^{1}H NMR spectrum of **4a** was invariant from −70–110 °C (the temperature at which the Bamford–Stevens reaction is relatively rapid), indicating a single major (chair) conformer.[19] Control experiments which involved partial decompositions of the lithium salts of **11b** and **11c** established that these did not interconvert, as would be expected.

These data thus show minimal stereoselectivity in 1,2-H shifts in alkylcarbenes. It is interesting to note also that these results agree with the results of Seghers and Shechter[21] for 1,2-phenyl migration to a cyclohexylidene center but do not coincide with the least motion calculations carried out recently, in which there was "an overwhelming preference" [2g] for axial H migration in cyclohexylidene. We have investigated these rearrangements using semiempirical molecular orbital methods and the results are described in the following paper.

Acknowledgment. Grateful acknowledgment is made to the Robert A. Welch Foundation (F-573) for support of this work.

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(12) (a) LIS NMR studies revealed only the H^e resonance within the limits of detection (<4% H^a). (b) Similar studies of **4c** revealed <6% H^e resonance.
(13) Even under strictly aprotic conditions (aside from the reagents) such as anhydrous THF, deuterium loss was extensive (~75%). It also noted that recovered ketone, in a reaction terminated prior to completion, had *not* lost deuterium.
(14) Anhydrous hydrazine stored over potassium hydroxide pellets led to ~20% exchange, and thus storage over KOH was avoided.
(15) At 100 MHz in deuteriochloroform solution, the olefinic protons in **5a** exhibited an AB quartet centered at δ 5.49 (J_{AB} = 10.0 Hz, ν_{AB} = 15.6 Hz), with the downfield doublet (R^1) split cleanly into doublets of doublets (J_{AC} = 4.9 Hz, J_{AD} = 1.9 Hz) owing to coupling with the pseudoaxial and equatorial protons of the methylene unit α to the double bond. The upfield doublet (R^2) was broadened into narrow, ill-resolved multiplets. The determination of the ratio of **5b** to **5c** involved planimetric integrations of multiple scans at a sweep width of 250 Hz of the A and B portions of the above-described AB quartet. Subtraction from each portion of the amount of d_0 (**5a**) present (determined by mass spectrum) then led directly to the ratio of **5b** to **5c.**
(16) It should be noted that the Bamford–Stevens reaction carried out on the partially exchanged **11b** or **11c** isolated by rapid column chromatography gave results essentially the same as those in Table I, but with greater uncertainty, since a d_0/d_1 ratio of 20/80 corresponds to d_0 (which has two olefinic protons) contributing 33% of the absorption in the olefinic region in the NMR. Since this must be subtracted to obtain the absorption due to d_1 material, an appreciable uncertainty arises in the derived migratory aptitudes.
(17) If x = deuterium isotope effect and y = the migratory ratio of H^a/H^e, then from the last column the following equations can be derived: $xy = 2.8$ and $y/x = 0.8$. This leads to $x = 1.9$ and $y = 1.5$.
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(19) In acetone-d_6 at 100 MHz, the α-axial proton (R^2 in **4a**) is sufficiently deshielded to be observed cleanly: δ 2.61 (d of d of d, J_{gem} = 14.3 Hz, J_{a-a} = 13.2 Hz, J_{a-e} = 5.7 Hz), where coupling is observed with the axial and equatorial protons on the β-methylene unit. The assignments were confirmed by observation of the spectra of **4b** and **4c.** These coupling constants are in excellent agreement with those determined for the analogous protons in **3,**[20] indicating that the *gem*-dimethyl groups at the 2 position in **4** do not appreciably change the conformation of **4** relative to **3.**
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Masked Stereoelectronic Control of 1,2-Hydrogen Shifts to an Alkylcarbene Center. A MINDO/3 and MNDO Study

Sir:

Recently we reported that little stereoelectronic control of 1,2-H shifts to a carbene center was apparent in the cyclohexylidene system **1.**[1] This, and also the results of Seghers and Shechter,[2] appeared to sharply contradict the theoretical considerations of a number of groups,[3] who stated that axial or axial-like (i.e., toward the empty orbital) migration should

Table I. Heats of Formation (Kilocalories/Mole) of Carbenes, Their Rearrangement Transition States, and Products[a]

	2	3	$2^{\ddagger}$	$3a^{\ddagger}$	$3e^{\ddagger}$	4	5
MINDO/3	71.2	44.2	71.9 (0.7)	45.7 (1.5)	45.6 (1.4)	19.2	−9.5
MNDO	88.6	60.7	110.5 (21.9)	84.6 (23.9)	84.3 (23.6)	15.3	−10.0

[a] Activation enthalpies are given in parentheses. See Scheme I for identification of structure numbers.

Table II. Selected Bond Lengths and Vibrational Frequencies Corresponding to the Reaction Coordinates of Some of the Species Depicted in Scheme I, Derived by MINDO/3 and MNDO Calculations[a]

	MINDO/3				MNDO		
	2	$2^{\ddagger}$	$3a^{\ddagger}$	$3e^{\ddagger}$	$2^{\ddagger}$	$3a^{\ddagger}$	$3e^{\ddagger}$
x	1.226	1.316	1.314	1.315	1.315	1.330	1.327
y	1.362	1.251	1.273	1.272	1.401	1.400	1.401
z	1.383	1.370	1.407	1.406	1.379	1.400	1.401
ν^b		928	815	819	1699	1824	1726

[a] See Scheme I for identification of x, y, and z. [b] Frequency (cm^{-1}) of the imaginary mode corresponding to the reaction coordinate.

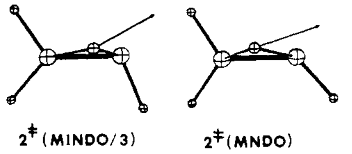
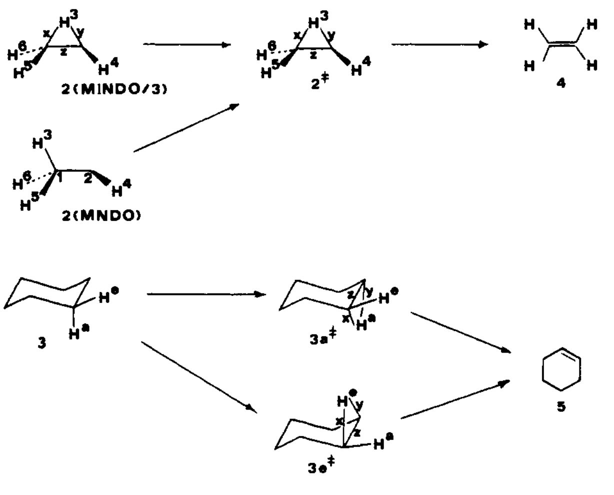

$2^{\ddagger}$(MINDO/3) $2^{\ddagger}$(MNDO)

Figure 1. ORTEP plots of the ethylidene to ethylene rearrangement transition states $2^{\ddagger}$ (MINDO/3 and MNDO) as viewed from a perspective above the rearranging hydrogen. The displacement vector shown, along with other much smaller ones not evident from this perspective, constitute the reaction coordinate.

Scheme I



strongly predominate. Indeed, two groups investigated cyclohexylidene itself by vastly differing approaches (semiempirical MO[3d] and least motion calculations[3g]) and both predicted H^a migration should prevail. It is also interesting to note in rigid bi- and tricyclic carbene systems, where the orbital alignment is not so ideal as in **1**, that considerably higher selectivity was observed.[4]

The low selectivity observed for H^a vs. H^e migration in **1** was thus very bothersome. We considered several factors which might be important in attenuating selectivity. Among these was the possibility that the 2,2-dimethyl substituents might have subtle effects both on the conformation of the ground-state carbene and on the corresponding transition state which would not be predictable by inspection of models. It was also possible, though less probable,[3] that the transition state for migration of a hydrogen atom toward the empty orbital and that for migration of a hydrogen atom toward the full (sp^2) orbital were nearly equal in energy. More likely, we felt that equilibration between twist-boat and chair conformations of the carbene might lead to lowered selectivity, but even under these circumstances a considerably higher selectivity than that observed might have been expected.[5] Another possibility was that stereoelectronic control is operative, but that the energy for a "limited torsional" process in which the H^e migrates toward the empty orbital with concomitant realignment of H^a is lower than the activation energy for the migration of either hydrogen atom. We report here the results of semiempirical calculations which favor this latter possibility.

Perusal of the literature shows that only two groups have investigated theoretically the 1,2 migration of a hydrogen to a carbene center in any detail, and that only one group has carried out a reaction path calculation.[6] Therefore, we felt that it was important to reinvestigate the ethylidene (**2**)-ethylene (**4**) and cyclohexylidene (**3**)-cyclohexene (**5**) systems (Scheme I) using the more modern semiempirical methods, MINDO/3[7] and MNDO[8] (based on the NDDO approximation). We felt it was important to use both methods, since it is known that MINDO/3 overestimates the stability of small rings,[9] and the transition state in question in fact contains a cyclic array of three atoms. The MNDO method does not appear to have nearly as large a bias favoring three-membered rings.[8]

Table I shows the calculated heats of formation of the various species studied using MINDO/3 and MNDO. The structures of **2** differ appreciably depending on which calculation is used, as shown in Scheme I. This is undoubtedly due to the overemphasis of the stability of three-membered rings on the part of MINDO/3. The methyl group in **2** (MNDO) is quite normal, with no appreciably distorted bond lengths or angles, and the dihedral angle 3124 is 86°. Structures **3** appeared to be quite normal with both methods except that, with MINDO/3, one H^a was somewhat biased toward the carbene center with a HCC angle of 98°. The transition states described here were located by carrying out reaction path calculations, using the distance between the migrating hydrogen atom and the migration terminus as the reaction coordinates.[10] The transition state structure was then refined by the procedure of McIver and Komornicki[11] by the minimization of the scalar gradient of the energy with respect to all geometrical variables. Finally the force constant matrix was calculated for each refined transition state, and each had the requisite single negative eigenvalue,[12] corresponding to the vibrational frequencies listed in the last line in Table II. Figure 1 shows ORTEP plots of $2^{\ddagger}$ (MINDO/3 and MNDO), including the displacement vectors obtained for the vibrational mode corresponding to the reaction coordinate. The structures of $3^{\ddagger}$ are very similar to $2^{\ddagger}$ in the reacting region of the molecule and are not shown (compare, however, bond lengths x, y, z in Table II). It is important to note that the displacement vectors shown in Figure 1 in fact correspond to a motion which leads to the product olefin.[12,13]

Finally, a limited configuration interaction (CI_0) calculation was carried out on **2** and $\mathbf{2}^{\ddagger}$ for both MINDO/3 and MNDO methods, which showed only minimal lowering of the calculated heats of formation of these species.[14]

Using the above-described methods, both H^3 and H^6 in **2** were migrated to the carbene center on the MINDO/3 and MNDO potential surfaces. It was found on the latter surface that migration of H^6 led to $\mathbf{2}^{\ddagger}$ which was the enantiomer of that derived from the migration of H^3; i.e., the activation enthalpies were identical ($\Delta H^{\ddagger} = 21.9$ kcal/mol).[15] A similar situation occurred for **2** on the MINDO/3 surface with the enantiomeric transition states being only 0.7 kcal/mol above that of the starting carbene. This small activation enthalpy is not surprising, considering that the structures of carbene **2** and the transition state $\mathbf{2}^{\ddagger}$ are very similar (see Table II). Similarly, migration of H^a and H^e in **3** led to almost identical transition states $\mathbf{3a}^{\ddagger}$ and $\mathbf{3e}^{\ddagger}$ which were not quite enantiomeric because the tetramethylene chain attached to the migration origin and terminus had differing conformations in the two transition states. As can be seen from Table I, the activation enthalpies for H^a and H^e migration are essentially equal within each method, but MNDO gives much higher $\Delta H^{\ddagger}$s than does MINDO/3.

What has been shown in this investigation is that, when calculations are carried out with no geometrical constraints, the molecules investigated have sufficient flexibility to rearrange with complete stereoelectronic control. That is, the transition state is one which has the migrating hydrogen very nearly aligned with the empty orbital, *regardless of the stereochemical origin of that hydrogen.*[16] Thus it appears unnecessary to consider other factors discussed above to be operative in the experimental system **1**. There still remains the question of why considerable selectivity has been observed with rigid bi- and tricyclic carbenes,[4] which will be the subject of a full paper.

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(10) The reaction path calculation consisted of calculating the ΔH_f's of the rearranging species as the distance between the migrating hydrogen and the migration terminus is shortened in 0.1 Å units from ~2.1 to 1.1 Å. Each structure was determined with complete geometry optimization with no constraints. Typically, such a reaction path calculation required ~6–10 min for **2** and ~2–2.5 h for **3** on a CDC 6600 computer.

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(15) It is interesting to note that the MNDO method gives $\Delta H_f(\mathbf{2}) - \Delta H_f(\mathbf{4}) =$ 73.3 kcal/mol, very similar to that (72.1 kcal/mol) obtained from an ab initio method, IBMOL-IV (double ζ basis set).[3e,f] In addition, the activation enthalpy to form the transition state $\mathbf{2}^{\ddagger}$ assumed by Yates group (27 kcal) is quite similar to that calculated by MNDO in this work.

(16) It is important to note that, with **2**, enantiomeric transition states could be arrived at by migrating H^3 directly, or rotating the methyl group 60° and migrating H^6, although this is not how the calculation was carried out. With **3** however, a 60° rotation would involve a chair → boat transformation, and this clearly did not occur in the reaction path calculation. Thus we have referred to "limited torsion" rather than rotation as the equatorial or equatorial-like hydrogen atom is migrated to the carbene center.

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Inhibition of Chicken Liver Carboxylesterase (EC 3.1.1.1) by Benzils. Direct Spectrophotometric Evidence for the Reversible Formation of Active-Site Hemiketal Adducts

Sir:

In 1927, using a crude preparation of pig liver carboxylesterase (EC 3.1.1.1), Willstätter et al.[1] convincingly demonstrated that an induction period in the enzyme-catalyzed hydrolysis of ethyl (±)-mandelate was caused by the presence of ethyl phenylglyoxylate as an impurity. The result is consistent with the subsequent observation that ethyl phenylglyoxylate has a relatively low $k_{\mathrm{cat.}}$ and a very low K_{m}.[1,2] This fact, coupled with the knowledge that carboxylesterases are more efficient in the hydrolysis of simple esters by a factor of 10^5–10^6 than the serine proteinases as exemplified by α-chymotrypsin,[3] led us to attempt to obtain direct evidence for the formation of addition compounds between chicken liver carboxylesterase[4] and α,β-dicarbonyl compounds.[5,6]

The ability of glyoxal to form addition complexes with urea[7] and of benzil, with hydroxide ion[8] and cyanide ion,[9] has long been known. Benzil (I) is a very powerful inhibitor of chicken liver carboxylesterase.[10] In 0.05 M phosphate buffer, pH 7.5, benzil has the characteristics of a classicial competitive inhibitor with $K_i = 1.0 \times 10^{-8}$ M against p-nitrophenyl acetate as substrate. This value is several orders of magnitude lower than that expected on the basis of a noncovalent (hydrophobic) interaction.[11]

The hemiketal (E-I) was postulated to account for the magnitude of K_i, and its existence is here established by the following experimental results. (1) Difference spectra of E-I obtained under conditions where [I] > [E] agreed quantitatively with spectra calculated for mixtures of I and E-I, based