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# A DFT Study of the Camphene Hydrochloride Rearrangement

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The rearrangement of camphene hydrochloride to isobornyl chloride is one of the best studied among the many early examples of Wagner−Meerwein rearrangement processes. However, many aspects of the reaction remain to be elucidated. A summary of early mechanistic studies is given. A proposal of new mechanistic possibilities is set forth and then tested by density functional theory (DFT) calculations. The uncertainties in configurations of camphene hydrochloride and isobornyl chloride are laid to rest by a comparison of computed and experimental carbon-13 and methyl proton chemical shifts.

## Introduction

In his book *A Step to Man*, John Platt[1] suggests that certain fields of science such as biotechnology and organic chemistry have made rapid progress by virtue of practicing a particular version of the scientific method which he dubs “strong inference”. The recipe for strong inference is the postulation of multiple hypotheses followed by critical experiments designed to test each with the elimination of those which do not meet the test. The process is to be iterated until a satisfactory solution is found. Mechanistic organic chemistry is replete with examples of the application of the strong inference mode of thinking. However, there are cases where the best of efforts have failed to produce a complete story. Such cases often become submerged in history, assume the attributes of solved problems, and disappear from textbooks and reviews. Such is the case for the formation of isobornyl chloride by the rearrangement of camphene hydrochloride.

The first notable attack on this problem was made by Meerwein and van Emster,[2] who measured the rates of rearrangement of camphene hydrochloride in a number of aprotic solvents and concluded that the isomerization occurred by a carbocation mechanism. While their outline of the mechanism described the steps given in Scheme 1 (route A), they used planer diagrams, not indicating the stereochemistry of starting material or product. They expressed the opinion that **1** was in equilibrium with camphene and hydrogen chloride, the latter serving as a catalyst for the reaction. Their conclusions were confirmed by Bartlett and Pöckel,[3a] who found that over a wide range of concentrations the rearrangement in nitrobenzene was second order (first order in camphene hydrochloride and first order in hydrogen chloride).[3b] They postulated the role of hydrogen chloride to be assisting with the departure of the chlorine in the form of the $HCl_2^-$ ion. They pointed out that the structure of product **2** had not been satisfactorily related to that of isoborneol, but accepted the established stereochemistry of Wagner−Meerwein rearrangements, i.e., inversion of configuration at the migration origin as well as at the terminus. They opined that the “noncatalyzed” rearrangement utilized HCl produced by the equilibrium of camphene hydrochloride with camphene and HCl, though no evidence of such an equililrium was provided. Shortly thereafter, the English chemists Nevell, de Salas, and Wilson[4] carried out an experimental tour de force with the aid of isotopically labeled hydrogen chloride, demonstrating that the rate of chloride exchange was faster than rearrangement and establishing that the presumed camphene−hydrogen chloride equilibration was not fast enough to account for the exchange rate. They pointed out that the consequences of postulating the intermediacy of an isobornyl cation **3** as in route A (Scheme 1) should be the formation of both isobornyl and bornyl chloride. While bornyl chloride may be the ultimate reaction product, it must form very much more slowly than isobornyl chloride, the kinetic product. To explain their observations, they proposed the rearrangement to proceed through a resonance-stabilized entity **5** combining the aspects of both the camphenyl and isobornyl cations (Scheme 1 route B). They concluded that **3** played no role in the rearrangement. Subsequently, Ingold[5] amplified the concept as an important example of a “synartetic” ion, which in today’s nomenclature would be identified as a nonclassical or carbenium ion.

Initially, the camphene hydrochloride rearrangement seemed to meet the criteria of enhanced rate and stereoselectivity required for nonclassical ion intermediates. Brown and Chloupek[6] found the rate of rearrangement to be only slightly above the solvolysis rates for a series of appropriately methyl-substituted chlorocyclopentanes. These results were interpreted as a failure to meet the criterion of rate enhancement. The argument in favor of a nonclassical bridged intermediate was discredited. Strangely, no comment was made about the high degree of stereoselectivity.

No reference was made to the subsequent rearrangement to bornyl chloride. From a computer search of the

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[1] Platt, J. R. *A Step to Man*; John Wiley & Sons: New York, 1966.

[2] Meerwein, H.; van Emster, K. *Ber. Dtsch. Chem. Ges.* **1920**, *53*, 1815; **1922**, *55*, 2500.

[3] (a) Bartlett, P. D.; Pöckel, I. *J. Am. Chem. Soc.* **1937**, *59*, 820; (b) **1938**, *60*, 1585.

[4] Nevell, T. P.; de Salas, E.; Wilson, C. L. *J. Chem. Soc.* **1939**, 1188.

[5] Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: New York, 1969; p 730.

[6] Brown, H. C.; Chloupek, F. J. *J. Am. Chem. Soc.* **1963**, *85*, 2322.

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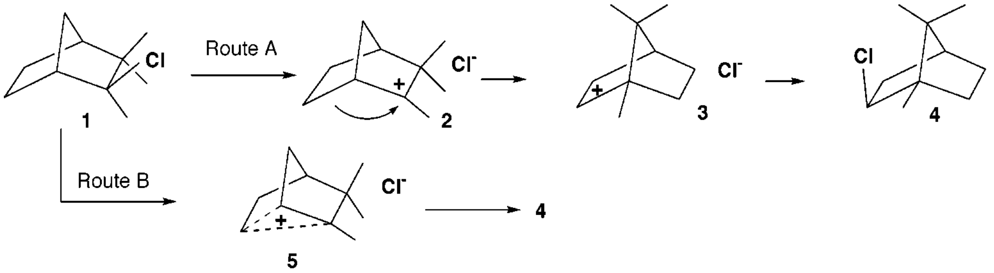
**Scheme 1**



literature, this paper appears to be the last identifiable experimental work on this system.

The requirements to be accommodated are to demonstrate a process of relatively low activation energy and a high degree of stereoselectivity. The reaction transition states should have some degree of ionic character to provide for the initial observations of Meerwein and van Emster.

The structures traditionally assumed for camphene hydrochloride and isobornyl chloride should be tested and justified. The second-order kinetics observed by Bartlett and Pöckel[3] should be preserved in any explanation. Since computational methods have proven increasingly powerful in attacking such subtle problems, the decision was made to utilize this tool as part of the strong inference methodology.

## Experimental and Computational Methods

Camphene hydrochloride was prepared in deuteriochloroform by the method of Carman and Shaw[7] which differs from the previously utilized addition of hydrogen chloride to camphene in that an iced solution of isoborneol is treated with phosphorus pentachloride in the presence of calcium carbonate. This method produces high yields of the chloride, but requires that the system be maintained at or near 0 °C, be concentrated, and then be hurried into the NMR instrument (Varian INOVA 400 MHz). The proton spectrum was found to produce methyl proton signals in agreement with those reported.[7,8] Carbon-13 chemical shifts were in excellent agreement with the data reported by Schneider et al.[9] It is noted here that carbon signals due to isobornyl chloride were noted within 5−10 min after introducing the sample into the probe (22 °C). However, when the sample was allowed to stand, with the addition of 2 mL of 1 M HCl in ether, for 1 week, no evidence of bornyl chloride was to be found. Specific examination for the presence of small amounts of camphene was negative in all cases.

For the NMR computations, the molecular geometries were determined at the DFT BPW91/6-311G* level and magnetic susceptibilities were calculated by the GIAO method embedded in Gaussian 94[10] using the BPW91/6-311G** basis set following the work of Barfield and Fagerness.[11] All structures in the mechanism study were derived from Becke3LYP/6-31G* calculations, following the recent suggestions of Schleyer and coworkers.[12] Excepting transition structures (TSs), zero-point energies were calculated at the HF/3-21G* level and scaled to the Becke3LYP/6-31G* level by the previously determined factor of 1.06.[13] All TSs reported met the criteria of a single imaginary frequency. Here the ZPEs were from Becke3LYP/6-31G* calculations.

## Results and Discussion

**The Question of Structures.** Previous workers have pointed out that no proof exists connecting the structure of isoborneol with that of isobornyl chloride.[3,4] A computer search of *Chemical Abstracts* did not offer any help in this matter. Similarly, there seems to be no identifiable, rigorous proof of the structure of camphene hydrochloride. It has been presumed through the century that these structures are well established. The best argument one can find is the consistency of the experimental results with the many extent studies of the Wagner−Meerwein rearrangement. Strong inference requires that this matter be addressed.

Recently, Forsyth and Sebag[14] have described an empirical method for correlating calculated GIAO shieldings with experimental chemical shifts to acquire information bearing on conformational problems. Isotopic magnetic shieldings ($\sigma_{\mathrm{IMS}}$) were calculated by the GIAO method at the BPW91/6-311G** level for norbornane, *exo*- and *endo*-norborneol, and the *exo*- and *endo*-norbornyl chlorides and plotted against their experimental carbon-13 chemical shifts (Figure 1). The experimental data were taken from the text by Levy and Nelson.[15] The relation relating computed shieldings and chemical shifts is

$$\delta(\text{predicted}) = -0.8321(\text{shielding}) + 153.9$$

The square of the correlation coefficient is 0.9799 for the 40-point plot. The 95% confidence levels are shown as dashed lines. Superimposed on the plot are the experimental chemical shifts for camphene hydrochloride plotted both against the computed shielding for this molecule (squares) and that for isocamphene hydrochloride (X's). The calculated chemical shifts for both molecules are compared to the experimental data in Table 1. The quality of the fit does not allow a distinction between these structures. The only points to fall on or outside the 95% confidence level are the C-2 carbons for both molecules.

Brown and Liu,[8] as well as Carman and Shaw,[7] reported the proton chemical shifts for the C-2 *endo*-methyl, C-3 *exo*-methyl, and C-3 *endo*- methyl as fol-

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[7] Carman, R. M.; Shaw, I. M. *Aust. J. Chem.* **1980**, *33*, 1631.

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[11] Barfield, M.; Fagerness, P. *J. Am. Chem. Soc.* **1997**, *119*, 9, 600.

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[13] Smith, W. B.; Amezcua, C. *Magn. Reson. Chem.*, in press.

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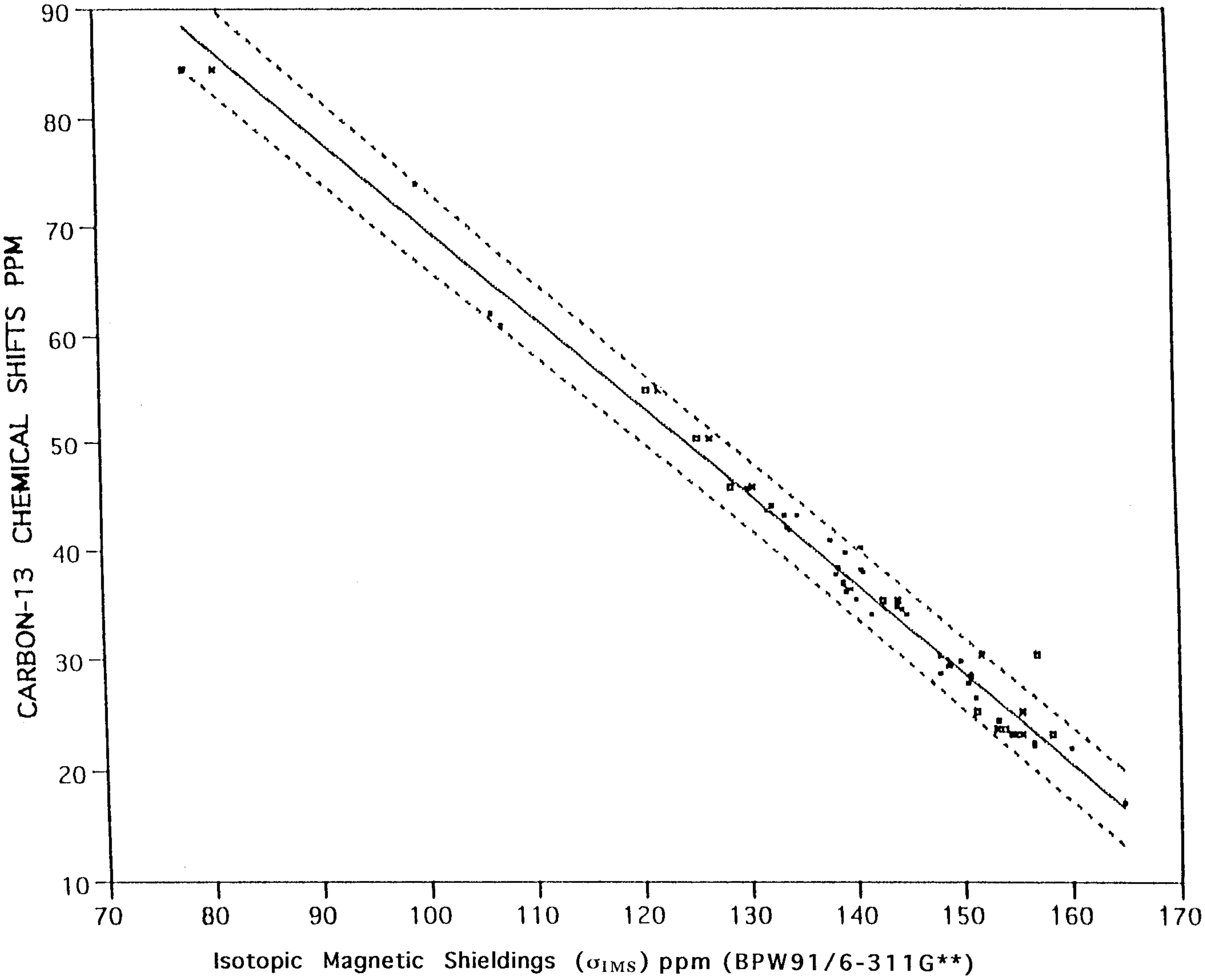

**Figure 1.** Plot of calculated isotopic magnetic shielding values vs experimental Carbon-13 chemical shifts. The small points are the calibration compounds determining the least squares line, the squares are for camphene hydrochloride, and the X's are for isocamphene hydrochloride. Dotted lines set forth the 95% confidence levels.

lows: 1.56 (1.59), 1.17 (1.20), and 0.97 (0.98) ppm, respectively. The computed values for these methyls for camphene hydrochloride (isocamphene hydrochloride) are 1.57 (1.58), 1.22 (1.00), and 0.96 (1.45). These results are clearly in line with the conventionally accepted structure for camphene hydrochloride.

While the carbon-13 results above are inconclusive, the same is not true for the isobornyl chloride case. The equation above was used to predict the carbon chemical shifts for isobornyl and bornyl chlorides. These data were then compared with the literature values for these shifts.[9] The calculated chemical shift data for the expected *exo*-isobornyl chloride agreed with the experimental shifts with an average deviation of ±0.9 ppm. When the experimental numbers were applied to the calculated bornyl chloride shifts, the average deviation increased to ±2.4 ppm. In contrast, the fit of the experimental bornyl chloride shifts to those calculated again produced an average deviation of ± 0.9 ppm. The exo structure for isobornyl chloride is thus confirmed.

**Mechanistic Considerations.** It seemed appropriate to return to the initially proposed mechanism of Meerwein and van Emster.[2] The ionization of the camphene hydrochloride to the camphenyl cation **2** (Scheme 1) and chloride ion is endothermic by 134.0 kcal/mol (Table 2). These numbers would be changed if one wished to include a correction for solvent polarity. However, current ab initio and DFT methods conduct solvent corrections as variations of the Onsager reaction field model,[16] and specific solvation effects cannot be modeled at this time. Of the four available solvent models in Gaussian 94 only the relatively simple Onsager model[17] can be used to optimize the molecule in the solvent cavity. By this method, placing the chloride ion in nitrobenzene ($\epsilon = 34.8$ D) produces no change in energy as compared to the value in a vacuum, while carrying the camphenyl cation through the same process lowers the energy only by 1.1 kcal/mol. Furthermore, in solvents with low dielectric constants such as chloroform ($\epsilon = 4.8$ D) the rearrangement still proceeds quite rapidly (see ref 4 and the NMR experiments described above).

Attempts to minimize the structure for the isobornyl cation **3** at semiempirical or low-level HF methods

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[16] Onsager, L. *J. Am. Chem. Soc.* **1936,** *58*, 1486.

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**Table 1. Calculated Isotopic Magnetic Shieldings ($\sigma_{IMS}$) (BPW91/6-311G**//BPW91/6-311G*) and Chemical Shifts[a] with Experimental Values**

| | $\sigma_{IMS}$ | $\delta$(calcd) | $\delta$(exptl) | deviation (ppm) |
|---|---|---|---|---|
| camphene HCl | | | | |
| C-1 | 120.96 | 53.3 | 55.1 | −1.8 |
| C-2 | 78.51 | 88.6 | 84.8 | 3.8 |
| C-3 | 128.79 | 46.8 | 46.1 | 0.7 |
| C-4 | 125.69 | 49.4 | 50.6 | −1.2 |
| C-5 | 154.43 | 25.5 | 23.4 | 2.1 |
| C-6 | 153.76 | 26.0 | 23.9 | 2.1 |
| C-7 | 142.66 | 35.3 | 35.7 | −0.4 |
| C-8 | 151.32 | 28.1 | 25.5 | 2.6 |
| C-9 | 158.23 | 22.3 | 23.4 | −1.1 |
| C-10 | 156.79 | 23.5 | 30.8 | −7.3 |
| Isocamphene HCl | | | | |
| C-1 | 122.34 | 52.2 | 55.1 | −2.9 |
| C-2 | 81.23 | 86.4 | 84.8 | 1.6 |
| C-3 | 130.87 | 45.1 | 46.1 | −1.0 |
| C-4 | 126.97 | 48.3 | 50.6 | 2.3 |
| C-5 | 154.78 | 25.2 | 23.4 | 1.8 |
| C-6 | 153.20 | 26.5 | 23.9 | 2.6 |
| C-7 | 144.03 | 34.1 | 35.7 | −1.6 |
| C-8 | 155.41 | 24.7 | 25.5 | −0.8 |
| C-9 | 155.46 | 24.6 | 23.4 | 1.2 |
| C-10 | 151.80 | 27.7 | 30.8 | −3.1 |

[a] Taken from the linear-regression line in the text.

**Table 2. Becke3LYP/6-31G* Energies for the Various Species in This Study[a]**

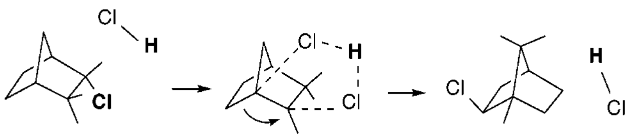
| structures | energy (hartrees) |
|---|---|
| chloride | −460.252 233 |
| HCl | −460.788 567 |
| $HCl_2^-$ | −921.091 415 |
| camphene | −390.407 715 |
| camphene hydrochloride | −851.213 327 |
| isocamphene hydrochloride | −851.229 052 |
| camphenyl cation | −390.747 586 |
| bornyl chloride | −851.220 842 |
| isobornyl chloride | −851.218 880 |
| Wagner−Meerwein TS (HCl catalyzed) | −1311.988 637 |
| Wagner−Meerwein TS (uncatalyzed) | −851.175 314 |

[a] All energies include the ZPE correction. For the stable entities, these were determined at the HF/3-21G* level and then scaled up by the factor 1.06 (Smith,W. B. and Amezcua, C. *Magn. Reson. Chem*. **1998,** *36*, S3−S10). The transition structure ZPE were determined at the Becke3LYP/6-31G* level.

invariably led to the formation of the camphenyl cation **2**. The minimization of **3** at the Becke3LYP/6-31G* level required 26 cycles, ultimately forming **2**. Examination of these steps showed the minimization path to proceed via several structures (cycles 9−11) closely resembling the carbon skeleton expected of the nonclassical ion **5**. At the Becke3LYP/6-31G* level, these structures invariably optimized to **2**. These results stand in contrast to the 2-norbornyl cation where the nonclassical ion structure is the energy minimum and the classical ion is a TS (all this at the Becke3LYP/6-31G* level).[12] Mechanisms postulating the formation of a stable intermediate resembling **5** seem to not merit further consideration.

Early workers prepared their camphene hydrochloride by the addition of HCl to camphene and concerned themselves with the reversibility of the reaction. Bartlett and Pöckel[3b] estimated the amount of HCl in freshly prepared solutions as <6%. No data were provided for this estimate. The energies for the species involved, corrected for ZPE, are given in Table 2. The addition reaction is found to be exothermic by 10.7 kcal/mol, corresponding to an equilibrium favoring **1** in excess of 99.99%. There are no experimental reports of ever finding camphene in solutions of pure camphene hydrochloride, though this does not preclude very minute amounts. This statement applies as well to the work reported here.

**Scheme 2**



Attention was turned next to the Wagner−Meerwein rearrangement of camphene hydrochloride in the prescence of hydrogen chloride. While mechanisms involving classical and nonclassical carbocations have been proposed at various points in time, it appears that no one has considered the possibility of a cyclic mechanism in which the role of the hydrogen chloride is not only to aid in the breaking of the $C_2$−Cl bond but also to stereospecifically supply the new chlorine via a five−membered cyclic structure as depicted in Scheme 2. This postulation accommodates not only the stereochemistry but also the observed second-order kinetics.

Starting materials and products were set up as indicated in Scheme 2, and an approximate transition structure was obtained by the linear synchronous transit method of Halgren and Lipscomb.[18] Optimization produced the TS shown in Figure 2. Only one imaginary frequency was found, and an indication of the normal vibrational modes associated with the reaction coordinate (Gaussview[10]) are represented in the figure. The original HCl proton is rapidly oscillating between the two chlorines. The migrating methylene describes an arc between original carbons 1 and 2, while these carbons move to and fro as the methylene approaches. The overall reaction enthalpy is 3.48 kcal/mol, while the activation enthalpy is 8.32 kcal/mol. As seen in Figure 2, the TS has the attributes of an ion pair. Two cases of ion-pair TSs have been reported recently.[19,20] Furthermore, as shown, the camphenyl portion of the TS is clearly a bridged structure. Thus we come back to the postulation of Nevell, de Salas, and Wilson,[4] the difference being that of a bridged transition structure, not a stable intermediate. To confirm that this TS is on the appropriate reaction path, an IRC was carried out at the HF/6-31G* level. The various structures confirmed the above result, clearly showing the reestablishment of the initial C−Cl bond in the starting material and the original HCl as well as the new C−Cl bond in the product and a new HCl accompanied by migration of the methylene group.

The preparation of camphene hydrochloride by the method of Carman and Shaw[7] was carried out at ice-bath temperatures in the prescence of calcium carbonate. This temperature was maintained until the sample was introduced into the NMR probe. It seems highly unlikely than any appreciable amount of HCl existed in the samples prepared in this fashion. Nevertheless, the rearrangement proceeds rapidly once the sample reaches the probe temperature (22 °C). On the basis of the results above, it seemed reasonable to postulate that the uncatalyzed reaction also proceeds through a cyclic ion-pair TS. This possibility was explored by the methods em-

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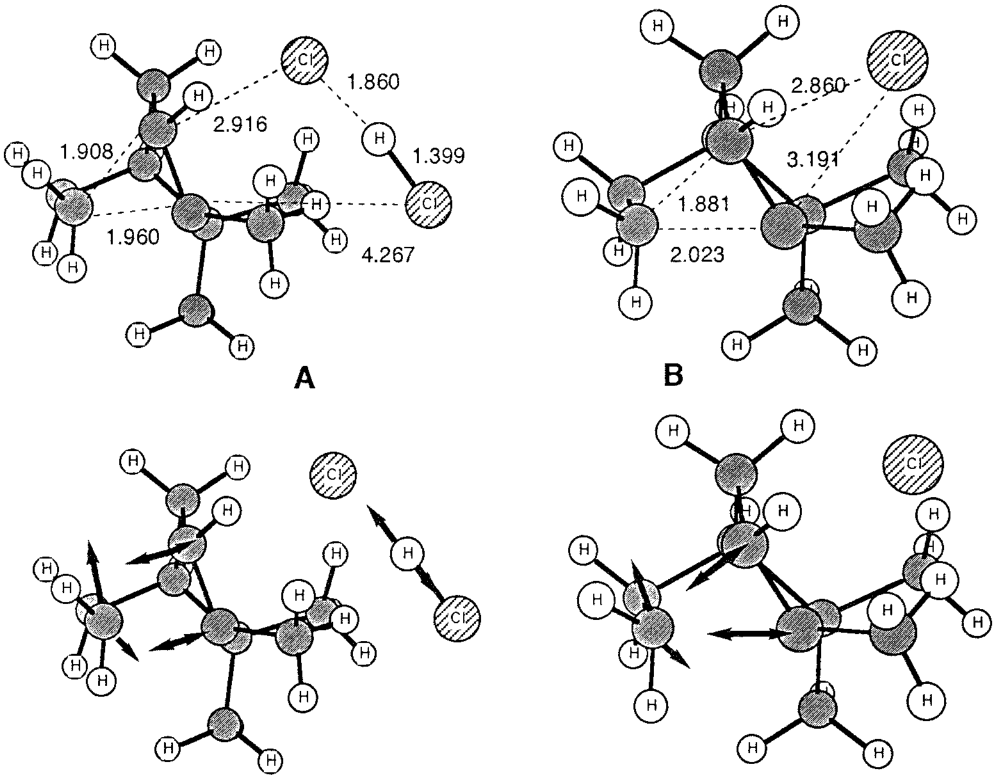

**Figure 2.** Ball and stick representations of the transition structures for the HCl catalyzed camphene hydrochloride rearrangement **A** and the uncatalyzed **B**. Bond distances are shown in the upper portion, while a representation of the normal vibrational modes is given in the lower.

ployed in the HCl catalyzed case above. The resultant TS is pictured in Figure 2 along with a representation of the normal modes associated with the TS. The chloride ion appears midway between carbons 1 and 2 and shows trivial motion. The migrating methylene describes a rapidly oscillating arc between the migration origin and terminus, which, in turn, move as described above. The calculated activation enthalpy was 23.85 kcal/mol. There appears to be no case where the HCl catalyzed and the uncatalyzed rearrangements were studied in the same solvent. Meerwein and van Emster[2] note only that the uncatalyzed reaction in solvents of low polarity was very slow.

## Conclusions

Early studies of the formation and rearrangement of camphene hydrochloride suffered from the unavailability of spectroscopic methods for analyzing structures and purity of products. In their study of the addition of hydrogen chloride to camphene, Brown and Liu[8] report the addition at −78 °C, forming **1**, to be complete in 1.5 min and totally rearranged to **4** in 10 min. This certainly corresponds to the experiences described above in obtaining the NMR spectra of pure **1**. The early kinetic methodology consisted of selective titrations with base. Organic solutions were shaken with cold water which was then titrated for HCl. Calcium hydroxide solutions were reacted with **1** and then back-titrated and corrected for the initial HCl determination. Isobornyl chloride was said not to react under these conditions. Brown and Liu[8] do not mention the equilibrium with camphene as a factor nor do Carman and Shaw[7] in their preparation from isoborneol. In the NMR work described above no evidence for camphene was found in the camphene hydrochloride spectrum or in that of the rearrangement product **4**. Calculated and experimental NMR chemical shifts were used to confirm the long-presumed structures for camphene hydrochloride and isobornyl chloride to be correct, in fact.

The proposal of a cyclic TS involving a five-centered ring which allows for simultaneous attack by hydrogen chloride to deliver the chlorine at C-1 while also helping to pull off the original chlorine at C-2 meets the requirements of the observed second-order kinetics, the high stereoselectivity, and a low enthalpy of activation. Similarly, the uncatalyzed rearrangement may also proceed via a cyclic ion-pair TS. This mechanism would preserve the observed stereochemistry of the reaction and account for the comparative slowness of the uncatalyzed reaction.

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**Supporting Information Available:** Summaries of all Becke3LYP/6-31G* and BPW91/6-311G** data (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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