Deamination of *trans*-2-Methyl- and *trans*-2-Phenylcyclopropylamines

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The deaminations of *trans*-2-methyl- and 2-phenylcyclopropylamine hydrochlorides in acetic acid solution have been examined. A major product in each case was an allylic chloride, and the amount of chlorides increased when the chloride ion concentration was increased. With the methyl-substituted amine, increasing the chloride ion concentration changed the major chloride product from crotyl chloride to methallyl chloride. The addition of lithium perchlorate led to a reduction in the amount of chlorides formed. These results indicate that an ion pair is involved in the reaction. The deamination of the related open chain amines gave only small amounts of chlorides. B3LYP/6-31G* calculations found cyclopropyldiazonium chloride to prefer to have the chloride ion over the cyclopropyl ring. The transition state was located, and when followed down to products, allyl chloride was found. Similar calculations for the methyl-substituted series led to crotyl chloride from the ion pair with one chloride ion and to methallyl chloride from the ion-triplet with two chloride ions. The deaminations of the corresponding nitrosoureas in basic methanol also were studied. The products were the expected ethers. The addition of azide ion led to azides that were largely formed by initial reaction with the diazonium ion to give a pentazene that lost nitrogen to give the azide. However, some of the azide was formed by an S_N2 displacement.

1. Introduction

The ring opening of cyclopropyl cations has received considerable attention.[1] Cyclopropyl derivatives undergo solvolysis at a relatively slow rate,[2] and the products are usually derived from allyl cations that are formed in a disrotatory process.[3] A comparison of cyclopropyl and isopropyl cations at the MP2/6-311+G** theoretical level (Table 1) found the following reaction to be exothermic by 32 kcal/mol:[4]

$$\triangleright^+ + \rangle \longrightarrow \triangleright + \rangle^+ \qquad \Delta H = -32 \text{ kcal/mol}$$
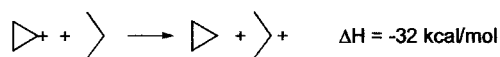
In view of the relatively high energy of the cyclopropyl cation, it is not surprising that it is formed with difficulty.

The deamination of cyclopropylamines provides a facile entry to the cyclopropyl cation system. These reactions have received extensive study by Kirmse and co-workers.[5] The reaction of cyclopropylamine with nitrous acid in acetic acid solution leads to allyl acetate and a small amount of cyclopropyl acetate (2.5%). The reaction with a deuterium-labeled cyclopropylamine shows that the cyclopropyl acetate was formed with inversion of configuration. When 3,3-dimethylbutyric acid or 2-ethylhexanoic acid was used as solvent, the amount of cyclopropyl esters increased to 7% and 10%, respectively. These
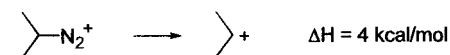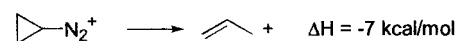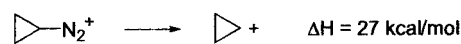
Table 1. MP2/6-311+G** Calculated Energies

compound	energy (*H*)	ZPE (kcal/mol)[a]
cyclopropane	−117.53843	48.9
cyclopropyl cation	−116.55508	39.4
diazocyclopropane	−225.53354	40.6
cyclopropyldiazonium ion	−225.90883	48.4
propane	−118.76708	62.0
2-propyl cation	−117.83523	53.2
2-diazopropane	−226.77113	53.7
2-propyldiazonium ion	−27.14385	57.5
allyl cation	−116.61317	41.2
nitrogen	−109.30156	3.5

[a] HF/6-31G* frequencies scaled by 0.893.

reactions presumably involve ion pairs,[6] which become even more important as one goes from acetic acid to acids having even lower dielectric constants.

The energetics of nitrogen loss from the diazonium ions suggests that the cyclopropyl cations are not intermediates in the reaction but rather that rearrangement to an allyl cation is simultaneous with the loss of nitrogen. The MP2/6-311+G** energy changes for the loss of nitrogen are:

$$\triangleright\!\!-\!N_2^+ \longrightarrow \triangleright^+ \qquad \Delta H = 27 \text{ kcal/mol}$$

$$\triangleright\!\!-\!N_2^+ \longrightarrow \diagup\!\!\!\diagup \qquad \Delta H = -7 \text{ kcal/mol}$$

$$\rangle\!\!-\!N_2^+ \longrightarrow \rangle^+ \qquad \Delta H = 4 \text{ kcal/mol}$$

Although the loss of nitrogen from the isopropyldiazonium ion is calculated to be slightly endothermic, the entropy change will be quite favorable so that the free
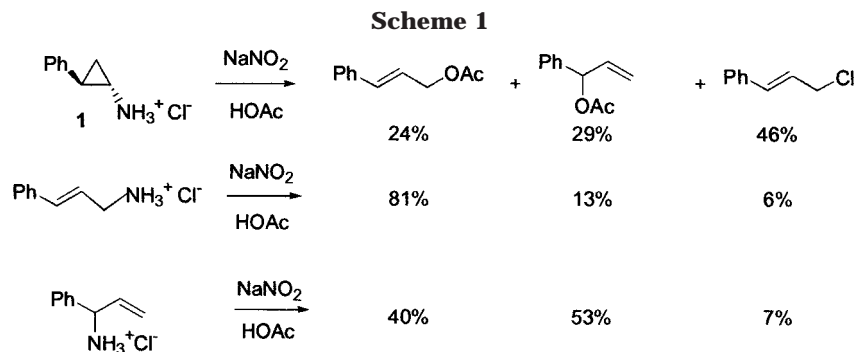
(1) Schleyer, P. v. R.; Sliwinski, W. F.; Van Dine, G. W.; Schollkopf, U.; Paust, J.; Fellenberger, K. *J. Am. Chem. Soc.* **1972,** *94,* 125.

(2) Roberts, J. D.; Chambers, V. C. *J. Am. Chem. Soc.* **1951,** *73,* 5034.

(3) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970. DePuy, C. H.; Schnack, L. G.; Hausser, J. W.; Wiedemann, W. *J. Am. Chem. Soc.* **1965,** *87,* 4006.

(4) Radom, L.; Hariharan, P. C.; Pople, J. A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973,** *95,* 6531.

(5) Kirmse, W.; Banert, K.; Bunse, M.; Gassen, K.-R.; Kurnianto, A. W. *Recl. Trav. Chim. Pays-Bas* **1986,** *105,* 272. Kirmse, W. *Top. Curr. Chem.* **1979,** *105,* 272.

(6) Huisgen, R.; Rüchardt, C. *Liebigs Ann. Chem.* **1956,** *601,* 21; first suggestion that ion pairs were involved in deamination reactions.

Scheme 1

energy change will be negative. In marked contrast to the isopropyldiazonium ion, the reaction of the cyclopropyldiazonium ion is quite endothermic, but the reaction forming the allyl cation is exothermic.

2. Deamination Reactions in Acetic Acid Solution

We were interested in gaining further information on the reactions of the diazonium ions, and therefore we have examined the deamination of *trans*-2-phenylcyclopropylamine (**1**) and *trans*-2-methylcyclopropylamine (**2**). These reactions have been studied by Kirmse et al.[7] They found that the deamination of the amines in acetic acid gave in both cases mixtures of the two possible ring opened allyl acetates. The results clearly indicate the reaction proceeds via conversion of the cyclopropyldiazonium ion into the corresponding allyl cation. We have used the corresponding amine hydrochlorides as the reactants, and this provided additional information about the process.

The deamination of **1** was effected by the treatment of a solution of the amine hydrochloride in acetic acid with sodium nitrite (Scheme 1). Besides the expected ring opened acetates, comparable amounts of chlorides also were found. No unrearranged cyclopropane derivatives were found. The addition of chloride ion led to a marked increase in the amount of chlorides formed (Figure 1), and they became the major product of the reaction. In contrast, when lithium perchlorate was added the yield of chloride product decreased from 56% with no added salt to 40% with the addition of 1.5 equiv of LiClO$_4$. This is the expected behavior for the reaction of an ion pair because perchlorate ion is nonnucleophilic and will not intercept the carbocation.[8]

The deaminations of 3-phenylallylamine (**3**) and 1-phenylallylamine (**4**) were examined under the same conditions and gave the products shown in Scheme 1. Here, the main products were acetates, and relatively little of the chlorides were found. The product ratios were quite different than that found in the deamination of **1**.

The deamination of **2** also was examined using the same reaction conditions to see if a smaller and weaker conjugating group such as methyl would affect the course of the reaction. The products were again acetates and chlorides (Scheme 2), and the amount of chlorides formed again increased markedly with increasing chloride ion concentration (Figure 2). It is interesting to note that whereas crotyl chloride was formed at low chloride ion
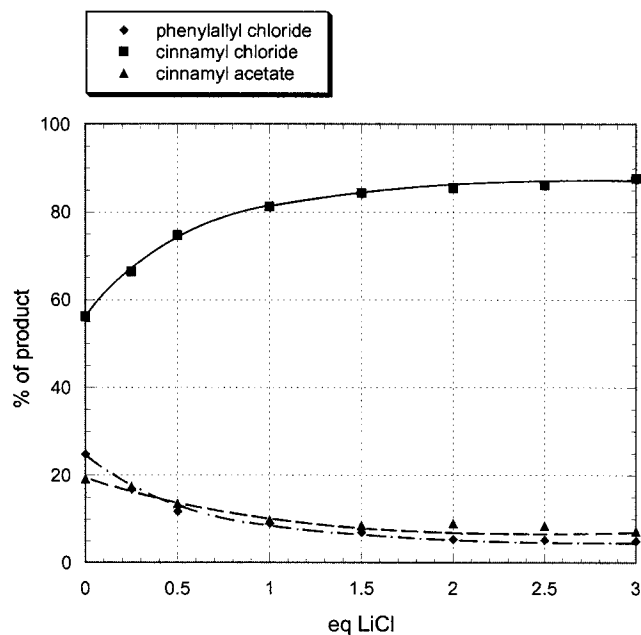
(7) Kirmse, W.; Urbach, H. *Chem. Ber.* **1972**, *105*, 832. Kirmse, W.; Schutte, H. *Chem. Ber.* **1972**, *105*, 824. Kirmse, W.; Schutte, H. *Chem. Ber.* **1986**, *119*, 3672.

(8) This is known as a special salt effect and has been studied in detail for the acetolysis of ex-norbornyl chloride by Winstein, S.; Robinson, G. C. *J. Am. Chem. Soc.* **1958**, *80*, 169.

Figure 1. Effect of lithium chloride on the product distribution in the nitrous acid deamination of *trans*-2-phenylcyclopropylamine.

concentrations, methallyl chloride was the major chloride at high chloride ion concentration. The effect of added perchlorate anion paralleled the effect seen for **1**. The percent of crotyl chloride decreased from 30% with no added lithium perchlorate to 8.5% when 2.5 equiv was added. The open chain amines corresponding to the products also were subjected to deamination, giving the products shown in Scheme 2. Again, the products derived from the deamination of the open chain amides were formed in a quite different ratio than that found in the deamination of **2**.

In the reactions of both **1** and **2**, the products formed were significantly different than those found from the related open chain amines. Clearly, the same intermediates are not involved in the two sets of reactions. The efficient capture of chloride ion in the cyclopropyldiazonium ion reactions, but not in the open chain deaminations, suggests that a cyclopropyl ring−chloride ion interaction is in some way intimately involved in the reaction. The effect of salt addition to the deamination reactions also showed that the chloride anion is captured when present in form of a tight ion pair with the diazonium ion.

3. Computational Studies

We have tried to model the reactions via B3LYP/6-31G* calculations in which the solvent was represented
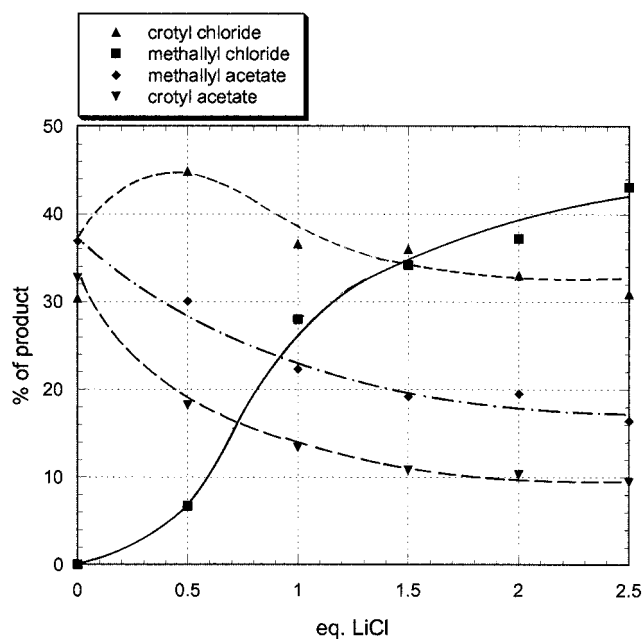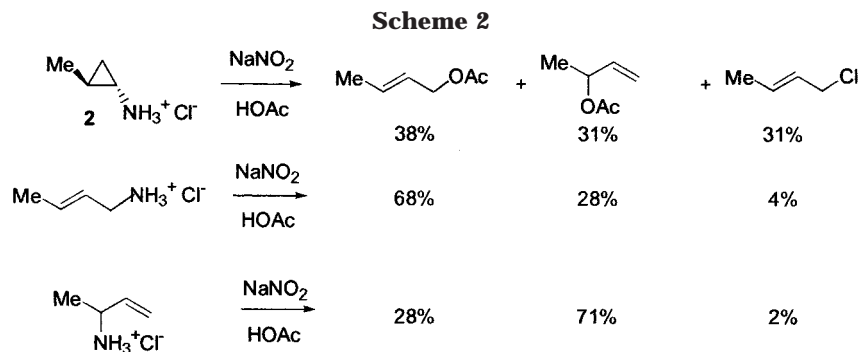
Scheme 2

Figure 2. Effect of lithium chloride on the product distribution in the nitrous acid deamination of *trans*-2-methylcyclopropylamine.

as a dielectric continuum having the dielectric constant of acetic acid (6.4). The SCI−PCM reaction field model[9] was used for the calculations. The calculated structures of two ion-pair conformations and of the transition state are shown in Figure 3. The preferred ion pair (**B**) has the chloride ion lying over the cyclopropane ring, presumably to interact with the partial positive charge at the cyclopropane carbons and hydrogens. It should be noted that the group attached to the N_2 of a diazonium ion bears most of the positive charge.[10] The energy of **B** was 8 kcal/mol lower in energy than the other ion pair (**A**) where the chloride ion is on the remote side of the cyclopropyl ring (Table 2).

A transition state was located (one imaginary frequency) and is shown in the figure. The C−N bond has lengthened from 1.410 Å in the ion pair to 1.972 Å in the transition state. Similarly, the C2−C3 bond has increased in length from 1.491 Å to 1.626 Å, showing that the remote cyclopropane bond is being broken. It is interesting to note that the hydrogens syn to the chloride ion were found to rotate inward, probably to achieve
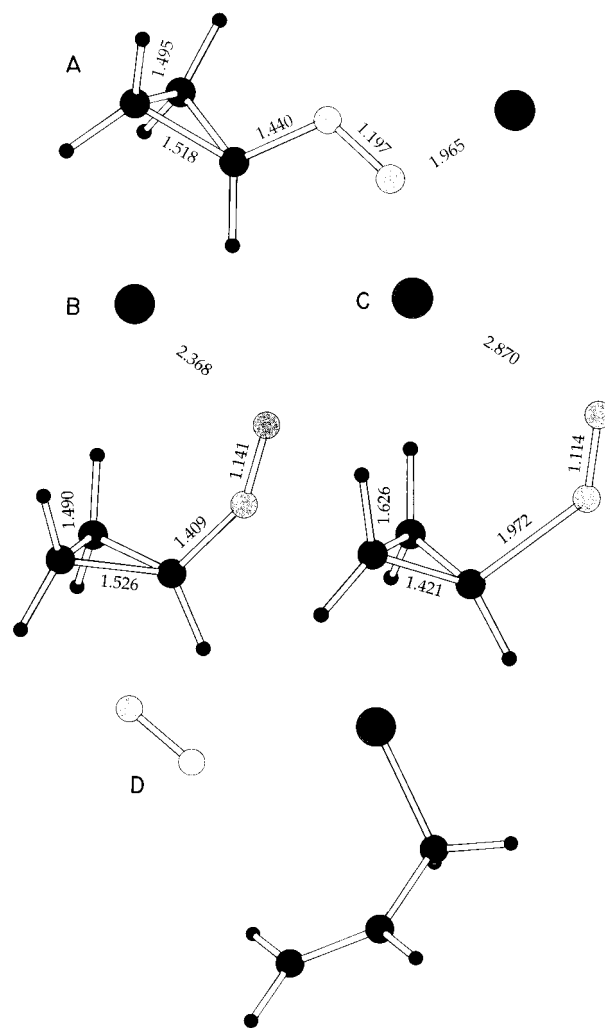

Figure 3. Calculated structures of cyclopropyldiazonium chloride ion pairs (A and B), the reaction transition state (C), and the products of the reaction (allyl chloride and nitrogen) (D).

Coulombic stabilization. The energy of the transition state was 15 kcal/mol above the ion pair. This is significantly smaller than the difference in energy between a cyclopropyldiazonium ion and a cyclopropyl cation plus nitrogen (see above).

An intrinsic reaction coordinate (IRC) calculation[11] was carried out starting with the transition state and following its path for reaction in both the forward and reverse directions. In the reverse direction it did give the ion pair,

(9) Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098. Clifford, S.; Keith, T. A.; Frisch, M. J., to be published.

(10) Wiberg, K. B.; Breneman, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 8765. Glaser, R.; Choy, G. S.-C.; Hall, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1109.

(11) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154; **1990**, *94*, 5523.

Table 2. B3LYP/6-31G* SCRF Calculated Energies, $\epsilon = 6.4$

compound	energy (H)	ZPE (kcal/mol)
cyclopropyldiazonium chloride (A)	−686.93357	51.4
cyclopropyldiazonium chloride (B)	−686.94669	51.4
transition state (C)	−686.91761	47.6

Table 3. Calculations for Methyl-Substituted Compounds, $\epsilon = 6.4$

| compound	energy (H)	ZPE[a]	ΔH_{rel}[a]
2-methylcyclopropyldiazonium chloride	−726.26548	69.0	0.0
transition state	−726.23826	65.6	13.7
crotyl chloride + N_2	−726.34935	66.4	−55.2
2-methylcyclopropyldiazonium dichloride	−1186.61616	68.9	0.0
transition state	−1186.59111	66.2	13.0
methallyl chloride + N_2 + Cl^-	−1186.68981	66.3	−48.8

[a] kcal/mol.

and in the forward direction, the C2−C3 distance continued to increase, the N_2 moved away, and the chloride ion moved in to form a bond with one of the carbons, giving allyl chloride. Thus, the calculations are in good accord with the experimental results.

The reaction of the methyl-substituted diazonium−chloride ion pair also was studied (Table 3). The structures of the compounds are available as Supporting Information. The ion pair and the transition state were similar to those in Figure 3. In the ion pair the length of the remote cyclopropyl C−C bond was 1.491 Å, and in the transition state it was 1.649 Å. The transition state had an energy 14 kcal/mol above the ground state. The path from the transition state to the products was followed to see to which of the two allylic carbons the chloride ion would become attached. In the transition state, the chloride ion is slightly closer to the terminal CH_2 than to the methyl-substituted carbon, and this persists on going to the product, which was crotyl chloride.

The effect of added chloride ion on the reaction probably involves an ion triplet with the methylcyclopropyldiazonium ion and two chloride ions. The structure of an ion triplet was located having one chloride ion above the cyclopropane ring and the other below the ring (Table 3). The transition state also was located, and its relative energy was significantly lower than that for the ion pair. The structural data also indicate that it is earlier along the reaction coordinate than that from the ion pair. For example, the remote C−C bond length in the ion-pair transition state is 1.645 Å,whereas in that derived from the ion-triplet it is 1.610 Å. Here. the chloride ion was slightly closer to the methyl-substituted cyclopropyl carbon. Following its path toward products, the chloride ion above the ring formed the product, which in this case is methallyl chloride. Apparently, the second chloride ion serves only to decrease the activation energy and to create an environment where the first chloride ion becomes attached to the carbon bearing the methyl group.

The phenyl-substituted cyclopropylamine did not lead to a change in the chloride product with added chloride ion. A plausible explanation is that the large size of the phenyl group either minimizes the formation of the ion triplet or distorts it in such a way as to not have an effect on the course of the reaction.

Scheme 3
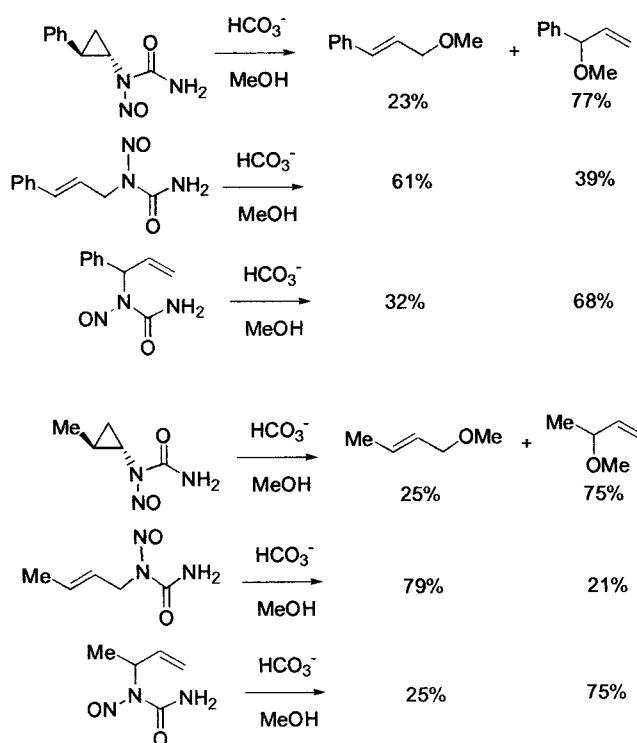
4. Deamination Reactions In Methanol Solution

It seems clear that the course of deamination reactions carried out in acetic acid solutions is dominated by ion-pair effects. It is possible to minimize such effects by going to a more polar solvent such as methanol.[12] The treatment of nitrosoureas or nitrosourethanes with base in methanol solution leads to hydrolysis with the formation of an alkanediazotate that further reacts in the fashion of a diazonium ion.[13] The nitrosoureas corresponding to *trans*-2-methylcyclopropylamines and *trans*-2-phenylcyclopropylamines were prepared and allowed to react in methanol, giving the products shown in Scheme 3. The product ratios were similar to those found by Kirmse.[7] The course of the reactions was similar to that found in acetic acid, except that chloride ion was not effectively captured, and the product ratios were somewhat different.

Chloride ion is not a very good nucleophile. Azide ion is much more effective both for S_N2 reactions and in capturing the carbocations formed in S_N1 reactions.[14] There is, however a problem associated with the direct reaction of the azide anion with a diazonium ion to give an intermediate pentazene that may lose N_2 to give an azide with retention of configuration.[15] Furthermore, the initially formed diazonium ion can react with base to form a diazoalkane with loss of stereochemistry.[16] Kirmse

(12) Ion pairs involving singly charged ions have been found to exist only in solvent having a dielectric constant less than about 40 (Fuoss, R. M.; Krauss, C. A. *J. Am. Chem. Soc.* **1933**, *55*, 1019).

(13) Kirmse, W.; Schutte, H. *Chem. Ber.* **1968**, *101*, 1674.

(14) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16.

(15) Kirmse, W.; Baron, J. W.; Seipp, U. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 924. Kirmse, W.; Schnurr, O.; Jendralla, H. *Chem. Ber.* **1979**, *112*, 2120.

(16) The data in Table 1 allow the relative acidities of the 2-propyl-diazonium ion and the cyclopropyldiazonium ion to be compared. The reaction of the cyclopropyldiazonium ion with 2-diazopropane to give the 2-propyldiazonium ion and diazocyclopropane is calculated to be exothermic by −2.4 kcal/mol.

Scheme 4
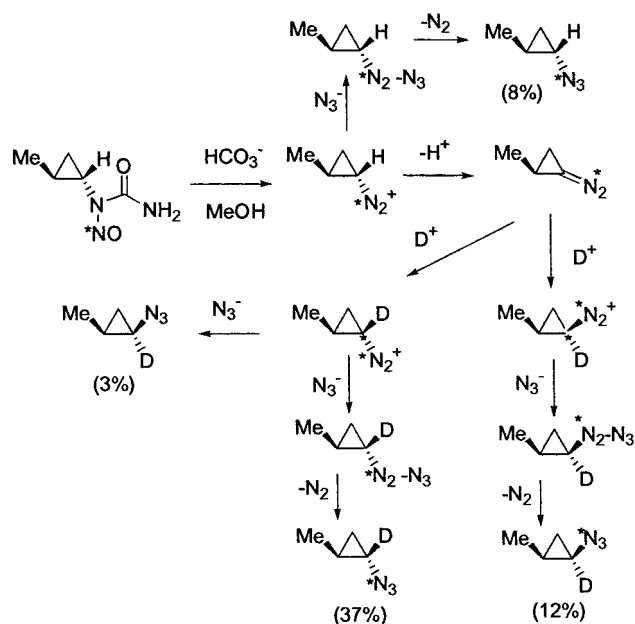
demonstrated these reactions through the use of a ^{15}N label and deuterated starting material and solvents in the deamination of *N*-nitroso-*N*-cyclopropylurea.[15] It was also shown that the deamination of the nitrosoureas of *trans*- and *cis*-2-methycyclopropylamines in dimethylamine afforded identical mixtures of *cis*- and *trans*-*N*,*N*-dimethyl-(2-methylcyclopropyl) amines.[17] The conclusion drawn from these results was that the deamination of these nitrosoureas proceeds entirely via the intermediacy of diazocyclopropane with loss of stereochemistry.

We have further studied this reaction by the deamination of ^{15}N-labeled *N*-nitroso-2-methylcyclopropylurea using DCO_3^- and CH_3OD. NMR spectroscopic analysis of the 2-methylcyclopropyl azide formed in the reaction showed the incorporation of 83% of deuterium in the trans isomer (45% of the product) and 100% of deuterium incorporation in the cis isomer (16% of the product). The ^{15}N label originally present in the nitroso group of the nitrosourea was detected in 97% of the trans azide and in 82% of cis isomer (Scheme 4). The two experiments showed that although all *cis*-2-methylcyclopropyl azide is formed via the intermediacy of 2-methyldiazocyclopropane, only 82% of the *cis*-2-methyldiazonium ions afforded the cis azide through azo coupling. In fact, 18% of the cis azide is formed by an S_N2 reaction mechanism. There are a number of examples of S_N2 displacements by nucleophiles such as iodide ion on cyclopropyldiazonium ions that are formed via basic cleavage of *N*-nitrosocyclopropylureas.[13]

Summary

The deamination of cyclopropylamines is unique in that ion pairs that lead to chloride products are involved in the reaction. This was shown by the effects of added chloride ion, which markedly increases the amount of chloride products, as well as the effect of lithium perchlorate, which significantly decreased the amounts of these products. It was possible to model these reactions by ab initio calculations at the B3LYP/6-31G* level

including a reaction field solvent effect calculation using the dielectric constant of acetic acid. The lower energy ion pair had a chloride ion lying above the cyclopropyl ring, The transition state was located, and it led to the observed chloride products. With *trans*-2-methylcyclopropyldiazonium ion, the ion pair with one chloride ion led to crotyl chloride as the products, and with the ion triplet with two chloride ions, it led to methallyl chloride, in agreement with the experimental results.

The diazonium ion formed via basic cleavage of *N*-nitroso-*trans*-2-methylcyclopropylurea was found to give rapid H/D exchange with methanol-*d*. Addition of azide ion led mainly to azide products formed via an intermediate pentazene, but a significant amount of the product was formed vi a direct nucleophilic substitution on the diazonium ion.

Experimental Section

Calculations. The ab initio calculations were carried out using Gaussian-95.[18]

General Information. FT NMR spectra were taken in $CDCl_3$ unless otherwise stated, and FT IR spectra were taken in CCl_4. Low resolution mass spectra obtained in the EI mode by GC–MS were obtained at an ionizing voltage of 70 eV and a gas chromatograph fitted with a 30 m × 0.25 mm i.d. capillary column coated with a 0.25 μm layer of SE–30. Mass spectra recorded in the CI mode were obtained using a DCI probe and isobutane as the reagent gas. The mass spectra of labeled compounds were obtained using a gas chromatograph fitted with a 50 m × 0.2 mm i.d. column coated with a 0.33 μm layer of cross-linked methyl silicone. The parameters used were the following: T_{inj} = 150 °C, T_{det} = 70 °C, T_{col} = 30 °C with a split ratio of 20/1. The GC was connected to a mass spectrometer with the ionization voltage set to 15 eV. Analytical GC measurements were obtained using a 50m × 0.2 mm i.d. capillary column coated with a 0.33 μm layer of cross-linked methyl silicone. Parameter set 1: T_{inj} = 150 °C, T_{det} = 270 °C, $T_{col/init}$ = 80 °C, $T_{col/final}$ = 250 °C, initial time 10 min, rate 15°/min. Parameter set 2: T_{inj} = 150 °C, T_{det} = 270 °C, $T_{col/init}$ = 30 °C, $T_{col/final}$ = 250 °C, initial time 10 min, rate 15°/min. Preparative gas chromatography was carried out using the following: column A, 4 ft × $^1/_4$ in. column fitted with 20% Carbowax 20M on Chromosorb P (80/100 mesh); column B: 15 ft × $^1/_4$ in. column fitted with 15% QF 1 on Chromosorb P (80/100 mesh). Silica gel column chromatography was done using 230–400 mesh silica gel unless otherwise stated.

Deamination of *trans*-2-Phenylcyclopropylamine Hydrochloride. To a 10 mL round-bottomed flask equipped with a magnetic stirrer was added 0.05 g of *trans*-2-phenylcyclopropylamine hydrochloride (Acros Organics, 0.29 mmol) in 2 mL of glacial acetic acid. To the solution was added 0.04 g of sodium nitrite (0.58 mmol) in small portions over a period of 1 h. After the addition was completed the solution was stirred for an additional 1 h. To the solution were added 10 mL of water and 10 mL of CH_2Cl_2. The organic layer was extracted with as many 10 mL portions of saturated $NaHCO_3$ as needed to neutralized the acetic acid. Drying of the organic layer over anhydrous sodium sulfate and solvent removal in vacuo yielded a light brown solid. Analysis of the product mixture with the analytical GC (parameter set 1) showed a 1:1.9:1.2 ratio of phenylallyl acetate (t_R = 14.3 min), cinnamyl chloride (t_R =

(17) Kirmse, W.; Seipp, U. *Chem. Ber.* **1974**, *107*, 745.

(18) Frisch, M. J.; Trucks; G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb; M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortis, J. V.; Foresman, J. B.; Cioslowski, J.; Sefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 95*, Development Version (Rev. D); Gaussian, Inc.: Pittsburgh, PA, 1995.

14. 8 min), and cinnamyl acetate (t_R = 16.8 min). Independent synthesis[19] confirmed the assignments of the NMR spectra.

Deamination of *trans*-2-Phenylcyclopropylamine Hydrochloride with Added Salts. The procedure was the same as described above. For each experiment *trans*-2-phenylcyclopropylamine hydrochloride (about 0.25 g), 2 molar equiv of NaNO$_2$, and a given number of molar equivalents of LiCl were used. The range of LiCl added was between 0.5 and 2.5 molar equiv in 0.5 unit steps. LiCl was added to the reaction solution and completely dissolved before NaNO$_2$ was added. The product distributions for each reaction was recorded by analytical GC and plotted as a function of the number of equivalents of LiCl added.

The reactions in the presence of lithium perchlorate were carried out in the same fashion. For each experiment a given number of equivalents of LiClO$_4$ were used. The range of LiClO$_4$ added was between 0.5 and 2.5 equiv in 0.5 unit steps. LiClO$_4$ was added to the reaction solution and completely dissolved before NaNO$_2$ was added. The product distributions for each reaction was recorded by analytical GC.

Deamination of *trans*-2-Methylcyclopropylamine Hydrochloride. To a 10 mL round-bottomed flask equipped with a magnetic stirrer was added 0.24 g of *trans*-2-methylcyclopropylamine hydrochloride[20] (0.43 mmol) in 2 mL of glacial acetic acid. To the solution was added 0.29 g of sodium nitrite (0.85 mmol) in small portions over a period of 1 h. After the addition was complete the solution was stirred for an additional 1 h. Then, 10 mL of water and 10 mL of CH$_2$Cl$_2$ were added to the solution, followed by extraction with as many 10 mL portions of saturated NaHCO$_3$ as needed to neutralized the acetic acid. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. Analysis of the product mixture with analytical GC (parameter set 2) showed a 1.2:1:1 ratio of methylallyl acetate (t_R = 5.1 min), crotyl chloride (t_R = 2.9 min), and crotyl acetate (t_R = 10.0 min). The solution was concentrated to 2 mL by fractional distillation of the solvent through a 20 cm distillation column packed with steel wool. The remaining liquid was separated into its components by preparative GC (column B, T_{col} = 70 °C, T_{inj} = 120 °C, T_{det} = 250 °C). The retention times were t_R = 4.3 min for crotyl chloride, t_R = 6.4 min for methylallyl acetate, and t_R = 8.5 min for crotyl acetate. NMR spectra were recorded of all compounds and compared to the spectra obtained from authentic samples[21] to confirm the assignments.

Deamination of *trans*-2-Methylcyclopropylamine Hydrochloride with Added Salts. The reactions with added LiCl were carried out as described for the phenyl-substituted derivatives. Methylallyl chloride was identified through isolation by preparative GC. The NMR of the sample matched the NMR taken of an authentic sample.[22]

Deamination of *N*-Nitroso-*N*-(*trans*-2-phenylcyclopropyl)urea in Methanol. In a 10 mL round-bottomed flask equipped with magnetic stirrer was placed 2 mL of methanol and 0.02 g of NaHCO$_3$ (0.24 mmol). *N*-Nitroso-*N*-(*trans*-2-phenylcyclopropyl)urea[7] (0.027 g, 0.19 mmol) dissolved in 2 mL of methanol was added, and the solution was stirred for 2 h. The solution, which initially was colored yellow, turned clear during this period. The solution was poured into a separatory funnel, and 20 mL of water was added. The aqueous layer was extracted with three 10 mL portions of CH$_2$Cl$_2$ and concentrated in vacuo. Analysis of the product mixture by analytical GC (parameter set 1) and separation into its components by column chromatography (10% ethyl acetate in pentane) yielded two compounds identified as (1-methoxy-allyl) benzene (77%, t_R = 10.3 min) and cinnamyl methyl ether (23%, t_R = 14.6 min).[13]

Deamination of *N*-Nitroso-*N*-(*trans*-2-phenylcyclopropyl)urea in ²H-Methanol and ²H-Sodium Bicarbon-

ate. *N*-Nitroso-*N*-(*trans*-2-phenylcyclopropyl)urea[13] (0.04 g, 0.18 mmol) dissolved in 2 mL of ²H-methanol was added to a solution of ²H-sodium bicarbonate (1.3 molar equiv, 0.02 g, 0.24 mmol) and 2.5 equiv of sodium azide (0.03 g, 0.45 mmol) in 2 mL of ²H-methanol. The solution was stirred for 1 h during which time the solution turned from pale yellow to clear. After 1 h, 10 mL of distilled water was added, and the aqueous layer extracted with three 10 mL portions of dichloromethane. The organic extract was dried over sodium sulfate and concentrated in vacuo. The NMR spectrum of the crude product showed that *trans*-2-phenylcyclopropyl azide was the only azide formed and that the peak at 3.1 ppm (C*H*N$_3$) had decreased in intensity by 83% compared to the peak at 2.2 ppm (C*H*C$_6$H$_5$). This indicated that 83% of the compound underwent an exchange of protons with deuterium.

Deamination of *N*-Nitroso-*N*-(*trans*-2-methylcyclopropyl)urea in Methanol. In a 10 mL round-bottomed flask equipped with magnetic stirrer was placed 2 mL of methanol and 0.3 g of NaHCO$_3$ (3.6 mmol). *N*-Nitroso-*N*-(*trans*-2-methylcyclopropyl)urea[7] (0.06 g, 2.85 mmol) dissolved in 2 mL of methanol was added, and the solution was stirred for 2 h. The solution, which initially was colored yellow, turned clear during this period. The solution was poured into a separatory funnel, and 20 mL of water was added. The aqueous layer was extracted with three 10 mL portions of CH$_2$Cl$_2$ and concentrated in vacuo. Analysis of the product mixture by analytical GC (parameter set 1) and comparison of the retention times with independently synthesized[20] or authentic samples identified the compounds as 3-methoxy-but-1-ene (t_R = 2.8 min, 74.9%) and 1-methoxy-but-2-ene (t_R = 3.4 min, 25.2%).

***N*-(¹⁵N)Nitroso-*N*-(*trans*-2-methylcyclopropyl)urea.** To a cold solution (ice bath) of 1.1 g of *trans*-2-methylcyclopropylurea[7] (9.6 mmol) in 17 mL of acetic acid/acetic anhydride (7:3) was added via syringe pump ¹⁵N-sodium nitrite (1 g, 15 mmol containing 98% ¹⁵N) in 4 mL of distilled water over a period of 1 h. After the addition was completed 100 mL of ice water was added, and the solution was placed in an ice/sodium chloride bath for an additional 1 h. During this period a light yellow precipitate formed. The precipitate was collected in a Buchner funnel by vacuum filtration and washed with ice water. Drying under vacuum yielded 0.52 g (37%) of *N*-(¹⁵N)-Nitroso-*N*-(*trans*-2-methylcyclopropyl)urea as a yellow powder (mp = 91–95 °C (decomp[7])). Mass spectroscopic analysis (CI) of the product showed that it contained 92% ¹⁵N label.

Deamination of *N*-(¹⁵N)Nitroso-*N*-(*trans*-2-methylcyclopropyl)urea in Methanol with Sodium Bicarbonate. *N*-(¹⁵N)Nitroso-*N*-(*trans*-2-methylcyclopropyl)urea (0.2 g, 1.4 mmol) dissolved in 2 mL of methanol was added to a solution of sodium bicarbonate (1.3 molar equiv, 0.34 g, 4.0 mmol) and 6 equiv of sodium azide (0.52 g, 8.0 mmol) in 2 mL of methanol. The solution was stirred for 1 h during which time the solution turned from pale yellow to clear. After 1 h, 10 mL of distilled water was added, and the aqueous layer was extracted with 3 × 10 mL portions of dichloromethane. GC analysis (parameter set 2) showed the presence of crotyl methoxide (20.3%, t_R = 2.6 min), 3-methoxy-but-1-ene (5.6%, t_R = 3.0 min), *trans*-2-methylcyclopropyl azide (45%, t_R = 4.3 min), and *cis*-2-methylcyclopropyl azide (15%, t_R = 4.8 min), as well as traces of crotyl azide (6%, t_R = 5.2 min).

Detection of the ¹⁵N Content of the Deamination Products by GC/MS. The reaction solution was concentrated to 2 mL by distilling the solvent through a 20 cm steel wool-packed column. Preparative gas chromatography (column A) was used to separate the ether components of the reaction mixture from the azide-substituted products. The azide fraction was collected in a U-shaped collector tube and dissolved in 0.5 mL of dichloromethane. To determine the ¹⁵N content of the reaction products a gas chromatograph−mass spectrometer combination was used (column of analytical GC, GC parameters: T_{inj} = 150 °C, T_{det} = 70 °C, T_{col} = 30 °C, split ratio 20/1, ionization current of the MS = 15 eV). *trans*-2-Methylcyclopropyl azide contained 89% of the ¹⁵N, *cis*-2-methylcyclopropyl azide contained 76% of the ¹⁵N label, and crotyl azide contained no ¹⁵N label. When the original ¹⁵N

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content was taken into account the values are 97% [15]N for *trans-* and 82% for *cis*-2-methylcyclopropyl azide.

Deamination of *N*-(^{15}N)Nitroso-*N*-(*trans*-2-methylcyclopropyl)urea in [2]H-Methanol and [2]H-Sodium Bicarbonate. *N*-(^{15}N)Nitroso-*N*-(*trans*-2-methylcyclopropyl)urea (0.2 g, 1.4 mmol) dissolved in 2 mL of [2]H-methanol was added to a solution of [2]H-sodium bicarbonate (1.3 molar equiv, 0.34 g, 4.0 mmol) and 6 equiv of sodium azide (0.52 g, 8.0 mmol) in 2 mL of [2]H-methanol. The azide products were isolated as described above. ^{1}H NMR spectroscopic analysis showed that for the trans compound 83% of deuterium was incorporated and for the cis compound 100% deuterium exchange occurred.