dence for significant internal or segmental motion in this very important 11-cis isomer. When viewed in combination with the chemical shift data on VI, a good picture of the "dynamical" structure is provided. The rapid segmental motion indicated for the C-13a, C-14, C-15 moiety from relaxation data arises presumably from the inability of the molecule to assume the normal planar, conjugated structure. These data would warn against the use of a static conformation for the 11-*cis*-retinal at least on the nanosecond time scale important in the reorientational motion of these molecules.

We believe this use of T_1 and chemical shift data to elicidate both structural and dynamical features of a moderate sized molecule emphasizes the importance of utilizing both techniques in concert. The two types of data have been shown here to provide complimentary information useful in molecular studies of both structure and motion.

Acknowledgment. This work was supported by the National Institutes of Health under Grants RR-574-03, GM 08521, and RO1-EY-00875. The computer program used in interpreting T_1 values in molecules undergoing anisotropic diffusion was developed for another purpose in conjunction with Professor J. D. Roberts at California Institute of Technology, and we appreciate his encouragement of this work. He is supported by the National Institutes of Health (GM 11072) and National Science Foundation. The Sherman Fairchild Distinguished Scholars Program at California Institute of Technology provided computer funds and partial support for one of us (D. M. G.) during 1973–1974. SB is a Deutsche Forschungsgemeinschaft Postdoctoral Fellow, 1973–1974. We also wish to thank Hoffmann-La Roche Chemical Co. for the generous gift of 11-*cis*-retinal and Mr. James C. Smith for assistance in acquiring data.

Cope Elimination and Meisenheimer Rearrangement with *N*,*N*-Dimethyl-3-aminohomoadamantane *N*-Oxide. Evidence for 3-Homoadamantene[1]

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Abstract: Decomposition of *N*,*N*-dimethyl-3-aminohomoadamantane *N*-oxide yielded dimers of bridgehead homoadamantene (9%), 4-homoadamantene (5%), *N*,*N*-dimethyl-*O*-(3-homoadamantyl)hydroxylamine (25%), homoadamantane (29%), 3-hydroxyhomoadamantane (2%), and *N*,*N*-dimethyl-3-aminohomoadamantane (12%). Elimination appears to take place with predominant formation of 3-homoadamantene. Trapping of the strained alkene was successfully carried out by Diels–Alder cycloaddition with 1,3-diphenylisobenzofuran. The Meisenheimer product was formed by the unusual migration of a tertiary group, 3-homoadamantyl, during reaction. Thermolysis of the amine oxide in the presence of furan gave a mixture containing 2-(3-homoadamantyl)furan.

The topic of the limits of Bredt's rule is of considerable current interest.[4–8] A variety of methods has been applied to generate these bridgehead alkenes, such as Hofmann elimination,[4] Corey–Winter[5] synthesis, bisdehalogenation of vicinal diiodides,[6] and type II photoelimination.[7] Although Cope elimination[9] of tertiary amine oxides is a well-known route to alkenes, this procedure has not been previously used for preparation of highly strained bridgehead double bonds. The present work reports the generation, as well as subsequent trapping, of 3-homoadamantene from pyrolysis of *N*,*N*-dimethyl-3-aminohomoadamantane *N*-oxide (**1**).

In addition to elimination, the unusual migration of a tertiary group, 3-homoadamantyl, by Meisenheimer rearrangement was observed. Meisenheimer rearrangement[9] generally occurs with a migrating entity capable of stabilizing a negative charge or radical. Very little has been reported[10] for purely alkyl systems.

Results and Discussion

Decomposition of *N*,*N*-dimethyl-3-aminohomoadamantane *N*-oxide[11] (**1**) at 140–175° (1 mm) provided a hydrocarbon mixture (**2**; 9%) composed of dimers of 3-homoadamantene, 4-homoadamantene[12] (**3**; 5%), *N*,-

(1) Paper X, Adamantanes and Related Compounds; preliminary communication, B. L. Adams and P. Kovacic, *J. Amer. Chem. Soc.*, **95**, 8206 (1973).

(2) Graduate School Fellow, 1973–1974.

(3) Taken in part from the Ph.D. thesis of B. L. Adams, 1974.

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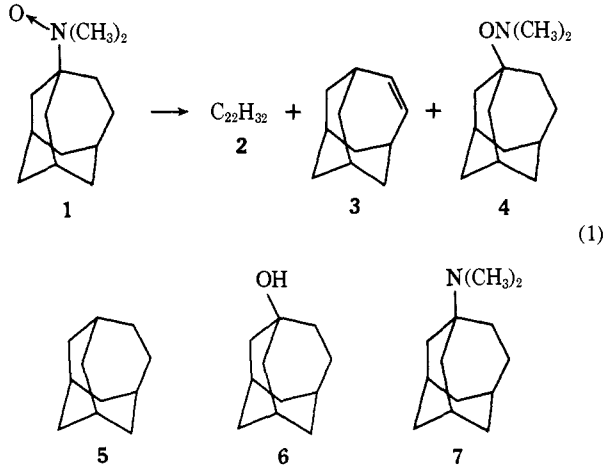
N-dimethyl-*O*-(3-homoadamantyl)hydroxylamine (**4**; 25%), homoadamantane[12] (**5**; 29%), 3-hydroxyhomoadamantane[13] (**6**; 2%), *N,N*-dimethyl-3-aminohomoadamantane[11] (**7**; 12%), and several unidentified, minor products (eq 1).



(1)

During reaction, products **3**–**7** distilled at 140–150° (1 mm) into the receiver cooled in Dry Ice–acetone. The dimers (**2**), however, sublimed only to the cooler portions of the pyrolysis flask, and were thus effectively separated from the other products. Gas chromatography indicated four components, a (29%), b (8%), c (3%), and d (60%), which were identified, in part, as dimers of homoadamantene by mass spectral molecular ions of *m/e* 296. Dimers a and d were further characterized by ir, nmr, and laser Raman spectral data, elemental analysis, and comparison to dimers from Hofmann elimination[1] and from rearrangement of 1-adamantylcarbene.[14]

Prior to our usage,[1] there were no literature reports[14,15] involving laser Raman spectroscopy in the identification of dimers of bridgehead alkenes, although it is an extremely valuable technique. A number of investigations with simple substituted cyclobutanes[16] and a few more complicated[17] types have been carried out. From the previous studies, as well as comparison to laser Raman spectra of homoadamantane, adamantane, and adamantene dimer,[18] we have tentatively assigned the bands 735, 935, and 980 cm^{-1} in **2a**, 731, 940, and 970 cm^{-1} in **2b**, and 752, 943, and 970 cm^{-1} in adamantene dimer as ring deformations of the cyclobutane structure (Table I). The Raman lines at low frequencies (**2a**, 221 cm^{-1}; **2d**, 236 cm^{-1}; adamantene dimer, 266 cm^{-1}) are of particular diagnostic value. Similar bands were observed[16] for substituted cyclobutanes (165 cm^{-1}, chlorocyclobutane; 150 cm^{-1}, bromocyclobutane; 144 cm^{-1}, diketene; 204 cm^{-1}, β-propiolactone) and are attributed to ring puckering. Few other vibrations occur in this region, the most notable being from carbon–halogen and the lattice. The shift to higher frequency ($\sim$70 cm^{-1}) might be expected owing to the increased rigidity imposed upon the cyclobutane ring by the polycyclic structure of **2**. To establish that the low frequency band is not simply due to lattice vibrations within the crystals, spectra of **2a** and **2d** were obtained in cyclohexane solution. Since these bands remained at approximately the same intensity compared with the rest of the spectrum, they must be of molecular origin.

Table I. Laser Raman Data[a,b]

2a	2d	Adamantene dimer	5	Adamantane
221	236	222	353	400
251	256	257 (s)	396	443
295	473	266	699	758
407	612	288	790	952
467	656	428	956	971
538	679	516	986	1099
652	721 (s)	567	1056	1221
694	731	702	1118	1316
714	809	752	1158	1440
735	940	772	1198	
807	952	943	1257	
902	970	970	1442	
935	982	999		
952	1050	1013		
980	1063	1059		
1040	1083	1159		
1050	1122	1208		
1096	1138	1237		
1116	1194	1263		
1138	1202	1444		
1203	1270			
1204	1280			
1274	1368			
1442	1448			
1494	1480			

[a] 100 to 1500 cm^{-1} scan. [b] Principal bands.

Amine oxide **1** can decompose to give theoretically two olefins, **8** and **9**, which could then dimerize to 16 possible geometric isomers. Since only four dimers were observed by glpc analysis and since three of these, a, b, and d, correspond to compounds isolated from rearrangement of 1-adamantylcarbene,[14] which can give only **8**, we conclude that elimination proceeds predominantly to give 3-homoadamantene. An alternative possibility is that **9**, if formed, rearranges rapidly to **8** *via* 1,3-hydride shift.[19]

8 **9**

We are unable to assign definite structures to the individual dimers on the basis of the available spectral data. However, a comparison[3] of laser Raman *vs.* ir spectra for each of the compounds, **2a** and **2d**, indicates several coincidental bands, six[20] and seven,[20] respectively. It has been suggested[17] that compounds with a high degree of symmetry possess fewer coincident bands than their less symmetrical isomers. The similar number of these bands indicates that **2a** and **2d** have a like degree of symmetry, thus disfavoring the highly symmetrical structure, **2** head-to-tail trans. Empirical

(13) H. Stetter and P. Goebel *Chem. Ber.*, **96**, 550 (1963).
(14) M. Farcasiu, D. Farcasiu, R. T. Conlin, M. Jones, Jr., and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **95**, 8207 (1973).
(15) Simultaneous disclosure was made in ref 14.
(16) J. R. Durig, W. H. Green, and N. C. Hammond, *J. Phys. Chem.*, **70**, 1989 (1966).
(17) D. N. Harpp and C. Heitner, *J. Org. Chem.*, **35**, 3256 (1970).
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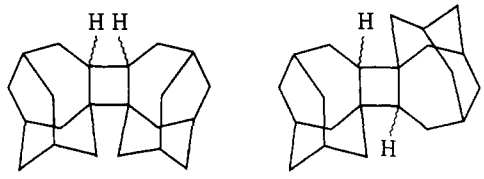
(19) H. Gerlach, T. T. Huong, and W. Müller, *J. Chem. Soc., Chem. Commun.*, 1215 (1972).
(20) A band within 10 cm^{-1} was considered coincidental.[17]

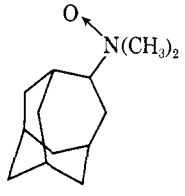
force field calculations[21,22] by Schleyer and coworkers indicate that **2** head-to-head trans has the lowest strain energy. While the dimerization is not necessarily thermodynamically controlled, these two lines of evidence lead to speculative assignment of the head-to-head trans structure to **2d**, and the head-to-tail cis configuration to **2a**.



2 head-to-head (cis or trans) from **8**

2 head-to-tail (cis or trans) from **8**

There are several plausible routes for formation of olefin **3**. It may be derived from the bridgehead alkene **8** by base-catalyzed isomerization or 1,3-hydride shift.[19] Another possibility entails reversal of Cope elimination.[23] 1,3 addition of *N,N*-dimethylhydroxylamine to **8** provides amine oxide **10** which then decomposes to



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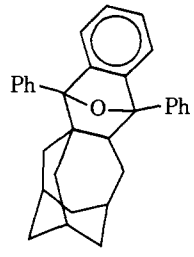
3. This type of reaction has been established with an open-chain system,[23] *e.g.*, treatment of 1-dodecene with *N,N*-dimethylhydroxylamine gave products derived from decomposition of *N,N*-dimethyl-2-aminododecane *N*-oxide. Further evidence that reverse Cope elimination is occurring in decomposition of **1** is provided by the tenfold increase in yield of **3** compared to the results from Hofmann elimination.[1] If only base catalyzed isomerization and 1,3-hydride shift were involved, similar yields of **3** would be expected in both cases.

Alcohol **6** is presumably formed[25] by reaction involving water of hydration present in **1**. The bridgehead olefin **8** would be expected to add water readily since other highly strained alkenes have been found[4a,c,7,8a] to undergo facile addition of weak Brønsted acids. An alternative possibility comprises solvolysis of **1**. Pyrolysis of the amine oxide in the presence of added water gives rise to no detectable amount of product. Apparently, solvolysis does not take place to any appreciable extent under these conditions. In addition, solvation of the amine oxide apparently prevents elimination or rearrangement from occurring readily.

Laughlin[23] has recently shown that the tertiary amine oxide can oxidize *N,N*-dimethylhydroxylamine during pyrolysis, which nicely rationalizes the previously unexplained formation of the parent tertiary amine, *e.g.*, **7**. A reasonable mechanistic scheme was advanced.

The reactivity of 3-homoadamantene (**8**) is in accord, as applied to the tricyclic area, with Wiseman's modification[4a] of Bredt's rule: the strain of a bridgehead double bond is closely approximated by that of the corresponding *trans*-cycloalkene. Olefin **8** has unsaturation trans in a seven-membered ring. Since *trans*-cycloheptene[24] and bridged *trans*-cycloheptenes in the bicyclic series[4c,5] have not been isolable at room temperature, it follows that **8** should also be labile under our reaction conditions. This is borne out by the observed dimerization and isomerization.

In order to obtain further evidence for the existence of 3-homoadamantene, trapping experiments were undertaken with 1,3-diphenylisobenzofuran (DPIBF) and furan. DPIBF has been used successfully to capture transient olefins in other systems,[4c,5,8b,24] including 3-homoadamantene from Hofmann elimination.[25] Decomposition of **1** at 145° (15 mm) in the presence of DPIBF gave a residue which, after purification by column chromatography and preparative thin layer chromatography, was identified as the Diels–Alder adduct **11**. The structural assignment was based on ir,



11

nmr, and mass spectral data, elemental analysis, and comparison to the corresponding product obtained from Hofmann elimination.[25] The absence of significant amounts of the isomeric adduct further supports the thesis that **8** is the predominant elimination product from **1**.

In another trapping experiment, amine oxide **1** was decomposed in a sealed tube in the presence of furan. Glpc analysis revealed formation of **4** (9%), **5** (23%), **6** (3%), **7** (18%), and 2-(3-homoadamantyl)furan (**12**; 30%). There was no evidence for dimers **2** and 4-homoadamantene. Compound **12** was identified by ir, nmr, and mass spectral data, as well as by elemental analysis. Formation of **12** represents an unusual aromatic substitution reaction. There are several possible mechanistic pathways which are consistent with the data. Compound **12** might be derived from intermediate **8** *via* Diels–Alder cycloaddition with furan to produce adduct **13**. Abstraction of an allylic proton, cleavage to regenerate the furan system, and then reprotonation gives rise to **12** (eq 2). An alternate possibility involves the bridgehead cation as precursor, formed by protonation of **8** (eq 3). In a third route, **12** may be formed by radical substitution (eq 4).

The Meisenheimer rearrangement product (**4**) was identified by ir and nmr evidence, elemental analysis, and chemical behavior. Treatment of the basic product with HI gave two neutral materials accompanied by disappearance of **4**. The major component was identified as 1-iodomethyladamantane (**14**) on the basis of ir, nmr, and mass spectral data. Also, comparison was made with authentic material synthesized by treatment of either 1-hydroxymethyladamantane or 3-hydroxy-

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(22) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **95**, 8005 (1973).
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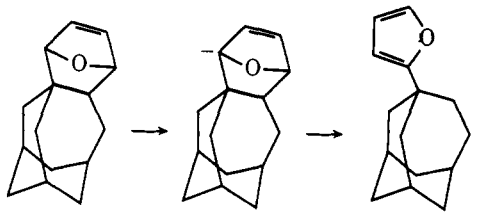

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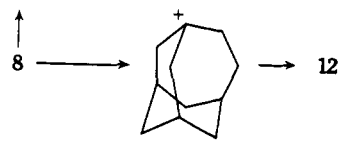

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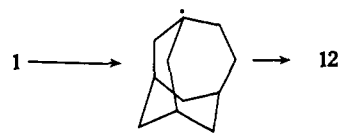
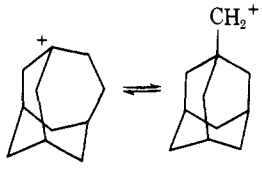


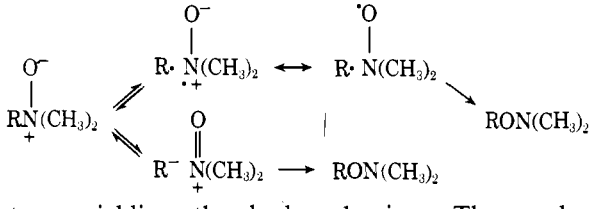
(4)

homoadamantane with HI, in yields of 57 and 78%, respectively. Interconversion of the 3-homoadamantyl cation and adamantylcarbinyl cation is well established,[26] eq 5.



(5)

The mechanism of the Meisenheimer rearrangement is considered to involve the initial homolytic cleavage of a carbon–nitrogen bond to give a radical pair[27–29] (eq 6). The alkyl radical can then recombine at the oxygen



(6)

(7)

atom, yielding the hydroxylamine. The analogous ionic mechanism,[28] eq 7, which entails formation of the carbanion intermediate, has fallen into disfavor on the basis of recent findings.[29]

The formation of homoadamantane (6) is analogous to the generation of neopentane[10a] in the Meisenheimer rearrangement of *N,N*-dimethylaminoneopentane *N*-oxide. Hydrocarbon has been postulated to derive from separation of the caged radical pair followed by hydrogen abstraction. Brauman and Sanderson[10a] noted a constant ratio of rearranged product to neopentane under varying conditions, leading them to the conclusion that these products were arising from competing reactions within the caged radical pair.

A comparison of the Cope and Hofmann[1,25] eliminations for generation of **8** indicates a number of similarities. The yield of products from elimination is almost identical for the two cases, rearrangement takes place as a competing process, and homoadamantane, 4-homoadamantene, and parent amine are also generated.

Experimental Section

Ir spectra were obtained with a Perkin-Elmer 137 spectrophotometer (calibrated with the 1601.8 cm^{-1} band of polystyrene). Varian T-60 and HA-100 instruments were used to obtain nmr data which are reported in ppm (δ) (in CCl_4) relative to tetramethylsilane as internal standard. Laser Raman spectra were obtained from a Ramex Spex 1401 spectrophotometer, measured from the green excitation line (19,436 cm^{-1}). Microanalyses were performed by Baron Consulting Company, Orange, Conn., and Dr. R. E. White. Some of the mass spectral data were provided by Dr. Michael Kurz. Glpc analyses were conducted on Varian Aerograph 1800, 1700, and 90P instruments with the indicated columns: (I) 3% SE-30 on Chromosorb P (30–60 mesh) 5 ft × 0.25 in., copper; (II) 15% Carbowax 20M and 5% NaOH on Chromosorb P (30–60 mesh) 10 ft × 0.25 in., copper; (III) 15% Carbowax 20M on Chromosorb W (45–60 mesh), 6 ft × 0.25 in., copper; (IV) 5% Carbowax 20M on Chromosorb W (45–60 mesh), 5 ft × 0.25 in., copper. Melting points (uncorrected) were obtained with a Thomas-Hoover capillary melting point apparatus.

***N,N*-Dimethyl-3-aminohomoadamantane *N*-Oxide[11] (1).** The amine oxide **1** was prepared from the tertiary amine **7** and H_2O_2 in methanol, as previously described.[11] Evaporation of solvent under vacuum at 40° gave a white solid which contained 1.5–2 molecules of water of hydration according to nmr and elemental analysis.

Pyrolysis of 1. Amine oxide **1** (1.4 g, 68 mmol)[30] was placed in a 15-ml, round-bottomed flask connected through a short-path distillation head to a 10-ml receiver cooled in an acetone–Dry Ice bath. The pyrolysis flask under vacuum (1 mm) was immersed in an oil bath preheated to 140°. Heating was continued to 180° during 1.5 hr. The distillate (0.90 g) was a homogeneous liquid and was analyzed by glpc on columns II and III. The following products were found: 4-homoadamantene[12] (**3**; 5%), *N,N*-dimethyl-*O*-(3-homoadamantyl)hydroxylamine (**4**; 25%), homoadamantane[12] (**5**; 29%), 3-hydroxyhomoadamantane[13] (**6**; 2%), *N,N*-dimethyl-3-aminohomoadamantane[11] (**7**; 12%), and several minor products. Spectral data for product **4** are: ir (neat) 2860, 1465, 1445, 1075, 1020, 883 cm^{-1}; nmr δ 2.3 (s, 6 H), 1.4–2.1 (m, 17 H); mass spectrum, parent ion, *m/e* 209.

Anal. Calcd for $C_{15}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.88; H, 11.22; N, 6.79.

A white solid (95 mg; 9%) which sublimed to the neck of the pyrolysis flask, was identified as a mixture of dimers of bridgehead homoadamantene. Glpc analysis on column IV indicated four components, **2a** (28%), **2b** (7%), **2c** (3%), and **2d** (62%). These products were identical with those from Hofmann elimination[1,25] on the basis of glpc coinjection. In addition, **2a** and **2d** showed identical ir, nmr, and laser Raman spectral data in comparison with the corresponding components from Hofmann elimination, for which satisfactory elemental analyses and mass spectra were obtained.

Pyrolysis of 1 with 1,3-Diphenylisobenzofuran (DPIBF). The amine oxide **1** (2.0 g, 8.5 mmol) and DPIBF (1.9 g, 7 mmol) were placed in a 25-ml, round-bottomed flask connected through a short-path distillation head to a 10-ml receiver cooled in an acetone–Dry Ice bath. Vacuum (15 mm) was applied and the flask was immersed in an oil bath at 140° for 1.5 hr. The vacuum was then adjusted to 0.2 mm in order to remove volatile products present in the reaction mixture. After the apparatus had cooled, the residue in the pyrolysis flask was taken up in 100 ml of benzene. Maleic anhydride was introduced to decompose excess DPIBF. After 50% NaOH in an equal volume of methanol was added to the benzene, the mixture was refluxed for 30 min. The organic layer was separated, washed with water, dried, and evaporated to approximately 3 ml. Column chromatography on alumina (10 cm, elution with benzene) yielded 0.95 g of slightly impure adduct. Preparative scale thin layer chromatography on silica gel (1 mm, elution with benzene) gave 0.57 g (14%) of the pure adduct after filtration and washing with ether; mp 188–190° (sublimation at 120° (0.2 mm) gave material melting at 188–189.5°); ir (KBr) 3000, 2895, 1595,

(26) J. E. Nordlander, S. P. Jindal, P. v. R. Schleyer, R. C. Fort, Jr., J. J. Harper, and R. D. Nicholas, *J. Amer. Chem. Soc.*, **88**, 4475 (1966).

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(29) (a) A. R. Lepley, P. M. Cook, and G. F. Willard, *J. Amer. Chem. Soc.*, **92**, 1101 (1970); (b) G. Ostermann and U. Schöllkopf, *Justus Liebigs Ann. Chem.*, **737**, 170 (1970).

(30) Calculated from nmr and elemental analysis data for the hydrated sample.

1490, 1445, 995, 785, 748, 701 cm^{-1}; nmr δ 6.95–7.80 (m, 14 H), 1.0–2.8 (m, 16 H); mass spectrum, molecular ion, *m/e* 418.[31]

Anal. Calcd for $C_{31}H_{30}O$: C, 88.95; H, 7.22. Found: C, 89.19; H, 7.18.

Pyrolysis of 1 with Furan. The amine oxide (0.30 g, 1.3 mmol) and furan (0.70 g, 10 mmol) were sealed in a glass tube and immersed in an oil bath preheated to 140°. The reaction mixture was kept at this temperature for 1 hr, and then was allowed to cool. The tube was broken and the resultant brown solution was analyzed by glpc on columns II and IV. Results indicate formation of homoadamantane (**5**; 23%), *N,N*-dimethyl-*O*-(3-homoadamantyl)hydroxylamine (**4**; 9%), 3-hydroxyhomoadamantane (**6**; 3%), 2-(3-homoadamantyl)furan (**12**; 30%), *N,N*-dimethyl-3-aminohomoadamantane (7; 18%), and a minor amount of unidentified material (~8%). No dimers (**2**) or 4-homoadamantene (**3**) were detected.

Spectral data for compound **12** include: ir[32] (neat) 2900, 1580, 1505, 1450, 1150, 1020, 904, 887, 790, 726 cm^{-1}; nmr[32] δ 7.2 (broad s, 1 H), 6.1 (m, 1 H), 5.8 (m, 1 H), 1.5–2.2 (m, 17 H); mass spectrum, molecular ion, *m/e* 218.

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 82.98; H, 9.04.

HI Cleavage of 4. A mixture of the basic material from Cope elimination [0.50 g containing **4** (0.12 g, 0.57 mol)] and constant boiling HI (10 ml) was refluxed for 8 hr. The solution was poured over ice and extracted with ether. After the ether solution was washed in succession with 0.1 *N* $Na_2S_2O_3$, 5% $NaHCO_3$, and water, the dried solution was evaporated, leaving 80 mg of neutral material. Analysis on column II indicated a mixture of iodomethyladamantane (75%), identified by comparison of ir and nmr spectra and glpc retention time to authentic material, and a product (25%) which has an ir spectrum consistent with the 3-iodohomoadamantane structure.

1-Iodomethyladamantane (14). 3-Hydroxyhomoadamantane (**6**), or the isomeric 1-hydroxymethyladamantane (1.0 g, 6.0 mmol) was heated at reflux in constant boiling HI (15 ml) for 1 hr. The reaction mixture was poured over ice and extracted with ether. The ether solution was washed in succession with 0.1 *N* $Na_2S_2O_5$, 5% $NaHCO_3$, and water. Evaporation of the dried solution gave 1.3 g (78%) of the iodide, mp 51–53°. Recrystallization from ethanol gave white plates, mp 52–53°; ir (CCl_4) 2800, 1435, 1335, 1190, 1095, 970, 915 cm^{-1}; nmr δ 3.0 (s, 2 H), 1.5–2.4 (m, 15 H); mass spectrum, molecular ion, *m/e* 276.

Anal. Calcd for $C_{11}H_{17}I$: C, 47.84; H, 6.20. Found: C, 47.53; H, 5.80.

(31) The aromatic region of the nmr spectrum was essentially identical with that of DPIBF adducts of bicyclo[3.2.2]non-1-ene and bicyclo[3.2.1]oct-1-ene; J. A. Chong Ph.D. Thesis, University of Michigan, 1971.

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Acknowledgment. We wish to thank the National Science Foundation and the Graduate School, University of Wisconsin—Milwaukee, for financial support, Professor Michael Kurz for some of the mass spectral data, Dr. R. E. White for some of the elemental analyses, and Professor P. v. R. Schleyer for providing data prior to publication.

The Mechanism of the Aminolysis of Acetate Esters[1]

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Received March 14, 1974

Abstract: The reactions of hydrazine with ethyl acetate, methoxyethyl acetate, and probably 2-chloroethyl acetate exhibit a change in rate-determining step with decreasing pH similar to that with methyl formate; no such change is observed with trifluoroethyl or phenyl acetates. Structure–reactivity correlations suggest identical transition state structures and rate-determining steps for the general base-catalyzed reactions of alkyl and phenyl esters, but for the uncatalyzed reactions there is a leveling of the rate with changing leaving group for the alkyl esters that requires a different mechanism from that of the phenyl esters. This change in mechanism and a requirement for proton transfer in the reactions of primary and secondary amines are also evident in the slow reactions of tertiary amines with alkyl esters. Bifunctional cyclic mechanisms are excluded by the effectiveness of tertiary amines as general base catalysts for hydrazinolysis. A mechanism of aminolysis is proposed that is consistent with these and other data. With most esters, the attack of amine to form the labile intermediate $T^{\pm}$ is rapid and reversible, and the rate-determining step at high pH is the trapping of this intermediate by proton removal with a general base, a proton switch through water (alkyl esters), or the direct breakdown of $T^{\pm}$ to products (phenyl esters). For very fast reactions, there is a change to rate-determining formation of $T^{\pm}$ accompanied by a sharp decrease in sensitivity to substituent effects. The application of these considerations to the mechanism of chymotrypsin catalysis is described.

The aminolysis of alkyl esters in aqueous solution proceeds through a tetrahedral addition intermediate, as shown by the existence of a change in rate-determining step with changing pH.[2,3] The assignment of the rate-determining step in the different pH regions has been made by determining the preferred direction of breakdown of the tetrahedral intermediate formed in the hydrolysis of the corresponding imidate as a function of pH.[3,4] For the aminolysis of methyl formate, it was shown that the formation of an anionic addition compound, T^-, is rate determining at high pH, and

(1) Supported by grants from the National Science Foundation (GB 5648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD 01247). A. S. was a Predoctoral Fellow of the National Institutes of Health (GM 212).

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