Amination of Acyclic and Cyclic Alkanes with Trichloramine–Aluminum Chloride[1,2]

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Abstract: Direct amination of several acyclic and alicyclic alkanes was effected with trichloramine–aluminum chloride. In general, rearrangement and degradation of the hydrocarbon substrate occurred. Isobutane and isooctane provided good yields of *tert*-butylamine. Isopentane, 3-methylpentane, and 2,3-dimethylbutane yielded mainly *tert*-butylamine and *tert*-pentylamine, in addition to many other basic products. Neopentane reacted sluggishly. In the alicyclic series, dicyclohexyl provided low yields of basic material. Norcarane gave 1-amino-1-methylcyclohexane in low yield. The initial step in the mechanism is believed to involve hydride abstraction from substrate by positive halogen, except for norcarane. Subsequent carbenium ion rearrangements and degradations lead to the observed products. The evidence indicates that steric factors play an important role.

Previous reports[6] have shown that the trichloramine–aluminum chloride combination can effect direct amination of various classes of organic compounds, including aromatics,[7-11] cycloalkanes,[12] alkyl halides,[13,14] and alkenes.[6] The cycloalkanes which were investigated included mono- (methylcyclohexane),[12,15] bi- (norbornane),[14,15] and tricyclic (adamantane)[16] types. All of the acyclic alkanes previously examined contained a phenyl substituent. Usually a tertiary benzylic hydrogen was involved in the substitution.[17-19] For example, 8-amino-*p*-cymene was obtained in 80% yield from *p*-cymene with *tert*-butyl bromide as promoter.[18]

The objective of the present work was to investigate simple, acyclic, purely alkane substrates with trichloramine–aluminum chloride in order to determine the scope of the amination reaction and to shed further light on the mechanism. Several additional cycloalkanes were also examined.

Results and Discussion

The reactions with trichloramine–aluminum chloride were generally carried out at −20 to +20 °C with a hydrocarbon:aluminum chloride:trichloramine molar ratio of 0.3:0.2:0.1. Yields are based on an equimolar relationship between the basic product and trichloramine.

Acyclic Alkanes. Isobutane. When this hydrocarbon was aminated at −5 to 0 °C under standard conditions, an 82–83% yield of *tert*-butylamine was obtained. Hydrogen chloride was evolved throughout the course of reaction. The product proved identical in all respects with known material. About 18 higher boiling components were also formed.

Isooctane. When isooctane was used as the substrate, product analysis pointed to a 74% yield of *tert*-butylamine, in addition to small amounts of *tert*-pentylamine and *tert*-octylamine. Gas chromatography of higher boiling fractions indicated many other basic materials (18–20).

Neopentane. Exposure to the aminating system resulted in a low yield of basic material. In contrast to the situation for tertiary alkanes, the reaction mixture was light yellow in color instead of the dark brown commonly observed. Gas chromatography of the crude basic products revealed the presence of *tert*-butylamine, *tert*-pentylamine, and many other components (13).

Isopentane. Amination of isopentane was carried out with trichloramine–aluminum chloride at −5 to 0 °C. The major products were *tert*-butylamine and *tert*-pentylamine in yields of 53 and 39%, respectively. The latter amine was identified by comparison with authentic material and from derivative melting points.

3-Methylpentane. When the hydrocarbon was subjected to trichloramine–aluminum chloride at 10 ± 3 °C, the basic product consisted of *tert*-butylamine (61% yield), *tert*-pentylamine (16% yield), and 2-amino-2-methylpentane (13% yield) which was identified from physical data and derivatives. Higher boiling amines were also produced. 3-Amino-3-methylpentane, the product expected from nonrearrangement, was not present in any significant quantity.

2,3-Dimethylbutane. Amination at −5 to 0 °C provided *tert*-butylamine and *tert*-pentylamine in 73 and 7–10% yields, respectively. In addition to higher molecular weight materials (4–5), a third major fraction is believed to be a mixture (inseparable under our GLC conditions) of 2-amino-2-methylpentane and 2-amino-2,3-dimethylbutane. The NMR spectrum of fraction three showed several methyl absorptions. When 2,3-dimethylbutane was employed[20] as a substrate in the Ritter reaction, *tert*-butylamine and 2-amino-2,3-dimethylbutane were formed as major products.

Cycloalkanes. Dicyclohexyl. In contrast to previous results with other cycloalkanes,[15] this compound provided extremely low yields of basic material consisting of at least three components which displayed similar retention times in GLC. Since the yield of basic products was so meager, the neutral organic fraction was investigated. Only about one-fourth of the material was distillable, the remainder being an intractable viscous sludge which appeared to undergo decomposition during distillation. The distillate consisted of two main components from GLC analysis. The absence of unchanged starting material and *n*-dodecane was shown by comparison with authentic samples. The infrared and NMR spectra, which contained no striking features, indicate a mixture of hydrocarbons of rearranged structure.

Norcarane. Norcarane afforded a low yield of identifiable, amine product. Only a small amount of the crude basic material proved amenable to distillation, the bulk being in the form of intractable tar. The sole substance isolated was 1-amino-1-methylcyclohexane, identified by comparison with known material and derivative formation. Of the alkanes studied, only this one evolved little or no acid gas during the course of reaction.

Mechanistic Considerations. The results are nicely rationalized on the basis of carbenium ions[21] as intermediates. The initial step in the amination reaction can be envisioned as hydride abstraction from the hydrocarbon, conceivably by positive halogen, eq 1 and 2 (the Cl^+ designation is used for simplicity).

$$AlCl_3 + NCl_3 \rightleftarrows Cl^{\delta+}(Cl_2NAlCl_3)^{\delta-} \quad (1)$$

$$RH + Cl^+ \rightarrow R^+ + HCl \quad (2)$$

Olah[22,23] and co-workers proposed similar behavior in the

Lewis acid catalyzed chlorination and bromination of alkanes and cycloalkanes. Alternatively, initiation may be effected by interaction of Cl^+ or H^+ (derived from HCl or H_2O) with olefin present in trace amounts in the starting hydrocarbon or generated during reaction. Involvement of methylene chloride[24] appears unlikely.[15]

Generation of carbenium ions from alkanes has been effected in a variety of ways by prior workers. For example, alkanes, such as adamantane, have functioned as substrates in the Koch[25] carboxylation and Ritter[26] reactions. Cationic species have been generated from alkanes in the presence of strong sulfuric acid. In this case, gross rearrangement usually does not occur.[27] Aromatics are reported to undergo alkylation[28] with alkanes in the presence of Lewis acid catalysts. Alkanes may be acylated with acyl halides and a Friedel-Crafts catalyst,[29a] if traces of initiators, such as olefins, are present. Carbenium ions have also been obtained from alkanes[30,31] by protonation with "super acid" (FSO_3H–SbF_5), primarily through the efforts of Olah and co-workers. For instance, exposure of methane to excess "super acid" below 80 °C produced *tert*-butyl, *tert*-hexyl, *tert*-heptyl, and higher homologous tertiary cations.[32] Hydrogen gas was liberated. Ethane, neopentane, and 2,2,3,3-tetramethylbutane also formed carbenium ions under the strong acid conditions,[32] as did neopentane upon exposure to hydrogen fluoride–antimony pentafluoride.[33] Carbenium ions have recently been generated from alkanes and acylium salts in acidic media.[34]

The mechanistic problem for isobutane can be resolved in a straightforward manner (eq 3).

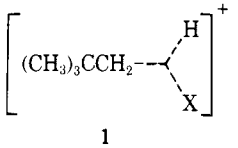
$$(CH_3)_3CH \xrightarrow[-HCl]{Cl^+} (CH_3)_3C^+ \xrightarrow{NCl_2^-} (CH_3)_3CNCl_2 \xrightarrow[-Cl^+]{+H^+} \textit{tert}\text{-}BuNH_2 \quad (3)$$

The *tert*-butyl cation so generated can combine with a nitrogen-containing nucleophile, followed by hydrolysis to the amine during workup. Isolation of *N,N*-dichloro-*tert*-butylamine from the amination of *tert*-butyl chloride[13] and of 1-*N,N*-dichloroaminoadamantane from amination of adamantane[16] was taken as evidence for participation by dichloroamide ion (or NCl_3). A reasonable route to the higher molecular weight products observed from isobutane, via *tert*-octyl cation, is set forth in the following equation:

$$(CH_3)_3C^+ \xrightarrow{-H^+} CH_2{=}C(CH_3)_2 \xrightleftharpoons{(CH_3)_3C^+} (CH_3)_3CCH_2C^+(CH_3)_2 \quad (4)$$

The data from isooctane are rationalized on the basis of the well-established, facile β-scission of the *tert*-octyl cation (eq 4). Trapping of the C_8 ion by a nitrogenous nucleophile accounts for the corresponding amine.

A plausible pathway for formation of *tert*-pentylamine from neopentane entails hydride abstraction, 1,2 shift, and then interaction with the nitrogen-containing nucleophile. The low yield is understandable in view of the lesser reactivity of primary vs. tertiary bonds[30,31,35,36] toward hydride abstraction. The formation of *tert*-butylamine may occur via **1** which has



X = H or Cl

1

literature[32] analogy for X = H. Since 1-amino-1-methylcyclohexane was obtained as the sole basic product from methylcyclohexane,[12] the reagent (NCl_3–$AlCl_3$) exhibits high selectivity. The preference for tertiary sites has also been observed with other hydrocarbons.[15,16]

Scheme I

$$(CH_3)_2\overset{+}{C}CH_2CH_3 \xrightleftharpoons{-H^+} (CH_3)_2C{=}CHCH_3$$
2 **3**

$$\mathbf{2} + \mathbf{3} \rightleftharpoons (CH_3)_2\overset{+}{C}CH(CH_3)C(CH_3)_2CH_2CH_3$$

$$\xrightleftharpoons{CH_3^-} (CH_3)_3C\overset{+}{C}HC(CH_3)_2CH_2CH_3$$

$$\xrightleftharpoons{CH_3^-} (CH_3)_3CCH(CH_3)\overset{+}{C}(CH_3)CH_2CH_3$$

$$\xrightleftharpoons{\beta \text{ scission}} (CH_3)_3C^+ + CH_3CH{=}C(CH_3)CH_2CH_3$$

The mechanistic aspects for isopentane are complicated since rearrangement and degradation are more profound. Scheme I sets forth a reasonable route[37–39] for formation of *tert*-butyl cation from isopentane. Supportive evidence for rearrangement of tertiary to secondary cations is provided by NMR spectroscopy in the case of the *tert*-pentyl cation.[31]

Analogously, amination of 3-methylpentane also proceeds with rearrangement and degradation. Formation of the six-carbon amine **9** can be envisioned as illustrated in Scheme II.

Scheme II

$$(CH_3CH_2)_2CHCH_3 \xrightarrow[-HCl]{Cl^+} (CH_3CH_2)_2\overset{+}{C}CH_3$$
4

$$\xrightleftharpoons{-H^+} CH_3CH_2C(CH_3){=}CHCH_3$$
5

$$\mathbf{4} \xrightleftharpoons{H^-} CH_3CH_2CH(CH_3)\overset{+}{C}HCH_3 \xrightleftharpoons{CH_3^-} CH_3CH_2\overset{+}{C}HCH(CH_3)_2$$
6 **7**

$$\mathbf{7} \xrightleftharpoons{H^-} CH_3(CH_2)_2\overset{+}{C}(CH_3)_2 \xrightarrow[2.\ H^+]{1.\ NCl_2^-} CH_3(CH_2)_2\overset{NH_2}{\overset{|}{C}}(CH_3)_2$$
8 **9**

The requisite alkenes for generation of *tert*-butyl and *tert*-pentyl cations may arise as shown in the following equations:

$$\mathbf{4} \text{ or } \mathbf{6} \xrightleftharpoons{-H^+} \mathbf{5} \quad (5)$$

$$\mathbf{7} \text{ or } \mathbf{8} \xrightleftharpoons{-H^+} \underset{\mathbf{10}}{CH_3CH_2CH{=}C(CH_3)_2} \quad (6)$$

At least four subsequent schemes[2] can be visualized. Either **5** or **10** can interact with cations **4** or **8**, and each possibility[2] leads to the *tert*-pentyl cation which can form *tert*-pentylamine, or be further degraded to *tert*-butyl cation according to Scheme I. Since other cations and alkenes are generated, a large number of pathways can be visualized which would lead to *tert*-butyl cation.

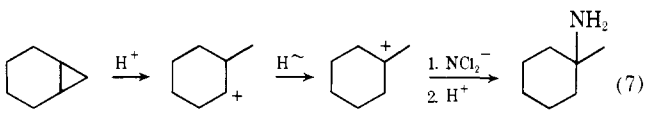
Fragmentation and rearrangement were also prominent with 2,3-dimethylbutane. Pathways to the observed products involving cation formation, subsequent olefin production, and olefin-cation combination, similar to those outlined for isopentane and 3-methylpentane, may be devised.[2] Whereas Olah observed conversion of the *tert*-hexyl cations to the *tert*-butyl cation only above 80 °C in FSO_3H–SbF_5,[30,31] we found that degradation of 2,3-dimethylbutane occurred at 0 to −5 °C in our system. The temperature difference may reflect the poorer solvating power of our medium.

Steric factors associated with the cationic precursor appear to play an important role. Most of the open chain alkanes, including the higher molecular weight ones, yielded *tert*-butyl-

amine as the principal product, derived from the least hindered cation, $(CH_3)_3C^+$, in systems containing a plethora of carbenium ions. Other data support this view. Dicyclohexyl gave only small amounts of basic material, in contrast to less hindered cycloalkanes (methylcyclohexane, decalin, and hydrindan).[12,15] Also, the C_6 amine from 3-methylpentane is derived from the least hindered cation (2-methyl-2-pentyl) from rearrangement. Similarly, both 2-(*p*-tolyl)pentane (**11**) and 3-(*p*-tolyl)pentane (**12**) produced the same product, 2-(*p*-tolyl)-2-pentylamine.[19] The size of the nucleophile may favor interaction with the least hindered carbocation. It is conceivable that amination is reversible.

An alternative approach involves the concept of hyperconjugation,[29b,40] which has been invoked to account for the greater stability of tertiary over secondary cations. The *tert*-butyl cation possesses the maximum number (nine) of hydrogens available for hyperconjugative interaction. The *tert*-pentyl cation has eight such hydrogens. A similar situation pertains for the number of α hydrogens present in the cations derived from **11** (five) and **12** (four). However, this rationalization is not consistent with other data. Thus, compare the number of hydrogens α to the positive center with yields of amine product for the following substrates: dicyclohexyl (five, <5%), decalin (five, 41%), hydrindan (five, 70%), and cyclohexane (four, 40%). Hence, one can conclude that steric influences play a predominant role. On exposure of various alkanes to FSO_3H–SbF_5, Olah found the *tert*-butyl cation to be the most stable alkylcarbonium ion.[30,31]

A reasonable route for formation of 1-amino-1-methylcyclohexane from norcarane is depicted in the following equation:



(7)

13 14

Protonation (by H^+ from traces of water or hydrogen chloride) of the cyclopropane ring gives **13** which rearranges to **14,** followed by eventual conversion to end product. Alternatively, the cyclopropane ring may be opened by Cl^+, leading eventually to tarry material.[2] Other sources of higher molecular weight products are possible by way of methylcyclohexene as an intermediate.[12] In a study[41,42] of the behavior of norcarane under acidic conditions (*p*-toluenesulfonic acid in acetic acid), **13** and **14** appeared to be precursors of a number of the products: alkenes (1-methylcyclohexene, 2-methylcyclohexene, 3-methylcyclohexene, and cycloheptene) and acetates.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were obtained with a Beckman IR-8 instrument, calibrated with the 1601-cm^{-1} band of polystyrene. A Varian T-60 instrument was used to obtain NMR data which are reported in ppm relative to tetramethylsilane as internal standard. Gas chromatography was performed with a Varian instrument (1700) with a 10 ft by ¼ in. column of UCON 50HB2000 and 5% NaOH on Chromosorb W (45/60).

Solutions were dried over anhydrous sodium sulfate. Amine samples were dried over sodium hydroxide pellets and stored in the cold. In some cases methylene chloride was distilled from calcium hydride prior to use, and a *slow* flow of nitrogen was maintained throughout the course of the amination reaction.

Physical properties, spectral data, and derivative melting points were determined from samples obtained by preparative GLC.

The hydrocarbons were used as received after their purity was checked by GLC. Isobutane was Matheson Co., pure grade. Neopentane and isopentane were Phillips, pure grade, 99 mol %. Isooctane was Eastman, practical grade. Dicyclohexyl, norcarane, 3-methylpentane, and 2,3-dimethylbutane were obtained from the Aldrich Chemical Co.

Preparation of Trichloramine Solution. A published procedure (method B) was used with methylene chloride as solvent.[7] Positive halogen analysis was carried out as previously described.[7] Caution: Use the necessary precautions when working with *N*-halamines.[43]

Amination of Isobutane. Aluminum chloride (53 g; 0.4 mol) was added to isobutane (116 g, 2.0 mol) in 100 ml of distilled methylene chloride at −60 °C in a flask provided with a dry ice–acetone condenser. After trichloramine (0.2 mol) in methylene chloride was added during 2 hr at −5 to 0 °C, the mixture was stirred for another hour as the temperature rose to 14 °C (reflux). Because of the high solubility of the desired basic product in water, isolation by the published standard procedure[43] was not successful. Therefore, the method of Campbell[44] and co-workers was adopted. The reaction mixture was cooled to −50 °C and then added to ice–hydrochloric acid (caution: use a large beaker to avoid overflow). On standing overnight, most of the unchanged isobutane had volatilized. The aqueous layer (about 1.6 l.) was separated, made strongly basic with 50% sodium hydroxide (200 ml), and the amine was removed by steam distillation. The distillate was collected in cold hydrochloric acid until the evolved material gave only a faintly basic test. The acid solution (1.3 l.) was evaporated to dryness at the aspirator, the residual solid (30 g) was dissolved in 25–30 ml of water, and 50% sodium hydroxide (20–25 ml) was added with cooling. After saturation with potassium carbonate, the amine was separated and dried over potassium hydroxide pellets and then distilled from potassium hydroxide pellets. The fraction, bp 44–49 °C, was found to be *tert*-butylamine, 82–83% yield (duplicate runs).

Identification was accomplished by comparison with authentic material (boiling point, infrared spectrum, and GLC) and by the preparation of derivatives; mixture melting points showed no depression: hydrochloride, mp 285 °C dec; authentic material, mp 285 °C dec; lit.[45] mp 270–280 °C; picrate, mp 198–200 °C; authentic sample, mp 196–198 °C; lit.[45] mp 198 °C; benzamide, mp 135 °C; authentic material, mp 135 °C; lit.[45] mp 134 °C.

The distillation residue (6 g, containing some water) was dissolved in methylene chloride, washed with water, and dried. After removal of solvent, distillation provided material, bp 45–70 °C at 20 mm, which comprised about 25% of the total crude basic product. GLC analysis revealed a gross mixture (18 components).

Amination of Isopentane. Amination was conducted according to the method for isobutane. The crude base, after standing over KOH, weighed 9 g. The various fractions from distillation were investigated by GLC. The yields of *tert*-butylamine and *tert*-pentylamine were 53 and 39%, respectively. For identification work, redistillation provided purer fractions of the main components. *tert*-Butylamine was identified by comparison with known material (infrared spectrum and GLC) and through derivative formation (picrate mp 198–200 °C). Similarly, *tert*-pentylamine was identified by comparison with authentic material (infrared spectrum and GLC). The picrate melted at 181 °C (lit.[45] mp 183 °C), and no depression was observed on mixing with the authentic *tert*-pentyl derivative.

Amination of Neopentane. Amination was conducted according to the method for isobutane. Since visual observation indicated absence of reaction at 0–10 °C, most of the trichloramine (0.2 mol) was added at 14–16 °C (reflux). Instead of the usual dark color present in alkane amination, the mixture was light yellow. Also, much of the catalyst was undissolved in contrast to the situation for tertiary alkanes and cyclohexane. After 5 h, 33% of the positive halogen still remained. GLC of the crude base, 1.5 g, pointed to the presence of *tert*-butylamine, *tert*-pentylamine, and many (13) other components. Distillation gave 0.8 g of amine, bp 76–79 °C, which was mainly *tert*-pentylamine (82% purity) by GLC analysis and infrared spectrum.

Amination of Isooctane. (1). When the general method (procedure A)[12] for methylcyclohexane was followed, about 2 g of crude base was isolated, only about 25% of which was separated by distillation. GLC analysis of the crude base and the distilled portion revealed the presence of 15–20 components.

(2). When the method for isobutane was used, except that isooctane was not dissolved in methylene chloride, about 7 g of crude amine was obtained. Fractionation gave *tert*-butylamine, bp 45–49 °C (74% yield, 77% of crude base). Identification was effected by the infrared spectrum, GLC, and derivatives (picrate, mp 198–200 °C; benzamide, mp 135 °C). A higher boiling fraction, bp 50–100 °C (15% of crude base), and residue (8% of crude base) were also obtained. GLC analysis of these two revealed the presence of many (18–20) components. GLC analysis in conjunction with known samples pointed to the presence of *tert*-octylamine and *tert*-pentylamine in small amounts.

The gas chromatogram of the higher molecular weight products resembled that of the corresponding material from isobutane.

Amination of 3-Methylpentane. In a 500-ml flask with paddle stirrer, Dewar condenser, thermometer, and addition funnel were placed 3-methylpentane (26 g, 39 ml, 0.3 mol) and 75 ml of methylene chloride. Aluminum chloride (27 g, 0.2 mol) was quickly added in one portion at about −10 °C. A cold solution of trichloramine (0.1 mol) in methylene chloride was added during 1 h at 10 ± 3 °C, followed by stirring for an additional 30 min at the same temperature. After workup as for isobutane, the volatile amines were distilled directly from the basic solution. The fraction boiling at 46–48 °C, 3.73 g, dried over sodium hydroxide pellets, was found to be *tert*-butylamine, greater than 98% pure by GLC. The remaining amines were separated, dried over sodium hydroxide, and distilled. A second fraction, bp 48–75 °C, wt 1.6 g, on GLC analysis, was found to contain *tert*-butylamine (0.75 g), *tert*-pentylamine (0.70 g), and 2-amino-2-methylpentane (**9**) (0.15 g). GLC analysis of the residue (2.7 g) indicated a mixture of *tert*-pentylamine (0.72 g) and **9** (1.28 g), as well as several higher boiling components. Identification of *tert*-butylamine (4.48 g, 61% yield) was accomplished by comparison to authentic material (GLC, NMR) and derivative formation, benzamide, mp 132–133.5 °C.

tert-Pentylamine: 1.42 g, 16% yield, bp 77 °C (micro) (lit.[45] bp 78 °C) picrate, mp 180–182.5 °C; hydrochloride, mp 233–234.5 °C dec (lit.[46] mp 234–236 °C).

Compound **9:** 1.28 g, 13% yield, bp 101 °C (micro) (lit.[47] bp 101–103 °C), ir (CCl_4) 1386, 1367 cm^{-1} (gem dimethyl); NMR (CCl_4) δ 1.0 (s, CH_3); picrate, mp 165–167 °C (lit.[47] mp 166 °C); hydrochloride, mp 204–207 °C (lit.[48] mp 190–198 °C). An expected product, 3-amino-3-methylpentane, was not formed to any appreciable extent; lit.[46] bp 102–104 °C; hydrochloride, mp 292 °C.

Amination at −10 °C gave a low yield (ca. 2 g).

2,3-Dimethylbutane. The procedure for 3-methylpentane was followed with 2,3-dimethylbutane (26 g, 39 ml, 0.3 mol). Trichloramine was added over 1 h at 0 to −5 °C. Distillation gave the following fractions (dried over NaOH), bp 44–46 °C, wt 5.3 g; bp 50–80 °C, wt 1 g; residue, wt 2.2 g.

Fraction 1 was found to be *tert*-butylamine (73% yield, >99% pure by GLC); picrate, mp 197–200 °C.

Fraction 2 was found to contain 0.66 g (7.5% yield) of *tert*-pentylamine identified by GLC comparison to authentic material, micro bp 75–76 °C; NMR spectral similarity to *tert*-pentyl alcohol; picrate, mp 179–181 °C. A second component was also present.

The residue contained trace amounts of *tert*-pentylamine, a substantial amount of the second component from fraction 2, and several (4–5) higher boiling materials. A sample of the second component from fraction 2 was obtained by preparative GLC, micro bp 101 °C; NMR (CCl_4) several methyl absorptions; picrate, mp 155–175 °C, which is apparently a mixture, inseparable by GLC, possibly of **9** and 2-amino-2,3-dimethylbutane; lit.[49] for 2-amino-2,3-dimethylbutane, bp 104–105 °C; picrate[50] mp 188–189 °C.

Several runs with 2,3-dimethylbutane consistently provided *tert*-butylamine in 70–75% yields and *tert*-pentylamine in 7–10% yields, in addition to the unidentified materials.

Dicyclohexyl. The procedure for 3-methylpentane was used with dicyclohexyl (50 g, 0.3 mol) and methylene chloride (150 ml). Trichloramine (0.1 mol) was added at 10–15 °C over 35 min, and the reaction mixture was then stirred for 30 min more. After workup the basic product was extracted with benzene. The dried solution was evaporated yielding 1.6 g of brown semisolid residue. GLC analysis pointed to the presence of at least three components which were not readily separable. Characterization was not attempted.

The organic layer was washed with water, 5% sodium bicarbonate, water, and then dried. After solvent removal, the dark brown oil was distilled to yield 8.3 g of light yellow oil, bp 80–90 °C at 0.6 mm. GLC analysis indicated two major components, both of which gave negative Beilstein tests for halogen. Dicyclohexyl and *n*-dodecane were ruled out by comparison with authentic materials. The rather featureless infrared spectra point to branched open-chain alkanes. The NMR spectra led to similar conclusions. The distillation residue was an intractable tar which was found to contain chlorine.

The amination of dicyclohexyl was examined at −5 to 0 °C. Workup provided a small amount (ca. 1 g) of crude basic material which was similar (GLC) to that obtained above. The organic layer was not examined.

Norcarane. In the apparatus used for 3-methylpentane were placed norcarane (21.6 g, 0.225 mol) and methylene chloride (175 ml). Trichloramine (0.075 mol) was added at 0–5 °C over 35 min. In contrast to prior alkanes, initial control of the temperature was more difficult and the reaction mixture began to take on the dark brown color after only a small amount of trichloramine was added. After addition of trichloramine was complete, the mixture was stirred for 20 min, cooled to −50 °C, and poured into 200 ml of 18% hydrochloric acid. After being stirred overnight, the organic layer was extracted with 18% hydrochloric acid. The combined acid fraction was extracted with ether and concentrated to ca. 100 ml at the aspirator. After basification with excess 50% caustic and cooling, the crude product was extracted repeatedly with pentane and with ether. The combined organic extract was dried, and the volatile solvent was removed under reduced pressure leaving a brown oil, 1.7 g.

GLC analysis indicated a single volatile basic product, 1-amino-1-methylcyclohexane, 10% yield, identified by comparison with authentic material (GLC, ir, NMR); micro bp 137–138 °C (lit.[51] bp 143 °C); picrate, mp 146–148 °C (lit.[52] mp 150–151 °C).

When the amination was conducted below −20 °C, similar results were obtained, a low yield of 1-amino-1-methylcyclohexane in addition to intractable residue.

Acknowledgment. We thank the Graduate School, University of Wisconsin-Milwaukee, and the National Science Foundation for financial support, and Dr. K. W. Field for helpful discussions.

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A Comparison of the Glutamate Dehydrogenase Catalyzed Oxidation of NADPH by Trinitrobenzenesulfonate with the Uncatalyzed Reaction

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Received September 12, 1975

Abstract: We have measured the rates of hydrogen transfer between trinitrobenzenesulfonate (TNBS) and ten 1,4-dihydropyridines and found them to be first order in both reactants. A plot of log k_2, the second-order rate constant for hydrogen transfer, against log K_d, the dissociation constant for cyano-complex formation, is linear with slope 0.57 if the nicotinamide analogues are excluded. The kinetic parameters for the glutamate dehydrogenase catalyzed hydrogen transfer between TNBS and NADPH or 3-acetylpyridine adenine dinucleotide (3APADH) have been determined and shown to be consistent with a random order mechanism in which at least one pair of equilibria, either K_1 and K_2 or K_1' and K_2' (eq 11), are established rapidly. Based on a comparison of the kinetic deuterium isotope effects for the enzyme catalyzed and spontaneous reactions and on a comparison of rate ratios for two 1,4-dihydropyridines, we conclude that there is greater carbon–hydrogen bond breakage at the transition state in the catalyzed reaction than in the spontaneous reaction.

Introduction

Nicotinamide coenzymes are essential cofactors in many enzyme-catalyzed hydrogen transfer reactions. Unlike many other essential cofactors, there have been few studies where the nonenzyme-catalyzed reactions serve as suitable models for the enzyme-catalyzed reactions. Some studies of note include models for alcohol dehydrogenases,[1-5] transhydrogenases,[6-8] and flavin reductases.[9,10]

In a related study Bates et al.[11] report that bovine liver glutamate dehydrogenase catalyzes the oxidation of NADH by trinitrobenzenesulfonate. They concluded[11] that the reaction must occur at the active site because the hydrogen atom transferred from the reduced coenzyme originates on the B side of the nicotinamide ring, as it does in the reductive amination of α-ketoglutarate and because added mononucleotides produce kinetic effects similar to those reported for the steady state oxidative deamination of glutamate. Several other dehydrogenases do not catalyze this reaction. Recently, Kurz and Frieden[12] reported that a series of 4-substituted-2,6-dinitrobenzenesulfonates react with NADH, obeying the Hammett relationship. We report here, a study of the kinetics of the glutamate dehydrogenase catalyzed reaction and the spontaneous reaction between TNBS and a series of 1,4-dihydropyridines.

Experimental Section

Materials. The following reagents were purchased from Sigma Chemical Co. and used without further purification: trinitrobenzenesulfonic acid, oxidized (NAD) and reduced (NADH) nicotinamide adenine dinucleotide, oxidized (NADP) and reduced (NADPH) nicotinamide adenine dinucleotide phosphate, oxidized (NMN) and reduced (NMNH) nicotinamide mononucleotide, and oxidized (3APAD) and reduced (3APADH) 3-acetylpyridine adenine dinucleotide. Nicotinamide, 3-acetylpyridine, 3-formylpyridine, 3-methyloximepyridine, 3-cyanopyridine, and benzyl bromide were purchased from Aldrich Chemical Co. and used without purification. Hexadeuterioethanol, 99%, was purchased from Merck and Co. and L-glutamic acid from Calbiochem. We prepared L-glutamic-*2-d* acid, greater than 99% isotopic purity, as previously described.[13] Glutamate dehydrogenase was purchased from Sigma Chemical Co. as a suspension in ammonium sulfate. The enzyme was prepared for use in 0.1 M potassium phosphate buffer, pH 7.6, as described previously.[14] Yeast alcohol dehydrogenase was obtained from Sigma Chemical Co. as a lyophilized powder. This powder was dissolved in 0.1 M potassium phosphate buffer, pH 7.6 containing 3 mM EDTA and dialyzed for 5 h in 900 ml of the same buffer, followed by three changes of 0.1 M phosphate buffer for 36 h. The enzyme solution was filtered through a 0.45 μ Millipore filter, and the concentration was determined from the absorbance at 280 nm.[15]

All spectra were recorded in 1-cm cuvettes in aqueous solution using a Cary Model 14 spectrophotometer. Repetitive scans were collected and stored with the aid of a Varian 620i computer which was interfaced directly to the photomultiplier of the spectrophotometer. Kinetic experiments were conducted using a Gilford Model 2000 spectrophotometer fitted with thermostated cell compartment, with the temperature controlled to ±0.1 °C. The pH was measured with a Radiometer Model 26 pH meter. Melting points were determined on Thomas-Hoover capillary melting point apparatus and are corrected.

***N*-Benzyl-1,4-dihydronicotinamide.** The method of Mauzerall[16] was followed using 0.25 g of *N*-benzylnicotinamide bromide[17] and 0.82 g of sodium dithionite. The yellow crystals obtained after two recrystallizations from aqueous ethanol had mp 105–122 °C (lit. mp