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The Azide Group as a Neighboring Group. Acetolysis of *trans*-2-Azidocyclohexyl *p*-Toluenesulfonate¹

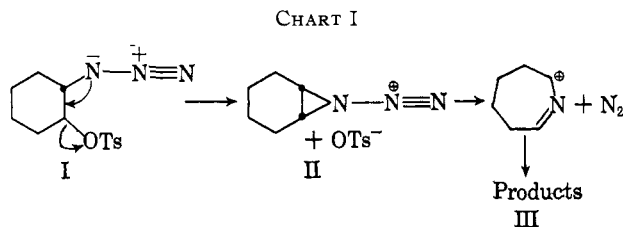
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Acetolysis of *trans*-2-azidocyclohexyl tosylate involves little or no anchimeric acceleration and yields the product of retention of configuration, *trans*-2-azidocyclohexyl acetate.

Comparatively little modern study has been made of the chemical effects of the electronic properties of the azido group.² The most extensive recent work is that reported by Smith, Hall, and Kan.³ In the acidities of substituted benzoic acids and anilinium ions, the *m*-azido group is electron withdrawing with a Hammett σ of 0.33–0.37, comparable to that of the halogens. This similarity of the inductive effect of the azide group with the halogens is in agreement with earlier studies of Philip⁴ on acidities of aliphatic acids. However, the difference between σ_p , 0.08–0.11, and σ_p^+ , –0.54, shows that the azide group can be a powerful electron donor in situations of strong electron demand.

In the present studies, we have examined the behavior of an azide function as a neighboring group in the acetolysis of *trans*-2-azidocyclohexyl tosylate (I) following the classic work of Winstein.⁵ In view of the electron-donating capabilities of the azide group, we looked particularly for evidence of the possible reaction sequence given in Chart I.



Results and Discussion

trans-2-Azidocyclohexyl tosylate was prepared by reaction of cyclohexene oxide with sodium azide followed by treatment with tosyl chloride in pyridine. Kinetics of acetolysis are summarized in Table I. The rates at the two higher temperatures correspond to $\Delta H^\ddagger = 30.2$ kcal./mole and $\Delta S^\ddagger = -3.5$ e.u. The acetolysis rate for cyclohexyl tosylate at 100° extrapolated from the data of Brown and Ham⁶ is 6.3×10^{-4} sec.⁻¹; the data of Roberts and Chambers⁷ give 8.8×10^{-4} sec.⁻¹. Hence, I is 2.6 – 3.6×10^{-3} as reactive as the parent compound at 100°.

The early conductivity work of Philip⁴ gave a value of 9×10^{-4} for the dissociation constant of an admittedly impure sample of azidoacetic acid in water at 25°; nevertheless, the derived value of σ^* of 0.96⁸ is in reasonable agreement with that expected from a cor-

TABLE I
ACETOLYSIS OF *trans*-2-AZIDOCYCLOHEXYL *p*-TOLUENESULFONATE

Temp., °C.	[ROTs], mole/l.	[NaOAc], mole/l.	10% <i>k</i> , sec. ⁻¹
75.0 ± 0.1	0.0815	0.112	0.012 ^a
100.0 ± .1	.0786	.112	0.226
119.6 ± .1	.0671	.112	1.83

^a Approximate value; only 10% of reaction was followed.

relation between σ^* and σ_m . From the known correlation between acetolysis rates of sulfonates and σ^* ,⁹ the corresponding value of ρ , –3.5, leads to an expected relative rate of 4×10^{-4} in the absence of anchimeric acceleration. Because of the approximate nature of the derived value of σ^* for the azide group, this value may be in error by as much as a factor of ten. It seems clear that there can be but little if any anchimeric acceleration associated with neighboring group participation by an azide function.

The products of the reaction scheme in Chart I would be expected to hydrolyze rapidly in water to adipic aldehyde. When the kinetic solutions were diluted with water and treated with dinitrophenylhydrazine reagent, no carbonyl derivatives were formed. In a preparative scale solvolysis, the acetolysis product was isolated. The infrared spectrum was identical with that of *trans*-2-azidocyclohexyl acetate. Reduction of the solvolysis product with lithium aluminum hydride gave *trans*-2-aminocyclohexanol identified as the hydrochloride. Thus, acetolysis of I is accompanied by complete retention of configuration implying that an intermediate "azidonium" ion is produced, although participation at the rate-determining transition state is small. Five-membered ring structures such as IV and V for this intermediate are probably unlikely; hence, we are left with II as the most likely structure. If this inference is correct, this study shows that II does not lose nitrogen readily as indicated in Chart I, but simply reacts with solvent with inversion to give the azido acetate with net retention of configuration. It may be noted that in its formation of a bridged ion which controls stereochemistry but without noteworthy rate acceleration, the azide group behaves very much as a pseudo-halogen group.



Experimental

trans-2-Azidocyclohexyl *p*-Toluenesulfonate.—*trans*-2-Azidocyclohexanol was prepared from cyclohexene oxide and sodium azide using the procedure of VanderWerf, Heisler, and McEwen.¹⁰

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This alcohol (11.1 g., 0.079 mole) was dissolved in 60 ml. of pyridine, cooled to -15° , and treated with 30 g. of *p*-toluenesulfonyl chloride. After 48 hr. at -8° , the mixture was poured into cold diluted sulfuric acid and extracted with chloroform. Solvent was removed from the washed and dried extract by vacuum evaporation and the residue was crystallized twice from hexane yielding 15.6 g. (67%) of white crystals, m.p. 56.5–57.0°.

Anal.¹¹ Calcd. for $C_{18}H_{17}N_3O_3S$: C, 52.9; H, 5.8; N, 14.3; S, 10.9. Found: C, 52.7; H, 5.6; N, 14.3; S, 10.7.

trans-2-Azidocyclohexyl Acetate.—A solution of 6.6 g. (0.047 mole) of *trans*-2-azidocyclohexanol in 12 ml. of pyridine and 30 ml. of pentane was treated with 5.5 g. of acetyl chloride. After stirring for several hours, the washed and dried organic solution was distilled, yielding 3.4 g. of product, b.p. 65–69° (0.9–1.0 mm.), n_D^{20} 1.4688.

Anal.¹¹ Calcd. for $C_8H_{13}N_3O_2$: C, 52.4; H, 7.1; N, 23.0. Found: C, 52.5; H, 7.3; N, 23.1.

Kinetics.—Glacial acetic acid was refluxed with acetic anhydride and a trace of toluenesulfonic acid and distilled. The material used for kinetics contained 0.06 mg./ml. of water by Karl Fischer titration.¹¹ A weighed amount of substrate was dissolved at room temperature and aliquots were sealed in am-

poules. Potentiometric titrations of kinetic points were made with a Metrohm potentiograph. Experimental infinity points agreed with the calculated infinities within 4%.

Acetolysis Products.—A solution of 13.6 g. (0.046 mole) of I and 3.8 g. (0.046 mole) of sodium acetate in 100 ml. of acetic acid was maintained at 120° for 120 hr. The cooled solution was made alkaline with aqueous sodium hydroxide and ice and extracted with pentane. Distillation of the washed and dried extract gave 3.5 ml. of a residue which was evaporatively distilled and maintained under vacuum to remove traces of pentane. The product in 37% yield, n_D^{20} 1.4706, had an infrared spectrum identical with that of *trans*-2-azidocyclohexyl acetate.

Two grams of this product was reduced with 1.1 g. of lithium aluminum hydride in ether. The reaction mixture was decomposed with a small amount of saturated aqueous ammonium chloride and the dried ether layer was distilled. The residue was dissolved in 6 *M* hydrochloric acid, evaporated, and crystallized three times from benzene–ethanol to afford white crystals, m.p. 174–175° (reported¹² for the hydrochlorides of 2-aminocyclohexanol: *trans*, m.p. 176–177°; *cis*, m.p. 189–190°).

Dinitrophenylhydrazine reagent added to aliquots of acetolysis solutions after addition of water gave no precipitates on standing.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CASE INSTITUTE OF TECHNOLOGY, CLEVELAND, OHIO]

Aromatic Amination with Hydrazoic Acid Catalyzed by Lewis Acids. Orientation, Activity, and Relative Rates¹

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Amination of toluene and chlorobenzene by hydrazoic acid in the presence of aluminum chloride or sulfuric acid yielded toluidines and chloroanilines. The predominant *ortho*-*para* orientation and relatively high amount of *meta* isomer suggest an electrophilic substitution mechanism involving an attacking species of high activity. Competitive amination gave values for the relative rate, $k_{\text{toluene}}/k_{\text{benzene}}$, which are in good agreement with those calculated from the selectivity relationship. The reaction of methyl azide with toluene–aluminum chloride produced *N*-methyltoluidines and a considerable amount of higher boiling basic material.

Introduction

Azides have been used for the direct amination of aromatic compounds under various conditions, such as Lewis acid catalysis, thermal initiation, and photolysis. The acid-catalyzed reactions are of most pertinence in relation to this investigation.

The literature contains several reports concerning amination with hydrazoic acid under Friedel–Crafts conditions. From Schmidt's laboratory came the disclosure that amines are formed from aromatic hydrocarbons and hydrazoic acid with sulfuric acid or aluminum chloride catalyst.² This lead was subsequently developed by other investigators.^{3,4} Aromatic azides have also been used in this type of transformation.^{5,6} For example, with benzene and aluminum chloride, phenyl azide was converted to diphenylamine.⁵ Intramolecular amination has been realized in the acid-catalyzed rearrangement of 9-azidofluorene to phenanthridine.⁷

There are numerous examples of aromatic amination by thermal decomposition of azides. The reagent list includes hydrazoic acid or ammonium azide,⁸ *o*-azidobiphenyls,⁹ benzenesulfonyl azide,^{10–13} and carbonyl azide.¹⁴

Photolysis of hydrazoic acid and alkyl azides in benzene, toluene, or nitrobenzene gave low yields of aromatic amines.^{3,15} Hydrazoic acid has also been decomposed by active nitrogen in the presence of benzene with formation of traces of aromatic amines.¹⁶

In addition to azides, compounds in the hydroxylamine class are known to function as aminating agents. Acid-catalyzed substitutions have been performed with hydroxylamine,¹⁷ hydroxylamine-*O*-sulfonic acid,^{3,18} alkyhydroxylamines,¹⁷ hydroxylammonium salts,¹⁹ and *N*-benzoyloxypiperidine.²⁰

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