Reactions of Alkanediazotic Acids at Near Neutral and Basic pH in $[^{18}O]H_2O$

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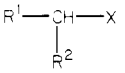
Abstract: The reactions of propane-1-diazotic acid (**1**) and optically pure (*S*)-1-phenylethanediazotic acid (**2**) are investigated in $[^{18}O]H_2O$ at near neutral (pH 7.0–8.5) and basic (pH >14) conditions. At near neutral pH, **1** yielded 1- and 2-PrOH (2:1), with both alcohols showing complete incorporation of ^{18}O from solvent. In the presence of NaN_3 the isomeric ratios of azides and alcohols were independent of the $[N_3^-]$. The ratio of PrN_3 to PrOH is linearly related to $[N_3^-]/[H_2O]$ for both primary and secondary products. In basic medium, **1** yields the same isomeric propanol ratio, but both alcohols contain significant and similar amounts of ^{16}O label. **2** in pH 8.5 buffer gives 1-phenylethanol with 20% net inversion and containing ~4% ^{16}O-labeled conservation product. In contrast the ethanolysis of **2** in a basic environment yields 29% conservation (alcohol) product and the overall stereochemistry of conservation and exchange (ether) products is 1% net inversion. These results indicate that the extent of ^{16}O conservation is not dependent on structure, but rather on the degree of proton-transfer-mediated equilibration of the original ^{16}OH counteranion with $[^{18}O]H_2O$, prior to C–N bond cleavage. It is also apparent that a nitrogen-separated ion pair, formed in a two-step process, is responsible for the high yield of rearrangement product, while the stereochemical outcome is determined at the ion-pair stage after nitrogen extrusion.

Metabolic activation of carcinogenic dialkylnitrosamines into electrophiles is known to be mediated by formation of alkanediazotic acid intermediates that eventually yield covalent alkylation adducts of DNA.[1-8] The generation and reaction of alkanediazotic acids by diazotization of primary amines and by hydrolysis of α-acyl-*N*-alkylnitrosamines have been intensely studied,[9] although the description of the transient intermediate(s) and the mechanisms by which it (they) affords products are still debated.[10,11] In the present study, which describes the hydrolysis of propane-1-diazotic acid (**1**) and optically active (*S*)-1-phenylethanediazotic acid (**2**),



1, $R^1 = CH_3CH_2$; $R^2 = H$; X = N=NOH

2, $R^1 = Ph$; $R^2 = CH_3$; X = N=NOH

3, $R^1 = CH_3CH_2$; $R^2 = H$; X = $N(NO)CH_2OAc$

4, $R^1 = CH_3CH_2$; $R^2 = H$; X = $N(NO)CO_2CH_3$

5, $R^1 = CH_3CH_2$; $R^2 = H$; X = $N{=}NO^-K^+$

6, $R^1 = Ph$; $R^2 = CH_3$; X = $N(NO)CO_2CH_2CH_3$

7, $R^1 = CH_3CH_2$; $R^2 = H$; X = NH_2

8, $R^1 = Ph$; $R^2 = CH_3$; X = $N{=}NO^-K^+$

9, $R^1 = CH_3CH_2$; $R^2 = H$; X = N(NO)COPh

10, $R^1 = CH_3CH_2CH_2$; $R^2 = {}^2H$; $X = NH_2$

our primary interest is in understanding the mechanism of product formation under near physiological conditions.

Table I. Deamination of 1-Propylamine (**7**) and Hydrolysis of (1-Acetoxypropyl)propylnitrosamine (**3**), Methyl *n*-Propylnitrosocarbamate (**4**), and Potassium Propane-1-diazotate (**5**) in $[^{18}O]H_2O$

entry	compd	reaction conditions[a]	atom % $[^{18}O]$-H_2O used	atom % ^{18}O[b] 1-PrOH	atom % ^{18}O[b] 2-PrOH	product (1-PrOH:2-PrOH)[c]
1	7	A	19.4	19.2 ± 0.7	19.3 ± 1.2	67.33
2	3	B	48.0	48.0 ± 3.0	47.0 ± 2.6	67.33
3	3	C	45.2	45.1 ± 1.2	45.0 ± 0.9	65.35
4	4	B	48.0	48.2 ± 1.3	47.7 ± 1.0	65.35
5	5	D	19.4	19.5 ± 1.4	19.0 ± 0.9	61.39
6	5	E	97.0	61.0 ± 1.0	62.1 ± 1.9	66.34[d]

[a] A, deamination carried out at pH 7.0 using nitrosylpentacyanoferrate(III); B, hydrolysis carried out at pH 8.0 in 0.1 M sodium phosphate buffer; C, hydrolysis carried out at pH 7.0 in 0.1 M sodium phosphate buffer in the presence of 60 units of porcine liver esterase (Sigma Type I); D, hydrolysis carried out at pH 7.0; E, hydrolysis carried out under basic conditions (pH >14). [b] Determined by GLC-MS. [c] Determined by GLC. [d] Corrected for diazoalkane-derived product.

Previously, it has been suggested, in part on the basis of differences in the extent of anion conservation, that the reactions of primary and secondary alkanediazotic acids differ, in that the former involve alkane diazonium ions, while the latter react via nitrogen-separated ion pairs.[10] However, the studies described herein indicate that in $[^{18}O]H_2O$ inclusion of the original $^{16}OH^-$ counterion in the transition state, as evidenced by formation of significant alcohol product containing the original counterion, is related to the pH of the reaction medium and not to the structure, as previously proposed. The key intermediate in the skeletal rearrangement process is a nitrogen-separated ion pair. However product stereochemistry is controlled at the ion pair level after nitrogen extrusion.

Experimental Section

Nitrosylpentacyanoferrate(III) was obtained from Kodak Chemicals and porcine liver esterase Type I from Sigma Chemical Co. (1-Acetoxypropyl)propylnitrosamine (**3**) was prepared by the method of Wiessler[12] and methyl propyl-nitrosocarbamate **4** by nitrosation of methyl *N*-propylcarbamate with N_2O_4.[13] Diazotate **5** and ethyl [(*S*)-1-phenylethyl]nitrosocarbamate (**6**) were synthesized as described by Moss

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(9) For review, see: (a) White, E. H.; Woodcock, D. J. In "The Chemistry of the Amino Group"; Patai, S., Ed.; Wiley-Interscience: New York, 1968; pp 440–483. (b) Keating, J. T.; Skell, P. S. In "Carbonium Ions"; Olah, G. A., Schleyer, P.v.R., Eds.; Wiley-Interscience: New York, 1970; Vol. 2, pp 573–653. (c) Friedman, L. In "Carbonium Ions"; Olah, G. A., Schleyer, P.v.R., Eds.; Wiley-Interscience: New York, 1970; Vol. 2., pp 655–713. Kirmse, W. *Angew. Chem.* **1976**, *88*, 273–283.
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Table II. Hydrolysis of Methyl 1-Propylnitrosocarbamate (**4**) and Potassium Propane-1-diazotate (**5**) in the Presence of Sodium Azide

		product yields, %[a]						product ratios × 10^2		
		PrOH		PrN_3						
compd	$[N_3^-]/[H_2O]$	1-PrOH	2-PrOH	1-PrN_3	2-PrN_3	2-PrOH/ 1-PrOH	2-PrN_3/ 1-PrN_3	PrN_3/ PrOH	1-PrN_3/ 1-PrOH	2-PrN_3/ 2-PrOH
4[b]	4.0×10^{-4}	39.7q	19.1	1.6	0.2	0.48	0.13	2.9	4.0	1.1
4[b]	2.1×10^{-3}	43.6	21.0	2.6	0.6	0.48	0.23	5.0	6.0	2.9
4[b]	1.0×10^{-2}	32.9	19.3	4.5	0.9	0.59	0.20	10.3	13.7	4.7
4[b]	5.4×10^{-2}	24.9	11.8	6.7	1.0	0.47	0.15	21.0	26.9	8.5
5[c]	2.1×10^{-3}	23.3[d]	11.2	0.2	0.03	0.48	0.15	0.7	0.9	0.3

[a] Yields determined by GLC (see Experimental Section). [b] Hydrolysis conditions: 0.1 M (pH 8.0) sodium phosphate buffer. [c] Hydrolysis carried out under basic conditions: 2 equiv of KO-*t*-Bu used in the synthesis of **5**. [d] Corrected for diazoalkane-derived products (~16%).

and Lane[14] with certain modifications (vide infra). The potassium *tert*-butoxide was sublimed and the diethyl ether dried over and distilled from sodium immediately before use.

GC–MS analyses of products employed a Bendix model 2200 gas chromatograph attached to an AEI MS902 mass spectrometer. The GC column, 0.1% SP1000 on Carbopak C (Supelco), was operated at 40 °C with a helium flow rate of 15 cm^3/min. Resolving power was approximately 1000. Spectra were scanned repetitively at 2 s/decade with a 4-s cycle time. Sample volumes were adjusted to keep water elution constant during elution of alcohol peaks to insure a constant degree of ion beam suppression, while individual components entered the ion source.

$[^{18}O]H_2O$ (Merck, Sharp and Dohme, Canada Ltd.) was stored and used in a N_2-purged glovebox desiccated with P_2O_5. The ^{18}O atom percent of the $[^{18}O]H_2O$ was periodically analyzed by determining the ^{18}O incorporation into propanal under conditions identical with those described for the hydrolysis of **3** and **4** (vide infra). Mass spectral determination of the atom percent ^{18}O in the propanal relied upon analysis of m/z 58 relative to m/z 60. This value is used in Table I for the "atom percent $[^{18}O]H_2O$ used" and corrects for any potential isotope dilution resulting from oxygen exchange with the phosphate buffer.

1-Propyl Studies. The deamination and hydrolysis studies were carried out on ~50 mM scale in 0.1 M sodium phosphate-buffered $[^{18}O]H_2O$ (pH specified in Table I) at 25 °C. The alcohol products were purified by microdistillation of the reaction solution and then analyzed by GC (Carbopack C/0.1% SP-1000). Control experiments to determine alcohol stabilities and recoveries were carried out, and reported product ratios are corrected. For isotope studies the GC–MS system was used to monitor the following ions (isotope): 1-propanol—m/z 33 (^{18}O), m/z 32 (^2H), and m/z 31 (^{16}O)—2-propanol—m/z 47 (^{18}O), m/z 46 (^2H), and m/z 45 (^{16}O).

For the hydrolysis studies in $[^2H]H_2O$ the buffer was repeatedly dissolved in $[^2H]H_2O$ and concentrated in vacuo to replace ^1H with ^2H.

In the hydrolysis of **5**, the *tert*-butyl alcohol product was monitored by GC to provide quantitation of excess KO-*t*-Bu present prior to hydrolysis. A byproduct was observed in the hydrolysis of **5** that was identical with methyl propylcarbamate by GC–MS and ^1H NMR.

Reaction studies using sodium azide were analyzed directly by GC (Carbopack C/0.1% SP-1000) without prior distillation. The 1- and 2-propanol and 1- and 2-propyl azide[15] products were quantitated by using a HP 3380A recording integrator. No attempt was made to analyze for propene.

1-Phenylethyl Studies. The hydrolysis of **6** (1.25 μmol) was carried out at pH 8.5 (0.01 M sodium phosphate) in 1 mL of 91.6 atom % $[^{18}O]H_2O$ at 25 °C. The 1-phenylethanol product (~90% yield) was then reacted with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[16] to afford a mixture of diastereomers. The *R,R* and *R,S* diastereomers were separated and quantitated by HPLC (column Ultrasphere ODS, 5 μm; solvent, methanol/water, 66:34; column temp 30 °C). On the basis of integration of peak areas (HP-3380A Recording Integrator), the 1-phenylethanol was formed with ~20% net inversion. The separated diastereomers[17] were analyzed by high-resolution chemical-ionization MS (AEI-Kratos MS-50) for the ratio of ^{16}O (m/z 339) to ^{18}O (m/z 341).

Results

The results of the deamination of 1-propylamine (**7**) by nitrosylpentacyanoferrate(III)[18] and the hydrolyses of (1-acetoxypropyl)propylnitrosamine (**3**), methyl propylnitrosocarbamate (**4**), and potassium propane-1-diazotate (**5**) appear in Table I. The deamination of **1** in $[^{18}O]H_2O$ affords 1- and 2-propanol in a ~2:1 ratio with complete incorporation of the ^{18}O label. Control experiments in $[^{18}O]H_2O$ demonstrate the structural and isotopic stability of the two alcohols to the reaction and isolation conditions. To determine that there is no rapid incorporation of ^{18}O label into the nitrosyl ligand prior to nitrosation, pyrrolidine was treated with nitrosylpentacyanoferrate(III) in $[^{18}O]H_2O$ under conditions identical with those used in the deamination of **7**. The *N*-nitrosopyrrolidine isolated (48% yield) contained no ^{18}O, indicating that the ^{18}O found in the isomeric propanols is incorporated from solvent after decomposition of the intermediate primary nitrosamine. When the deamination was carried out in $[^2H]H_2O$ no ^2H incorporation into the propyl chain was detected, signifying the absence of a diazoalkane to alcohol pathway at neutral pH.

The other entries in Table I show that the hydrolyses of **3**, with or without esterase catalysis, and **4** yielded results identical with the diazotization of **7**. There was no evidence for diazoalkane-derived products when reactions were run in $[^2H]H_2O$. Recovery experiments with **3** and **4** showed no solvent exchange of ^{18}O into the compounds prior to their hydrolysis.

Diazotate **5** was synthesized by treating **4** in anhydrous ether at ~−30 °C with sublimed potassium *tert*-butoxide.[14] Either 1 or 2 M equiv of butoxide (based on **4**) were used. After 30 min the ether solvent, unreacted **4** and any volatile products, such as alkyl carbonates and alcohols, were removed by concentration of the reaction mixture at -5 °C (10^{-2} mmHg) to afford a white solid residue. Since **4** is fairly volatile, it is readily removed under vacuum (−5 °C, 10^{-2} mmHg), and therefore all products from the subsequent addition of between 0.5 and 1.0 mL of buffered $[^{18}O]H_2O$ (0.1 M phosphate, pH 7.0) are derived exclusively from **5**. When 2 equiv of butoxide are used, the residue that is quenched contains ~1 equiv (0.5 mmol) of unreacted *tert*-butoxide, which was quantitated by GC analysis of *t*-BuOH after hydrolysis. If the base completely dissolved in the added water prior to protonation of **5**, the alkanediazotic acid would be hydrolyzed in a medium that is 0.5–1.0 M in $^{18}OH^-$. In the presence of ~1 equiv of excess *tert*-butoxide the hydrolysis of **5** involves significant amounts of diazoalkane intermediate, as indicated by the 16.0 ± 1.3% ^2H incorporation into 1-propanol when the reaction is carried out in $[^2H]H_2O$. When the 1- to 2-propanol ratio is corrected for the diazoalkane pathway, the results do not differ significantly from those reactions at near neutral pH.

A side reaction in the synthesis of **5** is formation of the anion of methyl propylcarbamate, the structure of which after hydrolysis is indicated by ^1H NMR and GC–MS. The denitrosated **4** is not observed in the pH 8.0 hydrolysis of **4**.

The hydrolysis of **5** at near neutral pH is also identical with the deamination of **7** in terms of product ratio, percent ^{18}O incorporation and lack of a diazoalkane intermediate. The hydrolysis of **5** under basic conditions is unique from the other entries in Table I, in that significant amounts of both alcohols contain oxygen not derived from ^{18}O solvent. An important observation is that the ^{18}O incorporation into the two isomeric alcohols is identical for all the reactions listed in Table I.

(14) Moss, R. A.; Lane, S. M. *J. Am. Chem. Soc.* **1967**, *89*, 5655–5660.
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(18) Maltz, H.; Grant, M. A.; Navaroli, M. *J. Org. Chem.* **1971**, *36*, 363–364.

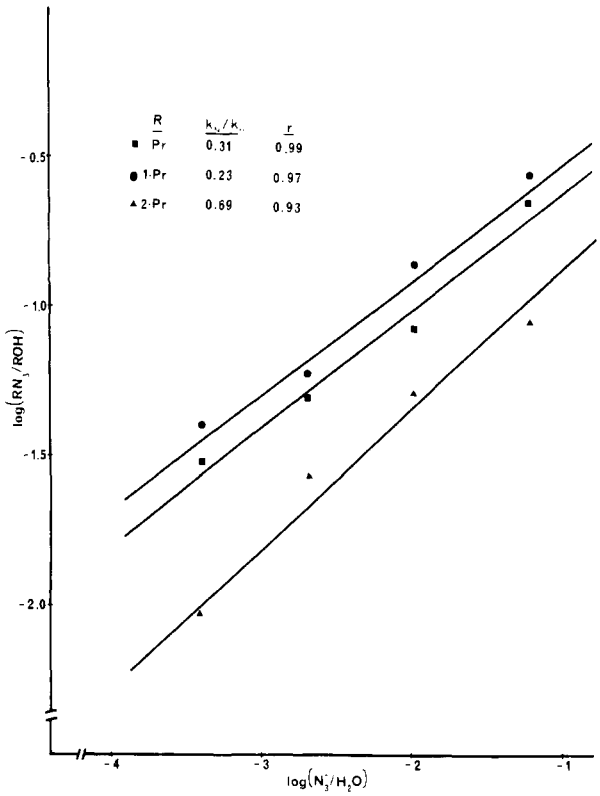


Figure 1. log–log plot of propyl azide/propanol ratio dependence on $[N_3^-]$. Nonlogarithmic values of k_N/k_H are shown with the corresponding correlation coefficients (r).

The results of the hydrolysis of **4** and **5** in the presence of sodium azide are shown in Table II. The ratios of isomeric alcohols and azides are not affected by increases in $[N_3^-]$, and the former is identical with that seen in the absence of azide (Table I). From Table II and Figure 1 (log–log plot), it is evident that the ratio of total azide to total alcohol is linearly related to $[N_3^-]/[H_2O]$. This is true for both the primary and secondary products (Figure 1), although k_N/k_H (Figure 1) is nearly double for the secondary products. Azide does not affect the alcohol product yields when **5** is hydrolyzed under basic conditions, after correction for diazoalkane formation. However, the yield of alkyl azides from **5** is ~10-fold less than that detected in the hydrolyses of **4** at pH 8.0. The low levels of alkyl azide isomers, coupled with the limits of our analytical precision, do not allow us to comment on whether the observed isomeric azide ratio decreases under the basic hydrolysis conditions that afford significant diazoalkanes. If there is a change in the isomeric azide ratio, it must be relatively small.

The results of the hydrolysis of **6** in $[^{18}O]H_2O$ at pH 8.5 appear in Table III. In a previous large-scale hydrolysis of **6** using identical conditions, the isolated yield of 1-phenylethanol product was 90% and the polarimetrically determined stereochemistry showed alcohol to be formed with 28.6% net inversion.[6] This compares to the presently reported 20.2% inversion determined by HPLC quantitation of the (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate diastereomeric derivatives. Recovery experiments demonstrate the stereochemical stability of the 1-phenylethanol under reaction conditions and the absence of ^{18}O incorporation from solvent into **6** prior to product formation. When the reaction was carried out in $[^2H]H_2O$, no significant ^2H was found in the alcohol product, indicating that diazoalkane was not an important alcohol precursor.

For comparison, the results reported by Moss and Landon for the ethanolysis of potassium (*S*)-(−)-1-phenylethanediazotate (**8**) in the presence of ~1 equiv of *t*-BuO^- are also listed in Table III.[19] The ether and alcohol formed in the solvolysis of **8** correspond to $R^{18}OH$ and $R^{16}OH$, respectively, from the hydrolysis of **6**. No attempt to analyze for styrene was made in the present experiment, although the yield must be ≤10%.[6] Under basic conditions **8** afforded 17.6% olefin.[19] The stereochemistry of $R^{18}OH$ and ROEt exchange[20] products from **6** and **8** does not differ significantly, although the yields do. The difference in exchange yield is accounted for by the reverse trend in the $R^{16}OH$ and ROH conservation[20] products. The retention of stereochemistry of the conservation products from **6** is ~33% of that from **8**.

Table III. Hydrolysis[a] of Ethyl [(*S*)-(−)-1-Phenylethyl]-nitrosocarbamate (**6**) in $[^{18}O]H_2O$ and Ethanolysis of Potassium (*S*)-(−)-1-Phenylethanediazotate (**8**)

	$R^c\ ^{16}OH^d$(OH)^e			$R^{18}OH^d$(OEt)^e		
		stereochemistry, %			stereochemistry, %	
compd	yield,[f] %	retention	inversion	yield,[f] %	retention	inversion
6	4	62	38	96	39	61
8	29	87	13	71	35	65

[a] Hydrolysis at pH 8.5 (0.01 M sodium phosphate buffer) in 91.6 atom % $[^{18}O]H_2O$. [b] Ethanolysis carried out in the presence of 1 equiv of KO-*t*-Bu.[19] [c] R = 1-phenylethyl. [d] Product from **1**. [e] Product from **2**. [f] Yields are normalized to 100%; actual alcohol yield from **1** is ~90%;[8] actual alcohol and ether yield from **2** is 61%.[19]

Discussion

Hydrolysis of Propyl Series. Hydrolysis at Neutral pH. The results in Table I (entries 1–5) indicate that at near neutral pH the products, and presumably the processes involved in their formation, are virtually identical, regardless of the propane-1-diazotic acid precursor used. The ratio of isomeric propanols is quite similar to that reported by Huisgen and Rüchardt for the thermal decomposition of *N*-nitroso-*N*-*n*-propylbenzamide (**9**) in DMF–H_2O and for the nitrosative deamination of **7** at 0 °C in the same solvent system.[21] In contrast to our studies at neutral pH in which no conservative capture of the original counterion ($^{16}OH^-$) is observed, these authors detected, from the decomposition of **9**, 9% benzoate esters, which contain 9% of the *iso*-propyl isomer. The differences between the thermolysis of **9** and the hydrolysis reactions at near neutral pH will be discussed below.

The failure to detect any alcohol product derived from conservative return of the $^{16}OH^-$ counterion at physiological pH is consistent with the ionization (i) (see Scheme I) of **1** to afford a propane-1-diazonium ion pair (a) that has a sufficient lifetime to become solvent separated (v) from the $^{16}OH^-$ gegenion, prior to any significant product formation. Ionization of **1** to a nitrogen-separated ion pair (b), by either a concerted (ii) or two-step process (i + iii), would yield [^{16}O]propanol from capture of the proximate $^{16}OH^-$ counterion by the highly reactive primary cation. It is also unlikely that free cations (e) are important in aqueous solution because of the strong stabilizing effect of solvation.[22,23]

A bimolecular backside displacement (xix) by solvent on diazonium intermediates a, d, g, and/or h could yield 1-Pr^{18}OH, and such a concerted process has been suggested to account, in part, for the 33% net inversion reported for the [1-^{2}H]-1-butyl

(19) Moss, R. A.; Landon, M. *J. Am. Chem. Soc.* **1970**, *92*, 5755–5756.

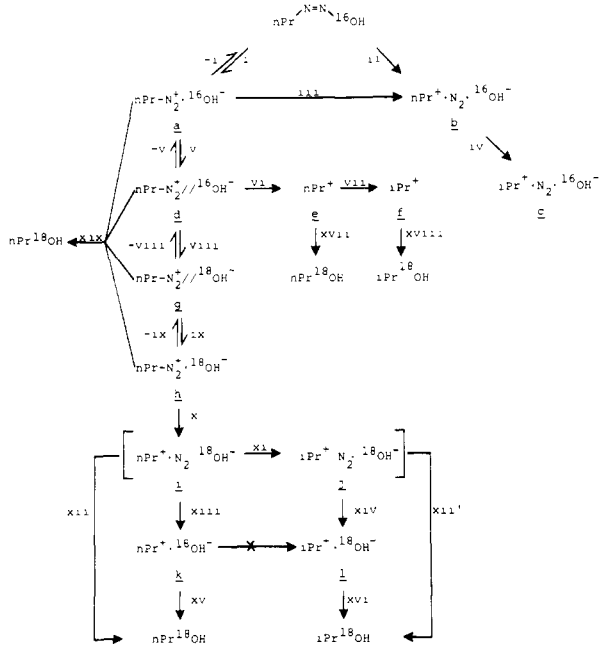
(20) The following nomenclature is used: external product results from attack by solvent or nucleophile dissolved in solvent on carbocation, no mechanistic or stereochemical implications are involved; internal product results from reaction of carbocation and anion within a nitrogen-separated or "regular" ion pair; exchange product contains counteranion derived from solvent; conservation product contains counteranion that was in the original alkane diazotic acid intermediate.

(21) Huisgen, R.; Rüchardt, C. *Justus Liebigs Ann. Chem.* **1956**, *601*, 1–18.

(22) For review, see: Bethell, D.; Gold, V. "Carbonium Ions An Introduction"; Academic Press: New York, 1967; pp 139–148. Bethell, D. In "Reactive Intermediates"; Jones, M., Jr.; Moss, R. A., Eds.; Wiley-Interscience: New York, 1978; Vol. 1; pp 131–135.

(23) Other evidence minimizing the significance of free carbonium ions may be found in: White, E. H.; Stuber, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2168–2170. Reference 9a.

Scheme I. Proposed Mechanistic Pathways for Conversion of Propane-1-diazotic Acid to Products



acetate formed during the deamination of optically active [1-^{2}H]-1-aminobutane (**10**) in glacial acetic acid.[24,25] However, the results in Table II show that the ratio of 1- to 2-propyl azide is impervious to a >100-fold increase in added sodium azide. Nucleophilic displacement on a diazonium ion intermediate should decrease the amount of rearrangement, since 2-propyl azide cannot be derived directly from a, d, g, or h, as rearrangement requires C–N bond breaking.[26] The failure of the highly nucleophilic azide ion to alter the propyl azide ratio implies that there is no concerted bimolecular interception of a diazonium ion species prior to isomerization.[27,28]

The ratio of alkyl azide to alcohol products is consistent with $[PrN_3]/[PrOH] = k_N[N_3^-]/k_H[H_2O]$, which is plotted as log ($[RN_3]/[ROH]$ vs. log ($[N_3^-]/[H_2O]$) in Figure 1. The small k_N/k_H ratios (Figure 1) for both primary and secondary product formation are not consistent with a preassociation mechanism[29] and hence are further evidence against a bimolecular process.[30] The k_N/k_H values are indicative of nonselective reactions occurring at near encounter-limited rates.[31-33]

The formation of intermediate i–j is consistent with the extensive rearrangement uniquely observed in deaminative reactions[9a,34,35] and the constancy of the small k_N/k_H ratio over a >100-fold increase in $[N_3^-]$. Streitweiser and Schaeffer have interpreted the deamination of optically active **10** in HOAc to yield net inverted 1-butyl acetate from a combination of backside displacement on the butane-1-diazonium ion yielding inverted product and solvolysis of a symmetrically solvated carbonium ion to give racemized acetate.[24] We would argue that after rearrangement, at the i–j stage, product stereochemistry is controlled at the ion pair level (k and l) after N_2 extrusion,[36] since the stereochemistry of 1-butyl products afforded by the ionization of [1-^{2}H]-1-butyl *p*-nitrobenzoate and the deamination of **10** are essentially the same, although in the former reaction no isomerization is observed.[24] A similar argument is detailed below for the reactions of optically active 1-phenylethanediazotic acid.

Basic Hydrolysis. The results of the hydrolysis of **5** under highly basic conditions (Table I, entry 6) require a transition state that maintains the presence of the original $^{16}OH^-$ counterion and yields the same extent of conservative return in both isomeric alcohols.[37] Thus, product formation cannot involve a, since rearrangement must come after C–N bond cleavage. Again the logical intermediate is a nitrogen-separated ion pair (b, c, Scheme I). As Southam and Whiting have stated, the preference of concerted path (ii, Scheme I) over the two-step path (i + iii) involves the "wielding of Ockam's Razor",[10] although it is obscure why process ii would be viable only under basic conditions. In any event, the integrity of a, which is evidenced by the failure of appreciable product to be formed by the processes that dominate in neutral medium (v → xii), must somehow be related to the basicity of the hydrolysis medium. Clearly the nucleophilicity of the solvent is not important, since the amount of exchange solvolysis is decreased under the more nucleophilic conditions.

The Coulombic attraction that holds species a or b together is moderated by the spatial separation effected by the intervening N_2. This charge separation has been suggested to account for the "hotness" (vibrational excitation) of the carbonium ions associated with alkanediazotic acid intermediates.[9a,35] H bonding and proton transfer from $[^{18}O]H_2O$ solvent to the $^{16}OH^-$ counterion in a will decrease the electrostatic attraction between the ions in a affording solvent separated d and g, the latter in equilibrium with tight ion pair h. Under strongly basic conditions H bonding and proton transfer will be retarded to the point that C–N bond breaking (iii) is able to successfully compete with process v. The effect of proton transfer on the degree of internal capture was first pointed out by White et al. to explain why the thermolysis in dioxane of *N*-nitroso-3,5-dinitrobenzamide in the presence of benzoic acid affords only 3,5-dinitrobenzoate esters.[38] However, when *N*-secbutyl-*N*-nitrosobenzamide is decomposed in the presence of 3,5-dinitrobenzoic acid, the yield of 3,5-dinitrobenzoate ester was 50% of the benzoate yield. The detection

(24) Streitweiser, A., Jr.; Schaeffer, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 2888–2893.

(25) No attempt was made to analyze for butanol conservation products in this study.

(26) In our mechanistic discussions cyclopropane intermediates have not been considered because of their minor role in product formation. (For review, see: Collins, C. J. *Chem. Rev.* **1969**, *69*, 543–549. Saunders, M.; Vogel, P.; Hagen, E. L.; Rosenfield, J. *Acc. Chem. Res.* **1973**, *6*, 53–59.)

(27) As pointed out by Kemp and Casey (Kemp, D. S.; Casey, M. L. *J. Am. Chem. Soc.* **1973**, *95*, 6670–6680) the use of rate constants to demonstrate selectively (azide vs. water) becomes moot as the rate of reaction of carbonium ions with nucleophiles approaches diffusion control. However, this does not alter the argument that 2-propyl azide does not arise via bimolecular attack on an intact diazonium ion.

(28) It has been suggested that in primary systems all products, including those resulting from rearrangement, arise from primary diazonium ions and that free primary carbonium ions are completely bypassed.[9c] It is important to note that the author defines a free carbonium ion as one "that displays no memory with respect to antecedents and products". This rigorous definition places diazonium ions, nitrogen-separated ion pairs, ion pairs, or any related asymmetric carbocation species in the same category. Thus, Friedman's treatment of amine diazotizations and related reactions does not conflict with the involvement of ion-pair intermediates, as proposed above, and in fact agrees with our suggestion that free cations are not formed in the deamination of **10**.[24]

(29) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161–169. Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689–4691; 4691–4692.

(30) In this case an enforced bimolecular process[29] could result from the reaction of carbonium ions with nucleophiles proceeding at rates greater than the rate of diffusion.

(31) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 751–762.

(32) Sneen, R. A.; Carter, J. V.; Kay, P. S. *J. Am. Chem. Soc.* **1966**, *88*, 2594–2595.

(33) Harris, J. M.; Raber, D. J.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1970**, *92*, 5729–5731.

(34) Rearrangement of 1-propyl tosylate in refluxing HOAc after an extended period of time yields only ~3% of 2-propyl acetate.[21]

(35) The adjectives "hot" (Ciereszko, L. S.; Burr, J. G., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 5431–5433. Roberts, J. D.; Lee, C. C.; Saunders, W. H., Jr. *Ibid.* **1954**, *76*, 4501–4510. Semenow, D.; Shih, C. H.; Young, W. G. *Ibid.* *80*, 5472–5475), "nonsolvated" (Crams, D. J.; McCarty, J. E. *Ibid.* **1957**, *79*, 2866–2875), "vibrationally excited" (Corey, E. J.; Casanova, J., Jr.; Vatakencherry, P. A.; Winter, R. *Ibid.* **1963**, *85*, 169–173), etc. have been used to describe the unique chemistry observed in deamination-type reactions.

(36) This suggestion is implicit in the review of White and Woodcock[9a] and the recent study of Cohen et al.[43]

(37) It could be argued that if the isomeric propyl carbocations react at diffusion-controlled rates, then the percent solvent incorporation in isomeric products will necessarily be the same.[27] However, in the reaction of **9** there is a difference in the degree of conservative return, which indicates that the two isomeric cations show different selectivity for water vs. benzoate.[21] The difference between k_N/k_H for 1- and 2-propyl compounds is further evidence that small selectivity differences could be observed if they existed.

(38) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6014–6022.

of some internal return product (benzoate ester) in the thermolysis of **9** in DMF/H_2O[21] is also consistent with sluggish proton transfer from the weak acid (H_2O solvent) to the benzoate counterion.[39] Moss et al. have also noted a greater integrity of nitrogen-separated ion pairs derived from octane-2-diazotic acids in basic as compared to acidic solution.[14,40] The ~10-fold decrease in the yield of total alkyl azide in base (Table II) is also consistent with the cohesiveness of species b in the basic medium that prevents azide from replacing $^{16}OH^-$ in species b and c.[41] Although there is a decrease in azide products, the isomeric azide ratio is essentially unaltered,[42] which again indicates that all product formation occurs after rearrangement and that a concerted displacement by nucleophile is not involved. As suggested for the neutral reactions, it is likely that b and c collapse by nitrogen extrusion to the corresponding counterion pairs prior to product formation. The "tightness" or "looseness" of these ion pairs will be affected by the solvent and pH[43] in much the same fashion as will b and c.

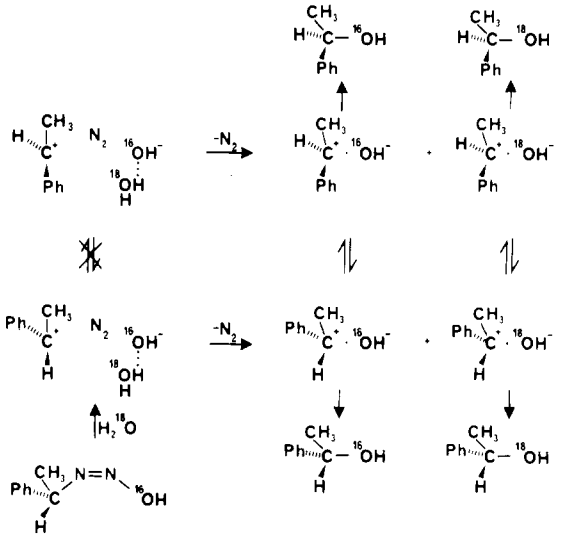
Hydrolysis of the 1-Phenylethane Series. There are two basic differences between the hydrolysis of **6** and ethanolysis of **8**: the yield and the stereochemistry of products derived from conservation of the original anion (^{16}OH or OH). There also exists one similarity: the stereochemistry of the exchange product.

In regard to the increased yield of conservation product from **8**, the integrity of nitrogen-separated ion pair was demonstrated to be enhanced in an environment that retards proton transfer from solvent to the OH^- counterion, i.e., very basic aqueous or nonhydrolylic media.[14,40] The effect of this increased integrity has been discussed above.

Alkanediazonium ions were suggested to be central in the chemistry of primary alkanediazotic acids.[10,21,24] Prime evidence for this conclusion is the failure to find significant amounts of product resulting from conservation of the original counteranion. In comparing the results in Table III and those for the propyl analogue (Table I), the similarity in the degree of conservative return in basic medium is rather striking (29% and 34%, respectively), despite the difference in the alkyl group structure (1-phenylethyl vs. 1-propyl). Another example of the insensitivity of the exchange/conservation partitioning to the structure of the alkyl group is the hydrolysis of potassium octane-2-diazotate in $[^{18}O]H_2O$.[14,40] The 27% conservation product formed is within experimental error of the values for the propyl and 1-phenylethyl studies.

Although the rapid exchange of solvent into the counteranion position at near neutral conditions prior to C–N bond ionization would account for the low yield of ^{16}O alcohol from **6**, the stereochemistry of conservative counterion capture would still be expected to yield predominantly retention product via internal "frontside"[44,45] capture, as is the case for **8**. However, the stereochemistry of conservation product from **6** and **8** is 24% and 73% net retention, respectively. The overall stereochemistry of alcohol products from **6** is 20% net inversion, as compared to ~1% net inversion of alcohol and ether products from **8**. Clearly the process that would formally be considered an internal "frontside" attack (Scheme II) by counterion or solvent decreases at near neutral pH. Alternatively, the situation can reflect an increase in external "backside" attack by counterion or solvent; however, this process should prevail in the more nucleophilic environment (EtO^- vs. H_2O),[46] and this is not the case (Table III). Analogously, addition of NaOAc to the deamination reaction of *trans*, *trans*-2-decalylamine in HOAc–H_2O does not affect the ratio of acetate to alcohol product or change the stereochemistry of the products.[43,47] Also the yield and stereochemistry of 2-octanol formed from the hydrolysis of optically active octane-2-diazotate were not affected by adding substantial amounts of NaN_3, and the octyl azide yield reflected a statistical reaction.[14,40] Therefore an increase in "backside" displacement by *external* nucleophile in the reaction of **6** can be ruled out.[48]

Scheme II. Proposed Pathway for the Hydrolysis of (*S*)-(−)-Phenylethane Diazotic Acid[a]



[a] The ratio of $^{16}O/^{18}O$ products is dependent on pH. For simplicity, attack by solvent outside of nitrogen-separated ion pair has been omitted.

The remaining alternative is that there is a decrease in retention from internal attack in neutral medium. Internal attack can yield retention product by "frontside" collapse or inversion product by cation rotation followed by "frontside" attack (Scheme II). These retention and inversion processes are competitive, in that as the lifetime of R^+ increases (either within a nitrogen-separated ion pair or ion pair) cation rotation will increase to the extent that any internal attack will afford racemized products. The influence of solvent on this intramolecular mode of inversion and retention has been discussed by Cohen et al. in their studies of the deamination of *trans,trans*- and *trans,cis*-1-decalylamines in water, dioxane, and sulfolane, each containing various amounts of HOAc.[43] Intramolecular inversion is thought to be accelerated in proton-donating solvents as a result of ion pair unpairing. In the case of decalylamines, this equilibrium results in preferential formation of the thermodynamically more stable equatorial product. In the 1-phenylethyl series, the enantiomeric alcohols are energetically equivalent, and thus an increase in ion pair unpairing at near neutral pH will direct the stereochemistry of internal return product toward racemization. Accordingly, the environment that results in the rapid exchange of original counteranion in the hydrolysis of **6** is also responsible for a decrease in the retention stereochemistry normally associated with internal return. A priori it might be anticipated that the greater dielectric constant of H_2O relative to EtOH may also increase the extent

(39) The bidentate nature of the benzoate counterion may account for the difference in yields of 1- and 2-propyl benzoate conservation products from the thermolysis of **9** reported by Huisgen and Ruchardt.[21]

(40) (a) Moss, R. A.; Reger, D. W.; Emery, E. M. *J. Am. Chem. Soc.* **1970**, *92*, 1366–1369. (b) Moss, R. A.; Fritz, A. W.; Emery, E. M. *J. Org. Chem.* **1971**, *36*, 3881–3885.

(41) It has been previously reported that both the yield and stereochemistry of 2-octanol formed in the hydrolysis of octane-2-diazotate under basic conditions are unaffected by carrying out the reaction in 7 M NaN_3 and that the yield of 2-octyl azide was only 10% of the alcohol yield.[14]

(42) The small yields of propyl azide make it impossible to detect slight changes in the azide ratio.

(43) Cohen, T.; Botelho, A. D.; Jankowski, E. J. *J. Org. Chem.* **1980**, *45*, 2839–2847.

(44) To avoid ambiguity it is assumed that the anion is immobile and the face of the carbocation closest to the anion is the frontside. The stereochemistry of this process on the basis of starting material is ambiguous since cation rotation within the ion complex can cause frontside attack to yield retained as well as inverted stereochemistry.

(45) Frontside attack by solvent H bonded to the anion within the nitrogen-separated ion pair has been proposed.[14,38,40]

(46) (a) Bender, M. L.; Glasson, W. A. *J. Am. Chem. Soc.* **1959**, *81*, 1590–1597. (b) Jencks, W. P.; Gilchrist, M. *Ibid.* **1968**, *90*, 2622–2637.

(47) Cohen et al.[43] specifically use simple ion pair species in their discussion but acknowledge that "an array of nitrogen-separated ion pairs" may be as likely.

(48) Other evidence against a displacement reaction in the 1-phenylethyl series can be found (ref. 38 and: Huisgen, R.; Rüchardt, C. *Justus Liebigs Ann. Chem.* **1956**, *601*, 21–39).

of ion pair unpairing. However, the stereochemical outcome resulting from the internal-return pathway was not significantly altered by nonpolar solvent when **8** was treated with triethyloxonium tetrafluoroborate in CH_2Cl_2.[19]

A remaining question is to determine which species—a nitrogen-separated or a simple ion pair—is responsible for the reaction's stereochemistry. Moss, in a series of elegant papers on the solvolytic chemistry of *sec*-alkanediazotates, has argued that nitrogen-separated ion pairs play the key role in the stereochemistry of diazotic acid reactions.[14,40,49] Although the significance of this species cannot be unequivocally ruled out, the solvolysis of 1-phenylethyl chloride in water affords 1-phenylethanol with 17.5% net inversion,[50] a value extremely close to that in Table I for the hydrolysis of **6**. As discussed above, even with a primary alkyl group, i.e., optically active **10**, the products from deamination of the amine and solvolysis of the corresponding benzoate ester show virtually the same stereochemistry.[24] Again, we suggest that stereochemical control is exerted after nitrogen extrusion at the ion pair level.

A final point may be made as to whether the ionization of 1-phenylethanediazotic acid to a nitrogen-separated ion pair is a two-step[51] or concerted process.[10] The rapid exchange of ^{18}O label at near neutral pH implies a nonconcerted process, despite the stability of the 1-phenylethyl cation. In basic media the rate of C–N and N–O bond cleavage may be fortuitously similar, as evidenced by the yield of conservation product. However, this is not formally a concerted reaction that does not proceed via an intermediate with a potential energy well.[52,53]

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Registry No. 1, 89017-33-4; **2**, 89017-34-5; **3**, 53198-41-7; **4**, 19935-85-4; **5**, 87549-57-3; **6**, 33290-13-0; **7**, 107-10-8; **8**, 30237-04-8; ^{18}O, 14797-71-8; N_3^-, 14343-69-2; NaN_3, 26628-22-8; (+)-PhC(OCH_3)(CF_3)C(O)Cl, 20445-33-4; (*R,R*)-PhC(OCH_3)(CF_3)C(O)OCH(CH_3)Ph, 39532-30-4; (*R,S*)-PhC(OCH_3)(CF_3)C(O)OCH(CH_3)Ph, 61184-95-0; (*R,R*)-PhC(OCH_3)(CF_3)C(O)^{18}OCH(CH_3)Ph, 89017-35-6; (*R,S*)-PhC(OCH_3)(CF_3)C(O)^{18}OCH(CH_3)Ph, 89017-36-7; 1-phenylethanol, 98-85-1; nitrosylpentacyanoferrate(III), 14636-58-9; 1-propanol-^{18}O, 89017-37-8; 2-propanol-^{18}O, 73569-91-2.

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(51) White, E. H.; Field, K. W. *J. Am. Chem. Soc.* **1975**, *97*, 2148–2153.
(52) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274–277.
(53) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161–169.

Reactivity of Free Cyclopentadienone in Cycloaddition Reactions

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Abstract: Reactions of polymer-generated free cyclopentadienone with several dienes and dienophiles are studied, giving yields and rate constants for each one. A new method for lifetime measurements of transient species is also described, showing its application to the elusive ketone.

Studies of cyclopentadienone (II) have been recently carried out by our group using the three-phase test.[1] The elusive ketone was generated from an insoluble polymer-bound precursor (I) and trapped by a second solid phase by using Diels–Alder reactions (Scheme I).

Thus, the ability of cyclopentadienone to react as a diene or as a dienophile in Diels–Alder reactions has been demonstrated. Consequently, the next step in the study of the reactivity of cyclopentadienone was to know how the nature and structure of trapping agents could influence the rate and yield of their pericyclic reactions with the ketone. It was also interesting to study the lifetime of free cyclopentadienone in the absence of any trapping agent.

Results and Discussion

Radioassay provides a convenient method for monitoring reactions on solid phases. Thus, cyclobutadiene[2] and metaphosphate[3] transfers were determined by using radioassay procedures. In this way, tritiation of polymeric precursor I was accomplished as shown in Scheme II. According to Korach,[4] 1,3-cyclopentadiene gave the monoepoxide VI, from which diol VII was formed by reaction with tritiated water. Dehydration of VII, followed by a keto–enol tautomerism, gave tritiated cyclopentenone which was brominated with NBS and then bounded to the solid phase as described.[1]

Radioassay of solid phase I indicated its functionalization degree; 4.5 mequiv/g of the cyclopentenone moiety was found to be polymer bound.

Dienophiles. Besides the previously[1] used polymeric monoester of acetylenedicarboxylic acid (IV), four solid-phase reagents have been tested by us as dienophilic trapping agents for cyclopentadienone: the polymeric monoester of maleic acid (VIII), the N-resin maleimide (IX), the polymeric crotonic ester (X), and the polymeric ester of 4-carboxy-2′,4′-dihydroxyazobenzene (XI).

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