Table II. Product Distribution in the Reaction of 1-Cyanonaphthalene with Phenylacetic Acid Derivatives in Acetonitrile

Carboxylic acid	% chemical yield[a] 3	4	6	Others
p-Methoxyphenylacetic acid (2a)	15	10	28	18 of **5**
m-Methoxyphenylacetic acid (2b)	65	16	32	
Phenoxyacetic acid (2c)	10	6.5	5	14 of **7**

[a] Chemical yield of isolated material relative to consumed starting material.

solvent cage to give, after hydrogen abstraction from a suitable hydrogen source, the various reduction products. If, on the other hand, the radical cation does not contain an acidic proton (quencher **2f**) proton transfer is unfavorable and consequently chemical transformations sluggish. In benzene the complex formed between photoexcited cyanonaphthalene **1** and the quencher cannot decay to ion pairs. Proton transfer and subsequent chemical transformations become thus unfavorable, while complex emission appears as significant deactivation mode.

The structure of the photoproducts obtained from irradiation of **1** with **2a–d** in acetonitrile and the product distribution as function of the acids used (Table II) are compatible with the suggested reaction pathway. 1-Cyanonaphthalene reacts at the substituted ring as expected for a process in which the naphthalene acts as electron acceptor. Deuterium incorporation in the reduction product **3** and addition product **4d** upon irradiation of cyanonaphthalene **1** in the presence of *p*-methoxyphenylacetic acid-*d* (**2d**) establishes that proton transfer from the acid to the cyanonaphthalene (**1**) is involved in the photoreaction. Deuterium incorporation in the recovered starting material indicates that the reduction product **3** is formed by disproportionation of 1-cyano-4-hydronaphthyl radical to cyanonaphthalene **1** and 1-cyano-1,4-dihydronaphthalene (**3**). The ratio between reductive alkylation and reduction products varies with the nucleophilicity of the benzyl radical involved; the more nucleophilic *p*-methoxybenzyl radical reacts faster with the 1-cyano-4-hydronaphthyl radical than the less nucleophilic *m*-methoxybenzyl radical, resulting in a more favorable ratio of reductive alkylation vs. reduction product.

References and Notes

(1) A. Weller, *Pure Appl. Chem.*, **6**, 115 (1968), and references therein.
(2) H. Beens, H. Knibbe, and A. Weller, *J. Chem. Phys.*, **47**, 1183 (1967).
(3) (K. H. Grellmann, A. R. Watkins, and A. Weller, *J. Phys. Chem.*, **76**, 469 (1972).
(4) M. Ottolenghi, *Acc. Chem. Res.*, **6**, 153 (1973).
(5) W. R. Ware, D. Watt, and J. D. Holmes, *J. Am. Chem. Soc.*, **96**, 7853 (1974); W. R. Ware, J. D. Holmes, and D. R. Arnold, *ibid.*, **96**, 7861 (1974).
(6) A. Lablache-Combier, *Bull. Soc. Chim. Fr.*, 4791 (1971), and references therein.
(7) R. M. Bowman, T. R. Chamberlain, C. W. Huang, and J. J. McCullough, *J. Am. Chem. Soc.*, **96**, 7369 (1974); K. Mizuno, C. Pac, and H. Sakurai, *J. Am. Chem. Soc.*, **96**, 2993 (1974).
(8) (a) C. Pac and H. Sakurai, *Tetrahedron Lett.*, 3829 (1969); (b) N. C. Yang and J. Libman, *J. Am. Chem. Soc.*, **95**, 5783 (1973); (c) J. A. Barltropp, *Pure Appl. Chem.*, **33**, 179 (1973); (d) J. J. McCullough, W. S. Wu, and C. W. Huang, *J. Chem. Soc., Perkin Trans 2*, 370 (1972).
(9) I. E. Kochevar and P. J. Wagner, *J. Am. Chem. Soc.*, **94**, 3859 (1972); P. J. Wagner and R. A. Leavitt, *ibid.*, **95**, 3669 (1973).
(10) G. H. Parsons, Jr., and S. G. Cohen, *J. Am. Chem. Soc.*, **96**, 2948 (1974); C. H. Parsons, Jr., L. T. Mendelsohn, and S. G. Cohen, *J. Am. Chem. Soc.*, **96**, 6643 (1974).
(11) R. S. Davidson and P. R. Steiner, *J. Chem. Soc C*, 1682 (1971).
(12) R. S. Davidson and S. P. Orton, *J. Chem. Soc., Chem. Commun.*, 209 (1974).
(13) G. H. Coleman, W. H. Holst, and R. D. Maxwell, *J. Am. Chem. Soc.*, **58**, 2310 (1936).
(14) A. C. Cope, *J. Am. Chem. Soc.*, **57**, 572 (1935).
(15) The quenching rate constants in acetonitrile are smaller than the diffusion rate constant, as expected for systems for which the free enthalpy of electron transfer is larger than −10 kcal/mol; D. Rehn and A. Weller, *Isr. J. Chem.*, **8**, 259 (1970).
(16) A kinetic deuterium isotope effect has been observed in the photoaddition of secondary amines to anthracene, see ref 8b.

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Stereochemistry at the Origin of 1,2-Hydride Shifts. Evidence for Micellar Control in Nitrous Acid Deamination Reactions

Sir:

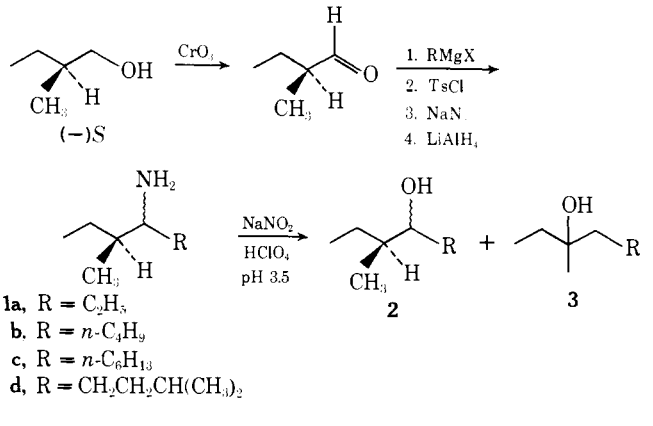
Wagner–Meerwein rearrangements of many chiral molecules afford optically active compounds rather than the racemic products expected from the intermediacy of trigonal planar carbocations. Obvious mechanisms for the conservation of chirality are: (i) formation of bridged, chiral cations; (ii) asymmetric solvation, including the formation of ion pairs. The response of a specific rearrangement to variations of the reaction medium may serve to distinguish between these alternatives. Moss[1] has shown that the stereochemistry of the nitrous acid deamination of 2-aminooctane is profoundly affected by aggregation of the alkylammonium ions in micelles. We report here on related observations concerning the stereochemistry at the origin of deaminatively induced 1,2-hydride shifts.

A series of 4-amino-3-methylalkanes (**1**) was prepared according to Scheme I. These amines were mixtures of 3*S*,4*S* and 3*S*,4*R* diastereoisomers which could not be separated. Nitrous acid deamination in aqueous perchloric acid (pH 3.5) afforded 55–60% alkenes, 15–20% 3-methyl-4-alkanols (by direct displacement), and 20–30% 3-methyl-3-alkanols (by 1,2-H shift) as the major products. Alcohols resulting from alkyl shifts were identified in minor quantities.[2]

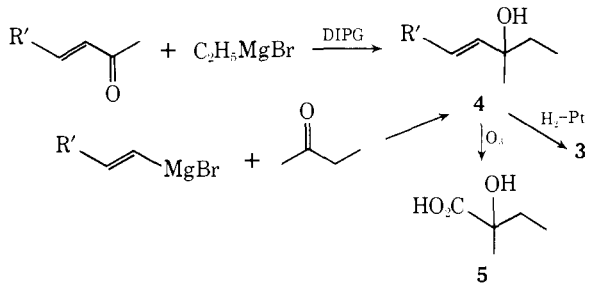
The absolute configuration of the tertiary alcohols **3** was established by correlation with 2-hydroxy-2-methylbutyric acid[3] (Scheme II). The unsaturated alcohols **4** were prepared optically active by Grignard reactions in the presence of 1,2,5,6-diisopropylidene-D-glucofuranose (DIPG).[4] Catalytic hydrogenation of **4** afforded **3** whereas ozonolysis yielded **5**. The alcohol **3d** had previously been correlated with linalool.[5] The configuration of **3a–d** is uniformly (+)*R*.

When deaminations of **1a–c** were run in 1 *M* solution, the stereochemistry of **3** was found to depend on the length

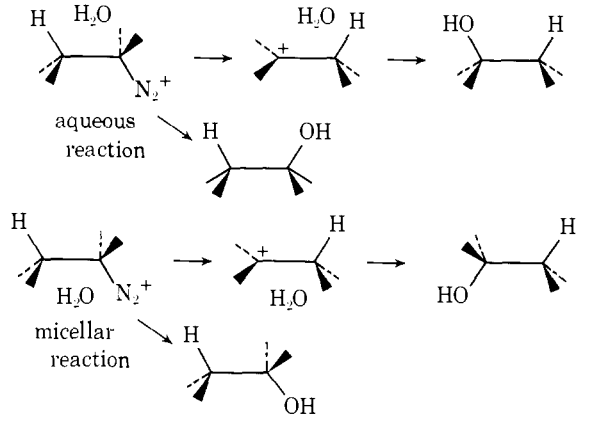
Scheme I



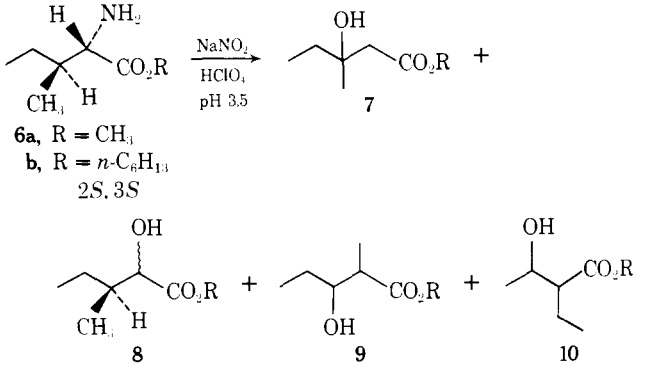
Scheme II



Scheme III



Scheme IV



of the alkyl chain. **3a** was formed with 3.6% retention, **3b** with 2.0% retention, and **3c** with 2.1% inversion. Micellar control became evident when **1a** and **1d** were deaminated at various concentrations.[6] Retention at C-3 predominates in dilute solution. Above the critical micelle concentration (cmc), however, the stereochemistry moves toward racemization and crosses over to ca. 7% inversion. Although the cmc's of **1a** (0.35 M) and **1d** (0.1 M)[7] differ substantially, the stereochemical results come very close if plotted against $F_m = (c_i - \text{cmc})/c_i$, the initial extent of micellation, as suggested by Moss[1] (Figure 1). The results obtained for the direct displacement at 2-octyldiazonium ions[1] have been included in Figure 1. Obviously, the transformation **1** → **3** is subject to a micellar effect of similar magnitude, but of opposite sign.

Both the displacement of the diazonium group studied by Moss[1] and the displacement of migrating hydrogen reported here are controlled by the preferential mode of solvent approach. If we consider an antiperiplanar conformation of the diazonium ion as a prerequisite of hydride shifts,[8] inverting solvolysis and retention at the migration origin are complementary processes. On the other hand, conditions favoring frontside return to the diazonium site will also favor inversion at the neighboring carbon (Scheme III). Incorporation of alkyldiazonium ions in micelles inhibits its backside approach of the solvent and enforces frontside return. We refer to the model of micellar effects which Moss has developed in some detail.[1]

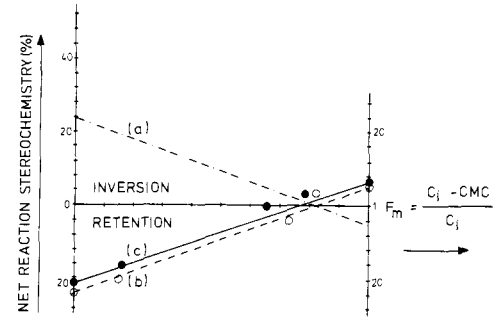


Figure 1. The stereochemical course of the 2-aminooctane → 2-octanol (a),[1] **1a** → **3a** (b), and **1d** → **3d** (c) transformations, with 1.6 M $NaNO_2$, 25°, $HClO_4$ (pH 3.5-4), vs. F_m.

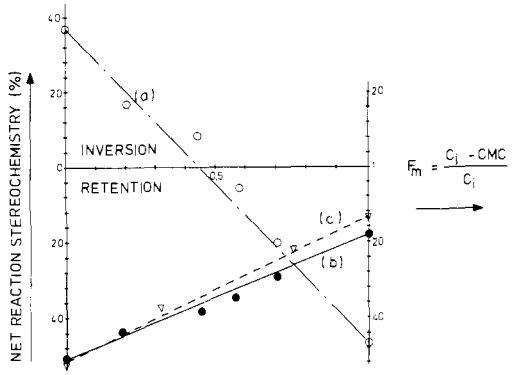


Figure 2. The stereochemical course of the transformations **6a** → **8a** (a), **6a** → **7a** (b), and **6b** → **7b** (c) vs. F_m.

The deamination of esters of isoleucine (**6**) enabled us to analyze the competing processes of Scheme III with a single compound. 1,2-Hydride shift to give methyl 3-hydroxy-3-methylvalerate (**7a**) (42%) was the major reaction in the deamination of **6a**, followed by elimination (40%). Direct displacement with formation of **8a** occurred to only 2.1% whereas **9a** (produced by methyl migration) and **10a** (the result of an ethyl shift) amounted to 1.6 and 6.3%, respectively. The absolute configuration of **7a** was established as (−)R by chain extension of 2-hydroxy-2-methylbutyric acid (**5**).

The stereochemical results shown in Figure 2 confirm the correlation between direct displacement and hydride shift postulated above. The concentration range in which these stereochemical changes occur is strongly affected by the ester group. The cmc's of **6a** (0.40 M) and **6b** (0.048 M) differ by a factor of ca. 10; nevertheless the stereochemical data of the **6a** → **7a** and **6b** → **7b** transformations nearly coincide on the F_m scale. As compared to the deamination of amines (Figure 1), all isoleucine data (Figure 2) display a shift toward retention of configuration. This effect may be due to the presence of the neighboring ester group and deserves further investigation.

The micellar control of stereochemistry at the origin of 1,2-hydride shifts suggests that the conservation of chirality at such centers is due to asymmetric solvation.[9] Hydrogen-bridged ions, if involved, do not play a product-determining role. These conclusions are limited so far to tertiary → secondary shifts and may not apply to less stable carbocations. Research on secondary → primary shifts is in progress in our laboratory.

References and Notes

(1) R. A. Moss, C. J. Talkowski, D. W. Reger, and C. E. Powell, *J. Am. Chem. Soc.*, **95**, 5215 (1973).

(2) Product ratios are given in the Ph.D. Theses of H. J. Ratajczak and G. Rauleder, Ruhr-Universität Bochum, 1975. The extent of hydride shift (and of other rearrangements) increased with concentration (F_m) at the expense of direct displacement. E.g., with **1d** the extreme values (percent of alcohol fraction) were 52.4 → 36.8% **2d** and 38.7 → 52.5% **3d** (F_m 0 → 1).

(3) The configuration of (−)-**5** is *R*: B. W. Christensen and A. Kjaer, *Acta Chem. Scand.*, **16**, 2466 (1962).

(4) T. D. Inch, G. J. Lewis, G. L. Sainsbury, and D. J. Sellers, *Tetrahedron Lett.*, 3657 (1969).

(5) Y. R. Naves, *Helv. Chim. Acta*, **30**, 278 (1974). For the configuration of linalool, cf. R. H. Cornforth, J. W. Cornforth, and V. Prelog, *Justus Liebigs Ann. Chem.*, **634**, 197 (1960); G. Ohloff and E. Klein, *Tetrahedron*, **18**, 37 (1962).

(6) The deamination of **1d** has been studied previously: W. Kirmse and H. Arold, *Chem. Ber.*, **104**, 1800 (1971). Although the results are in qualitative agreement, the previously reported rotations have not been reproduced in the present work and may have been due to small impurities of high specific rotation. $[\alpha]^{20}D$ of **3d** is only 0.78°. In the present work, optical purities have been estimated both by polarimetry and by NMR in the presence of tris(3-(trifluoromethylhydromethylene)-*d*-camphorato)europium(III) = Optishift II. Satisfactory agreement was reached with all samples, but only after multiple GLPC in the case of **3d**.

(7) The cmc's given refer to deamination conditions;[1] without added sodium salts the cmc of **1a** is 0.72 *M*, and that of **1d** 0.25 *M*.

(8) Hydride shifts induced by deamination proceed with predominant inversion at the migration terminus: W. Kirmse, H. Arold, and B. Kornrumpf, *Chem. Ber.*, **104**, 1783 (1971); W. Kirmse and D. Krause, *ibid.*, in press.

(9) Counterion effects are also in accord with the model of micellar control. The stereochemistry of 7 was independent of concentration (49 ± 1% retention) when chloride was the counterion in the deamination of **6a,b**.

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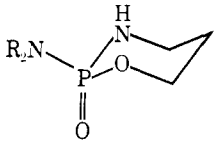
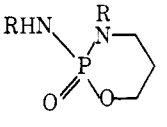
Molecular Structure of the Carcinostat Isophosphamide

Sir:

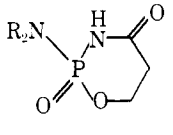
Among the diverse properties of Cyclophosphamide (**1**) (Cytoxan, Endoxan) are its potent carcinostatic action in the treatment of human cancers and its strong immunosuppressive properties in tissue transplants.[1]



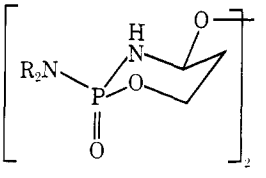
1



2



3



4

R = CH_2CH_2Cl

Isophosphamide (**2**) (Ifosfamide) an isomer of **1** also shows considerable promise in these respects,[2] and similar metabolic pathways have been found.[3]

Recent X-ray studies on **1**[4] and two of its metabolites, **3**[5] and **4**,[6] have shown that the P=O group is axial in each case although the ring is substantially buckled away from a chair form in **3** owing to the presence of the sp^2 carbonyl carbon. Numerous experimental results have been summarized which show that in solution some phosphorus substituents prefer the axial position in 2-oxo-1,3,2-dioxaphosphorinanes (**5a**) while others tend to be equatorial (**5b**). Although the R group in trivalent analogs of **5** prefers the equatorial position in solution when R = Me_2N (**6a**),[7] it has come to our attention that the phosphorus substituent displays a greater tendency to be axial (**6b**) when it is Me,[8] PhNH,[9a] or *t*-BuNH.[9b] This observation has been ascribed

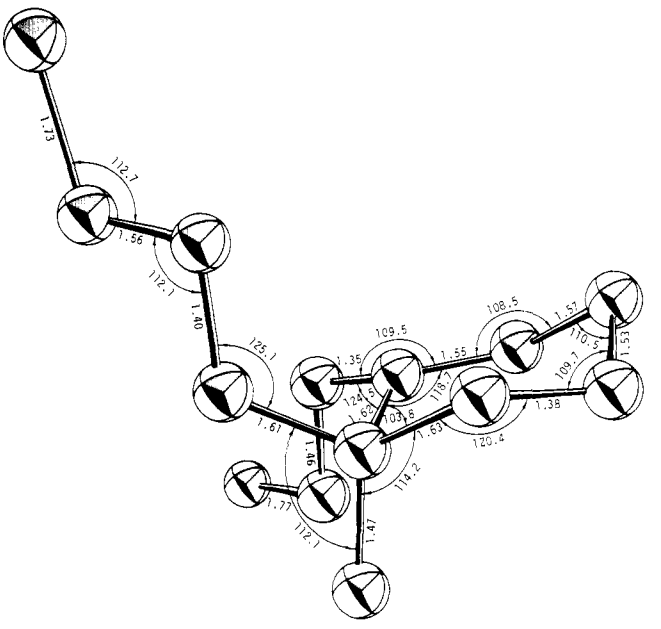
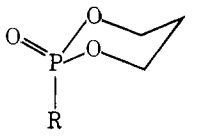
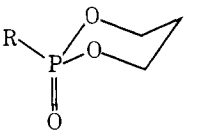


Figure 1. Isophosphamide.

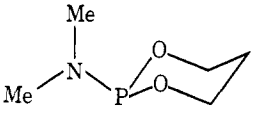


5a

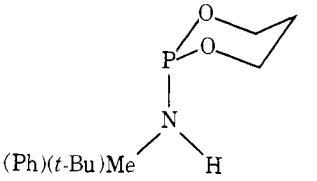


5b

R = H, OMe, halogen R = alkyl, Ph, dialkylamino



6a



6b

to the small steric requirements of an NH hydrogen under the ring coupled with the strong proclivity of the phosphorus lone pair to be equatorial.[7-10] Because the P=O group and the phosphorus lone pair in these ring systems prefer the equatorial position in the absence of steric effects of the R group,[7-10] it was of considerable interest to determine the orientation of the $ClCH_2CH_2NH$ group in Isophosphamide (**2**) since stereochemical inversion at phosphorus has been shown to be accompanied by distinct changes in chemical properties.[7]

Crystals of **2** were grown by slowly cooling a saturated boiling ether solution. A single crystal was selected for X-ray diffraction study and assigned to the orthorhombic space group P_{bca} after analysis of the Laue symmetry and the observed systematic absences. The unit cell parameters are a = 13.29 (1), b = 21.16 (1), and c = 8.78 (1) Å. Intensity data were collected on a four-circle diffractometer equipped with a scintillation counter. Positions of all nonhydrogen atoms were determined by a combination of Patterson analysis and subsequent electron density map calculation. Figure 1 shows a computer drawing of the molecular