2-Norbornanediazonium Ions Revisited

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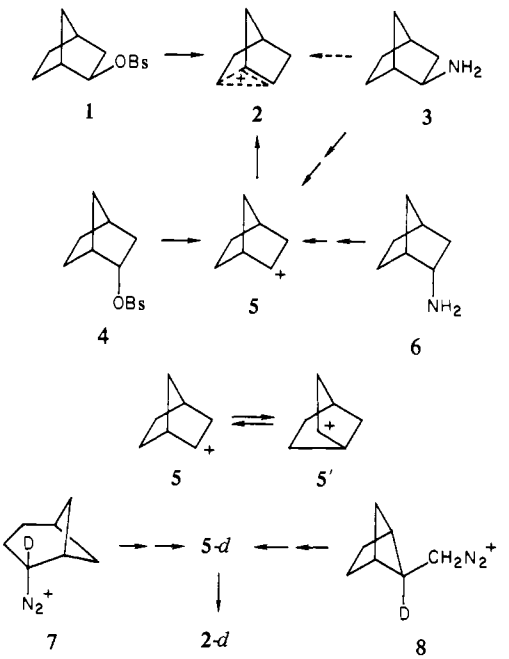
Abstract: The reactions of 2-norbornanediazonium ions have been reinvestigated with the aid of optically active and deuterium-labeled precursors. Enantiomeric purities were determined by direct VPC methods, and deuterium distributions by ^2H NMR spectroscopy. The product pattern is strongly affected by the polarity of the solvent. *exo*-Diazonium ions **13** in water yield racemic exo alcohol (≤0.1% endo). In carboxylic acids, the fraction of endo ester and the enantiomeric purity of the exo products increase with decreasing polarity of the solvent. *endo*-Diazonium ions **14** in water produce 10% of endo alcohol with full retention of configuration, and 90% of racemic exo alcohol. In carboxylic acids, the fraction of endo ester decreases with decreasing polarity of the solvent while the enantiomeric purity of the exo products increases. Our studies do not support a classical 2-norbornyl cation that undergoes endo attack and may be trapped prior to rearrangement. The formation of endo products is more reasonably attributed to competitive reactions (k_s, k_Δ) of the norbornanediazonium ions. Optically active exo products are typical of nonpolar solvents and originate most probably from unsymmetrical ion pairs. Model studies with optically active bicyclo[3.2.1]oct-3-en-2-amine (**36**) provide conclusive evidence that ion-pair collapse may lead to optically active products even in the case of delocalized achiral carbocations.

Acetolyses of both *exo*-2-norbornyl brosylate (**1**) and *endo*-2-norbornyl brosylate (**4**) produce exclusively *exo*-2-norbornyl acetate. The exo/endo rate ratio is 350. Furthermore, acetolysis of optically active **1** gave completely racemic *exo*-acetate, and **4** gave *exo*-acetate that was at least 93% racemic.[1,2] Winstein proposed that ionization of **1** was assisted by the C(1)–C(6) bonding electrons and led directly to the achiral bridged ion **2**. In the unassisted (or weakly solvent-assisted) solvolysis of **4**, the bridged ion **2** can be formed only after the rate-determining step. An alternative explanation was put forth by H. C. Brown: rapid equilibration of open ions, **5** ⇄ **5′**, combined with steric hindrance to endo departure of the leaving group and endo approach of a nucleophile.[3,4]

Nitrous acid deamination of *exo*- and *endo*-2-norbornylamine (**3** and **6**) in acetic acid, proceeding by way of the corresponding diazonium ions, gave results which are difficult to reconcile with either of these views.[5,6] The major features of Berson's more detailed study[6] are (1) formation of *endo*-2-norbornyl acetate (2% from **3**, 4.7% from **6**), (2) partial retention of optical activity in the *exo*-acetate (11% with **3**, 18% with **6**), and (3) little, if any, racemization in the *endo*-acetate from **6**. The authors conclude that the products cannot be derived solely from classical 2-norbornyl cations (**5** ⇄ **5′**). They propose a mechanism in which the open 2-norbornyl cation (**5**) is formed first and is captured competitively with its conversion to the bridged species **2** (Scheme I).

Scheme I



Originally, we had no reason to question these proposals. In fact, we have adduced strong evidence for the consecutive intervention of open and bridged ions in deaminatively induced Wagner–Meerwein rearrangements of acyclic systems.[7] Closer inspection, however, revealed some deficiencies of the proposed mechanism. Experimentally, we approached the 2-norbornyl cation by ring expansion routes from **7** and **8**.[8,9] Although neither of these reactions can lead directly to the bridged species **2**, we have not been able to trap the 2-norbornyl cation in an unsymmetrical form. Theoretically, it is difficult to envisage an activation barrier separating **5** from **2**. In acyclic compounds, the formation of a bridged ion is associated with a substantial relocation of nuclei and with an increase in strain. None of these arguments applies to the norbornyl case.

The alleged trapping of unsymmetrical 2-norbornyl cations has had some impact on the nonclassical ion controversy. Schleyer[4] admits that the deamination studies "provide strong evidence favoring the classical norbornyl cation. Other interpretations ... are possible. I hope that further investigations will provide decisive answers". Such investigations are also invited by advances in methodology. Bartlett[2] felt the need for "several moles of fully resolved norbornylamines ... and better VPC columns to separate substantial portions of all products". Today asymmetric synthesis offers convenient routes to optically active 2-norbornyl derivatives which avoid the resolution of racemates.[10–12] More importantly,

(1) Winstein, S.; Trifan, D. S. *J. Am. Chem. Soc.* **1949**, *71*, 2953; **1952**, *74*, 1147, 1154. Winstein, S.; Clippinger, E.; Howe, R.; Vogelfanger, E. *Ibid.* **1965**, *87*, 376.

(2) For reviews, see: Bartlett, P. D. "Nonclassical Ions"; Benjamin: New York, 1965. Sargent, G. D., in Carbonium Ions, Vol. III (Olah, G. A., Schleyer, P. v. R., Eds.), Wiley-Interscience: New York, 1972, Chapter 24.

(3) Brown, H. C. *Spec. Publ. Chem. Soc.* **1962**, *16*, 140; *Chem. Br.* **1966**, 199; *Tetrahedron* **1976**, *32*, 179.

(4) Brown, H. C. "The Nonclassical Ion Problem" (with comments by P. v. R. Schleyer); Plenum Press: New York, 1977.

(5) Corey, E. J.; Casanova, J.; Vatakencherry, P. A.; Winter, R. *J. Am. Chem. Soc.* **1963**, *85*, 169.

(6) Berson, J. A.; Remanick, A. *J. Am. Chem. Soc.* **1964**, *86*, 1749.

(7) Kirmse, W.; Krause, D. *Chem. Ber.* **1975**, *108*, 1855. Kirmse, W.; Ratajczak, H. J.; Rauleder, G. *Ibid.* **1977**, *110*, 2290. Kirmse, W.; Prolingheuer, E. C. *Ibid.* **1980**, *113*, 104. Kirmse, W.; Loosen, K.; Prolingheuer, E. C. *Ibid.* **1980**, *113*, 129.

(8) Kirmse, W.; Siegfried, R. *J. Am. Chem. Soc.* **1968**, *90*, 6564, and unpublished results.

(9) Kirmse, W.; Wroblowsky, H. J., unpublished results. For the solvolysis of the analogous tosylate (unlabeled), see: Wiberg, K. B.; Hess, B. A. *J. Am. Chem. Soc.* **1966**, *88*, 4433.

(10) Sauer, J.; Kredel, J. *Tetrahedron Lett.* **1966**, 6359.

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Table I. Nitrous Acid Deamination of *exo*- and *endo*-2-Norbornylamine

	water		acetic acid		3,3-dimethyl-butyric acid, % y	2-ethylhexanoic acid	
	% y[a]	% ee[b]	% y	% ee		% y	% ee
			exo amine (3)				
exo alcohol	99.9	2 ± 2	23.8	20 ± 1	23.1	20.5	40 ± 1
endo alcohol	0.1		<0.1		<0.1	<0.1	
exo nitrate			2.1	3 ± 2			
exo ester			72.8	10.5 ± 1	70.8	70.6	42 ± 1
endo ester			1.2	98 ± 2	6.0	8.8	98 ± 2
			endo amine (6)				
exo alcohol	89.8	4 ± 2	8.7	15 ± 1	7.6	4.4	47 ± 1
endo alcohol	10.2	98 ± 2	0.9	98 ± 2	0.5	0.2	
exo nitrate			3.4		0.2		
exo ester			83.6	20.5 ± 1	89.4	93.9	68 ± 1
endo ester			3.4	98 ± 2	2.3	1.5	98 ± 2

[a] Relative yields. Minor products of unknown origin (e.g., 2-norbornanone) have been omitted. [b] Enantiomeric excess (=optical purity) = 2 (% enantiomer that is in excess) − 100%.

Table II. Deuterium Distribution in **15**-*d*

	15-*2-d*/15-*1-d*	
precursor, conditions	H_2O (R = H)	CH_3OH (R = CH_3)
3-*2-d*, HNO_2 (pH 3.5)	47.5/52.5	
6-*2-d*, HNO_2 (pH 3.5)	48/52	
9, 0.06 N NaOD/D_2O, *hν*	50/50	
10-*2-d*, 0.3 N $NaOCH_3/CH_3OH$		55.5/44.5
12-*2-d*, 0.3 N $NaOCH_3/CH_3OH$		60/40
9, 0.3 N $NaOCH_3/CH_3OD$, *hν*		56/44

we have been able to separate the enantiomers of both *exo*- and *endo*-2-norbornanol on capillary columns coated with optically active polypropylene glycol. Thus the enantiomeric purity of the deamination products may be established with small samples and without prior exo/endo separation. Last but not least, the use of deuterium labels has been greatly facilitated by the advent of ^2H NMR spectroscopy.

Results

Deamination in Water. The nitrous acid deamination of optically active *exo*-2-norbornylamine (**3**) in dilute perchloric acid (pH 3.5) afforded racemic *exo*-2-norbornanol. The fraction of *endo*-2-norbornanol was ≤0.1%. In contrast, optically active *endo*-2-norbornylamine (**6**) yielded 10% of *endo*-2-norbornanol with full retention of configuration and 90% of virtually racemic *exo*-2-norbornanol (Table I). Similar results came from the aqueous deamination of the deuterated amines **3**-*2-d* and **6**-*2-d*. The *exo*-2-norbornanol thus obtained showed a slight excess of *1-d* over *2-d* (Table II). We hesitate to invoke a secondary isotope effect as systematic errors in our ^2H NMR integrations cannot be excluded. Only a small fraction of the total deuterium (<5%) was found in other positions, in agreement with Corey's ^1H NMR data[5] and with Roberts' work on ^{14}C-labeled norbornylamines.[13] Consequently, 6,2- and 3,2-hydride shifts are minimal, and the racemization observed with optically active precursors is almost entirely due to Wagner–Meerwein rearrangements.

The photolysis of tosylhydrazone anions generates aliphatic diazo compounds[14] which are protonated by hydroxylic solvents to give diazonium ions and products derived therefrom[15] (Scheme II). Irradiation of 2-norbornanone tosylhydrazone (**9**) in dilute aqueous sodium hydroxide yielded 94.2% of *exo*-2-norbornanol and 5.8% of *endo*-2-norbornanol. Comparison with the results

Scheme II

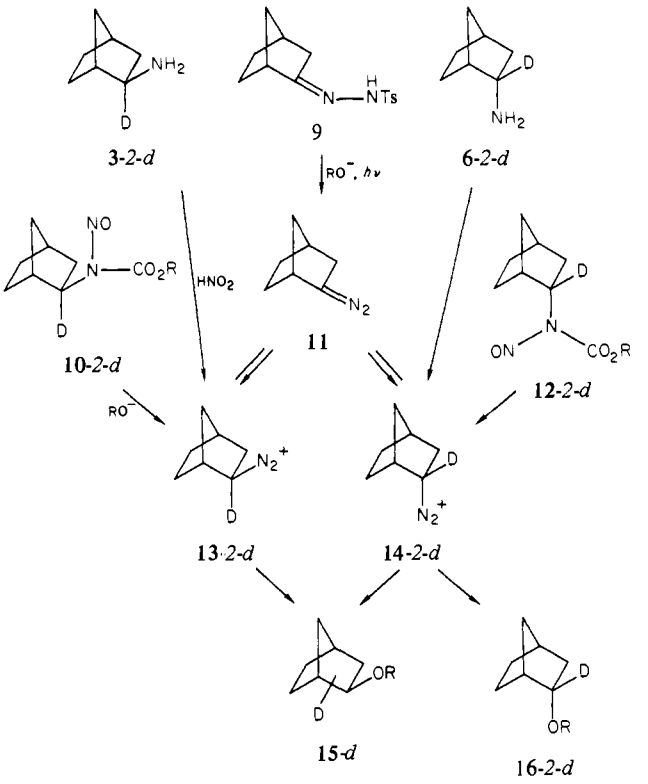


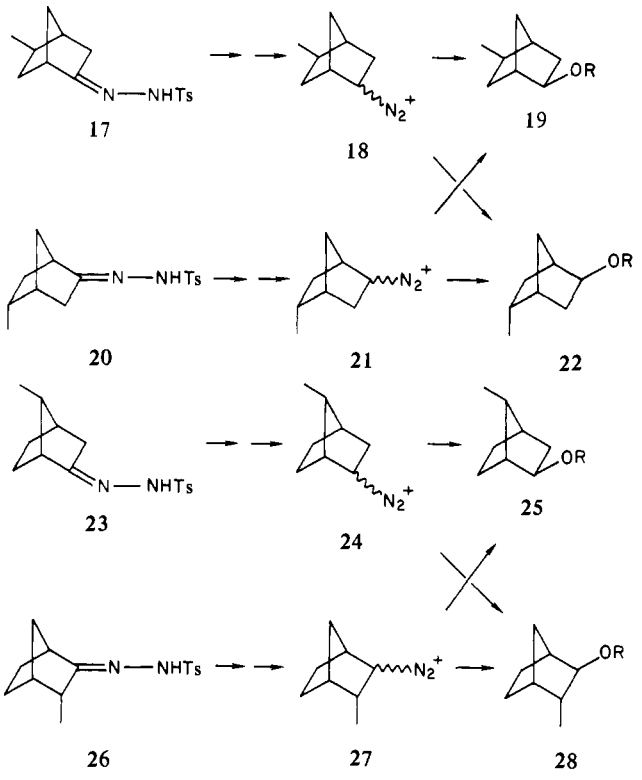
Table III. Product Ratios Obtained from the Photolysis of Methylnorbornanone Tosylhydrazones[16] (Scheme III)

precursor	ratio	R = H (0.5 N NaOH)	R = CH_3 (0.3 N $NaOCH_3$)
17	**22**/19	1.34	0.95
20	**22**/19	1.51	1.86
23	**28**/25	1.46	1.01
26	**28**/25	1.54	1.82

from **3** and **6** suggests that *exo*- and *endo*-2-norbornanediazonium ions (**13** and **14**, respectively) contribute to product formation in an approximate 1:1 ratio. Photolysis of **9** in D_2O/DONa produced **15**-*2-d* and **15**-*1-d* (R = H) in equal amounts. This means 4% retention of configuration, if the 48:52 ratio observed with **3**-*2-d* and **6**-*2-d* is taken as standard. Very similar results have been obtained with Wagner–Meerwein related pairs of methylnorbornanone tosylhydrazones, e.g., **17**/**20** and **23**/**26** (Scheme III).[16]

(11) Horton, D.; Machinami, T. *J. Chem. Soc., Chem. Commun.* **1981**, 88.
(12) Oppolzer, W.; Kurth, M.; Reichlin, D.; Moffatt, F. *Tetrahedron Lett.* **1981**, 2545; *Helv. Chim. Acta* **1981**, *64*, 2802.
(13) Roberts, J. D.; Lee, C. C.; Saunders, W. H. *J. Am. Chem. Soc.* **1954**, *76*, 4501.
(14) Dauben, W. G.; Willey, F. G. *J. Am. Chem. Soc.* **1962**, *84*, 1497.
(15) For a review, see: Ando, W. In "The Chemistry of Diazonium and Diazo Groups"; Patai, S., Ed.; Wiley-Interscience: Chichester, 1978; Part 1, p 362.
(16) Kirmse, W.; Hartmann, M.; Siefgried, R.; Wroblowsky, H. J.; Zang, B.; Zellmer, V. *Chem. Ber.* **1981**, *114*, 1793.

Scheme III

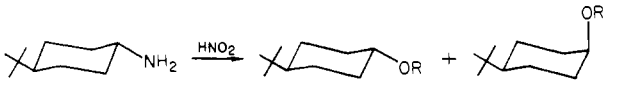


The data in Table III correspond to 6% and 3% retention of configuration, respectively.

Deamination in Methanol. The photolysis of **9** in CH_3OD/CH_3ONa led to a significant increase of the **15**-*2-d*/**15**-*1-d* ratio (Table II). Even stronger effects were found with the methylnorbornane tosylhydrazones **17**, **20**, **23**, and **26** (Table III). Photolyses of tosylhydrazones generate mixtures of epimeric diazonium ions. The individual reaction patterns of *exo*- and *endo*-norbornanediazonium ions in methanol remain to be elucidated. Unfortunately, the nitrous acid deamination of amines fails in alcohols. The alkaline cleavage of nitrosoamides leads initially to diazonium ions of specified configuration, but subsequent epimerization by way of the diazo compound may occur.[17] We argued that epimerization of the deuterated diazonium ions **13**-*2-d* and **14**-*2-d* in methanol via diazonorbornane (**11**) must be associated with exchange of the deuterium for hydrogen. Starting with the deuterated *exo*-carbamate **10**-*2-d* and observing the ^2H NMR spectra of the products, we should "see" only deuterated ethers originating from the *exo*-diazonium ion **13**-*2-d*. The exo ether **15**-*d* was formed with significant retention of configuration (10–12%), and the yield of endo ether **16**-*2-d* was ca. 2%. Analogous considerations apply to the *endo*-carbamate **12**-*2-d* which yielded **15**-*d* with ca. 20% excess of -*2-d* and 6–7% of **16**-*2-d*. These data are reminiscent of Berson's results in acetic acid.

Deamination in Carboxylic Acids. The deamination of both *exo*- and *endo*-2-norbornylamine in glacial acetic acid gave results (Table I) which were in excellent agreement with those of Berson.[6] The enantiomeric purity of the *endo*-acetate from **6**, previously derived by rather indirect methods as 85 ± 12%, was now determined with greater precision (98 ± 2%). With the aid of VPC, the enantiomeric purities of other minor components were established for the first time. The only racemic product was *exo*-2-norbornyl nitrate. The presence of 2 M lithium nitrate raised the yield of *exo*-2-norbornyl nitrate to 15%. We assume nucleophilic capture of the 2-norbornyl cation by nitrate ion which may arise by oxidation or disproportionation of nitrite.

Table IV. Deamination of *trans*-4-*tert*-Butylcyclohexylamine



29

	R			
solvent	H	OCOR'	H	OCOR'
water	97		3	
acetic acid	28.5	54.3	1	16.2
3,3-dimethylbutyric acid	25.8	38.4	1.6	34.3
2-ethylhexanoic acid	25.7	34.3	1.6	38.4

The deamination reactions in water and in acetic acid differ appreciably in the distribution and enantiomeric purity of the products. Acetic acid ($N = -2.05$,[18] $E_T(30) = 51.8$ kcal/mol[19]) is less nucleophilic and less polar than water ($N = -0.26$,[18] $E_T(30) = 63.1$ kcal/mol[20]). If the polarity of the solvent is dominant, the effects seen in acetic acid should be accentuated in less polar carboxylic acids with large alkyl groups. When we used 3,3-dimethylbutyric acid and 2-ethylhexanoic acid ($E_T(30) = 42.3$ kcal/mol[19]) as solvents, we observed increasing yields of endo ester from *exo*-amine **3**, decreasing yields of endo ester from *endo*-amine **6**, and increasing enantiomeric purities of both exo alcohols and exo esters (Table I).

Discussion

Origin of the Endo Products. A common feature of all endo products is complete conservation of enantiomeric purity. Variation of the solvent reveals that the endo products from **3** and **6** must arise by different reaction paths. The exo diazonium ion in water gives very little, if any, endo alcohol. In carboxylic acids the fraction of endo ester increases with decreasing polarity of the solvent. The opposite tendency is observed with the *endo*-diazonium ion: the yield of endo products has its maximum in water and decreases with decreasing polarity of the solvent (Table I). These data are incompatible with a classical 2-norbornyl cation as the common precursor to the endo products from both **3** and **6**.

The response of *exo*-2-norbornanediazonium ions to variation of the solvent is unexceptional. A good case for comparison is the deamination of *trans*-4-*tert*-butylcyclohexylamine (**29**) because it proceeds with predominant retention of configuration in water.[21] With decreasing polarity of the solvent, the fraction of inverted ester increases dramatically (Table IV). The cyclohexanediazonium ions generated from **29** are more sensitive to solvent effects than *exo*-2-norbornanediazonium ions. Remarkably, the fraction of the inverted alcohol remains small (cf. also Table I). The water (or hydroxide ion) responsible for alcohol formation is generated in the diazotization process and is disposed primarily for front-side attack.

We have made analogous observations with a variety of aliphatic diazonium ions. Regardless whether these diazonium ions react in water with partial inversion or partial retention, the formation of inverted esters is always favored in nonpolar carboxylic acids. We suggest a solvolytic displacement (k_s) process as the appropriate mechanism. Direct displacement of the solvent on norbornanediazonium ions[2,6,22] has been disregarded previously because the results *in a single solvent* (acetic acid) were compatible with the formation of classical cations. Corey[5] objected on the

(17) For reviews, see: White, E. H.; Woodcock, D. J. In "The Chemistry of the Amino Group"; Patai, S., Ed.; Wiley-Interscience: London, 1968; p 440. Kirmse, W. *Angew. Chem.* **1976**, *88*, 273; *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 251.

(18) Bentley, T. W.; Schadt, F. L.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1972**, *94*, 993.

(19) Marcus, Y.; Pross, E.; Hormadaly, J. *J. Phys. Chem.* **1980**, *84*, 2708.

(20) Reichardt, C. *Angew.* Chem. **1979**, *91*, 119; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 98.

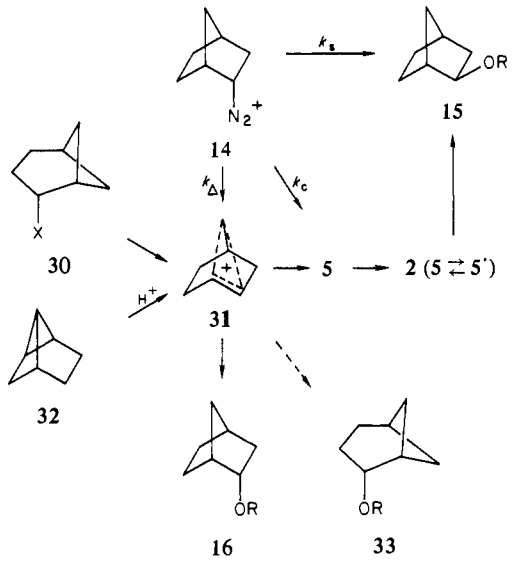
(21) Lamaty, G.; Tapiero, C.; Wylde, R. *Bull. Soc. Chim. Fr.* **1968**, 2039. Maskill, H.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1462.

(22) (a) Berson, J. A.; Ben-Efraim, D. A. *J. Am. Chem. Soc.* **1959**, *81*, 4094. (b) Evidence for concerted backside displacement on deamination of substituted 2-*exo*-norbornylamines has been reported by Collins and Benjamin (Collins, C. J.; Benjamin, B. M. *J. Am. Chem. Soc.* **1970**, *92*, 3182.

Table V. Relative Reaction Rates of Brosylates (25 °C)

brosylate	displacement by $R_4P^+N_3^-$ in toluene[23]	acetolysis[2]
exo-2-norbornyl	0.014	517
endo-2-norbornyl	0.026	1.47
cyclohexyl	1.0	1.0
cyclopentyl	56	32

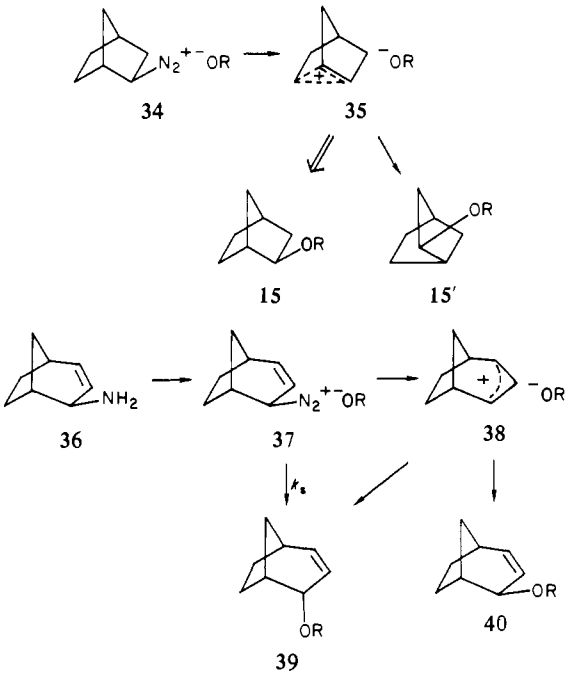
Scheme IV



grounds that a k_s process "should be far less likely for deamination than for sulfonate solvolysis" and argued that "the *exo*-diazonium ion is clearly not subject to backside displacement for steric reasons". We have shown that the S_N2 reactions of *exo*- and *endo*-2-norbornyl brosylate with N_3^- proceed at similar rates which do not indicate extreme steric hindrance[23] (Table V). The high rate of ionization, rather than shielding of the endo face, precludes significant solvent assistance in the acetolysis of *exo*-2-norbornyl brosylate. Streitwieser[24] has emphasized that the compressed energy scale in deaminations brings the rates of several competing processes closer together. Therefore, k_s processes may well contribute to the decomposition of norbornanediazonium ions in nonpolar solvents. We note that even the solvolysis of *exo*-2-norbornyl brosylate in 2-ethylhexanoic acid yielded 2% of endo ester.

The endo products from *endo*-2-norbornanediazonium ions must be of different origin, the solvent dependence pointing to an ionic precursor. The classical 2-norbornyl cation is excluded by the results obtained in water, which imply predominant endo substitution of the chiral intermediate. The 7-bridged norbornyl cation (**31**) plays an important role in the rearrangements of bicyclo[3.1.1]heptyl derivatives (**30**)[8,25] and in the protonation of tricyclo[3.2.0.$0^{2,7}$]heptane (**32**).[26] Both reactions afford similar exo/endo ratios of 2-norbornyl products which increase with decreasing nucleophilicity of the solvent and with increasing temperature (Scheme IV). Rearrangement of **31** to the conventional (6-bridged or rapidly equilibrating) norbornyl cation apparently competes with solvent capture. The 7-bridged ion (**31**) may also be accessible from *endo*-2-norbornanediazonium ions (**14**). The compressed energy scale in deaminations[24] is held responsible for participation of the C(1)–C(7) bonding electrons in the dissociation of **14** but not of *endo*-2-norbornyl brosylate (**4**). As a rule, k_Δ processes provide low-energy reaction paths

Scheme V



and are therefore more prominent in sulfonate solvolysis than in deamination.[17,25] The present case is an exception to this rule because the formation of **31** from norbornyl precursors is associated with an increase in strain energy.[27]

The reactions in Scheme IV produce bicyclo[3.1.1]heptanol (**33**) in trace amounts, if at all. This is due to the unsymmetrical charge distribution (different strain of the resonance structures) in the 7-bridged ion (**31**) which may be counterbalanced by charge-stabilizing groups. The deamination of 1-methyl-2-*endo*-norbornylamine in water afforded 19% of 2-methylbicyclo[3.1.1]-heptan-2-ol and 17% of 1-methyl-2-*endo*-norbornanol.[23b] The same ratio (but a higher yield) was obtained from 2-methyl-2-bicyclo[3.1.1]heptylamine, supporting the 7-bridged ion as a common intermediate.

Origin of the Optically Active Exo Products. The enantiomeric purity of the exo esters from *exo*-amine (**3**) is inferior to that of the exo esters from *endo*-amine (**6**) (Table I). These observations suggest that the optical activity of the exo esters from endo amine is due, at least in part, to solvolytic displacement (k_s) processes which were discussed explicitly in the preceding paragraph.

The optically active exo products from *exo*-amine (**3**) provide the strongest evidence for a chiral norbornyl cation. However, as Collins[28] and Schleyer[4] have emphasized, the symmetry of the entire carbocation system, cation and anion, has to be taken into account. Deamination in carboxylic acids generates diazonium carboxylate ion pairs which decompose to give carbocation–carboxylate ion pairs.[17,29] Even if the norbornyl cation in **35** is bridged, the ion pair **35** may be unsymmetrical because the anion is closer to C(2) than to C(1). If ion-pair collapse occurs before the counterion has achieved a symmetrical location, partial retention of configuration results.

In order to substantiate the ion-pair hypothesis we chose the structurally related but unquestionably delocalized bicyclo[3.2.1]octenyl cation (**38**). The "product spread" which is often observed in the deamination of isomeric allylamines has been interpreted in terms of ion-pair collapse,[17,29] nonplanar (twisted) allylcations,[30] and direct displacement of the solvent on allyl

(23) (a) Banert, K.; Kirmse, W. *J. Am. Chem. Soc.* **1982**, *104*, 3766. (b) Banert, K. Dissertation, Ruhr-Universität Bochum, 1982.
(24) Streitwieser, A., Jr. *J. Org. Chem.* **1957**, *22*, 861.
(25) For a review, see: Kirmse, W. *Top. Curr. Chem.* **1979**, *80*, 275.
(26) Davis, D. D.; Johnson, H. T. *J. Am. Chem. Soc.* **1974**, *96*, 7576. Streu, J., unpublished results (Diplomarbeit, Ruhr-Universität Bochum, 1981).
(27) Endo attack at substituted norbornyl cations *after* Wagner–Meerwein rearrangements has been reported: Benjamin, B. M.; Collins, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 3183. Collins, C. J.; Benjamin, B. M. *J. Org. Chem.* **1972**, *37*, 4358. These observations cannot be explained by competitive k_s, k_Δ reactions and stand in contrast to our results with the parent 2-norbornanediazonium ions (Table I).
(28) For a review, see: Collins, C. J. *Chem. Soc. Rev.* **1975**, *4*, 251.
(29) Huisgen, R.; Rüchardt, C. *Liebigs Ann. Chem.* **1965**, *601*, 1, 21.

Table VI. Nitrous Acid Deamination of *exo*-Bicyclo[3.2.1]oct-3-en-2-amine (**36**)

	water		acetic acid		2-ethylhexanoic acid	
	% y	% ee	% y	% ee	% y	% ee
exo alcohol	98.6	2 ± 3	24.1	59 ± 2	22.6	73 ± 2
endo alcohol	1.4		0.5		1.7	51 ± 2
exo ester			63.2	30 ± 2	41.3	55 ± 2
endo ester			12.2	65 ± 2	34.4	73 ± 2

diazonium ions.[31] In the case of *exo*-bicyclo[3.2.1]oct-3-en-2-amine (**36**), twisting of the allyl cation **38** is prohibited by the rigid bicyclic structure, and solvolytic displacement leads to endo products (**39**). Therefore, retention of configuration in the exo products (**40**) must be due to ion-pair collapse. As expected, the nitrous acid deamination of optically active **36** in water yielded ≥98% of racemic exo alcohol (**40**, R = H). Deaminations in acetic acid and in 2-ethylhexanoic acid led to increasing endo substitution and to increasing optical activity of all products (Table VI). In contrast to the norbornyl case, the endo esters (**39**) were not enantiomerically pure. Obviously, the allylic cation **38** undergoes some endo attack whereas the symmetrical (bridged or rapidly equilibrating) norbornyl cation does not. Retention of configuration in the exo products was indicated by comparing the CD spectra of **36** and **40** (R = H). If the π-delocalized allylic cation **38** gives rise to optically active products via collapse of unsymmetrical ion pairs, an analogous reaction path for the σ-delocalized norbornyl cation (**2**) seems likely.

Conclusion

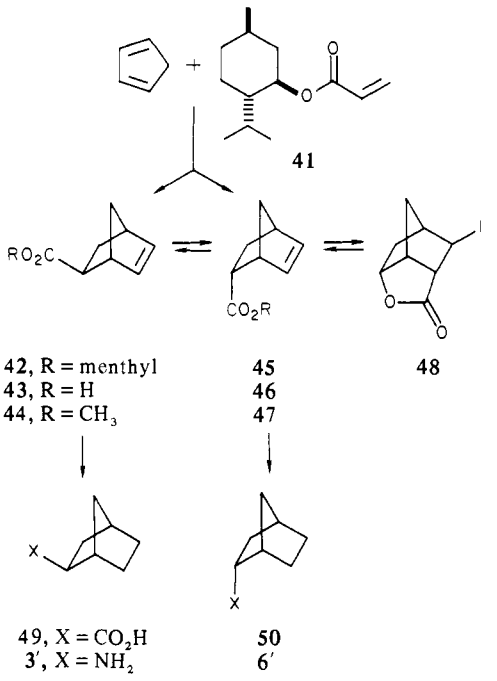
The present reinvestigation of 2-norbornanediazonium ions does not support a classical norbornyl cation which undergoes endo attack and may be trapped prior to rearrangement. The formation of endo products is more reasonably attributed to competitive reactions (k_s, k_Δ) of the norbornanediazonium ions. Optically active exo products are typical of nonpolar solvents and originate most probably from unsymmetrical ion pairs. Our observations redefine, but do not resolve, the nonclassical ion problem. Product studies cannot distinguish a rapidly equilibrating and highly exo-selective classical norbornyl cation[4] from the bridged species.

Experimental Section

General Information. Proton (^{1}H) NMR spectra were determined in the indicated solvent on a Bruker WM-80 (80 MHz) or a Bruker WM-250 (250 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. Deuterium (^{2}H) NMR spectra were recorded in CCl_4 on a Bruker WM-250 spectrometer (38.39 MHz). Optical rotations were determined on a Perkin-Elmer 141 polarimeter. High-pressure liquid chromatography (HPLC) was performed on a LDC instrument with a 25 × 1.5 cm silica gel column (Si 60, 5 μm, Machery and Nagel).

Gas chromatography (GC) was performed on a Siemens Sichromat 1 equipped with glass capillary columns. Peak areas were obtained by electronic integration (Pye Unicam DP88). (−)-(*S*)-2-Methyloxirane,[32] $[\alpha]^{20}_D$ −12.5° (neat) was polymerized with solid potassium hydroxide according to Price and Osgan[33] to give optically active PPG; mp 65 ± 2 °C, $[\alpha]^{20}_D$ 21.5 ± 0.2° (*c* 1.3, $CHCl_3$). Soft glass capillaries of 120–150-m length were pretreated and coated with optically active PPG, following the directions of Schomburg and Husmann.[34] The columns used in this work had ca. 3 × 10^5 theoretical plates and separation numbers of ca. 65 (cyclopentanone vs. cyclohexanone). Temperature, retention times, separation factors (α), and resolution (R_s) for the relevant pairs of enantiomeric alcohols were as follows: *exo*-2-norbornanol (**15**-OH) 65 °C, 261 min, α = 1.012, R_s = 1.45; *endo*-2-norbornanol (**16**-OH) 65 °C, 295 min, α = 1.009, R_s = 1.13; *exo*-bicyclo[3.2.1]oct-3-en-2-ol (**40**-OH) 71 °C, 439 min, α = 1.008, R_s = 1.06; *endo*-bicyclo[3.2.1]oct-3-en-2-ol (**39**-OH) 71 °C, 525 min, α = 1.018, R_s = 2.56 (R_s = 1.5 will usually achieve base-line resolution, R_s = 1.0 corresponds to ca. 85% resolution).

Scheme VI



Preparation of Optically Active 2-Norbornylamines. Sauer's procedure[10] was followed with minor modifications (Scheme VI). The BF_3-catalyzed Diels–Alder reaction of cyclopentadiene and (−)-menthyl acrylate (**41**) (CH_2Cl_2, −78 °C) afforded the menthyl 5-norbornene-2-carboxylates **42** and **45** in 76% yield. Alkaline hydrolysis (KOH, methanol, 6 h reflux) gave an exo:endo (25:75) mixture of the corresponding acids, **43** and **46** (84% yield), which were separated by iodolactonization.[35] The exo acid **43** obtained of this stage had an ee of 66%. The iodolactone **48** was recrystallized from ethanol–water to constant optical rotation, $[\alpha]^{20}_D$ −110.6° (*c* 1.0, $CHCl_3$). Reductive cleavage of **48** (zinc dust, acetic acid, 35 °C)[35] afforded endo acid **46** which was hydrogenated (Pd–C, ethyl acetate, 1 atm of H_2, room temperature) and subjected to Curtius degradation.[36] (−)-(1*S*,2*R*,4*R*)-2-Norbornylamine (**6'**) was purified by preparative GC (Carbowax + KOH, 140 °C). The enantiomeric purity (99 ± 1%) was determined by GC of the *N*-(trifluoroacetyl)-(*S*)-prolylamides.[37]

The endo acid **46** (from enantiomerically pure iodolactone **48**) was converted to its methyl ester **47** (CH_2N_2, Et_2O) and equilibrated (0.2 M $NaOCH_3$, 8 h reflux). The mixture of esters, **44** and **47**, was hydrolyzed (KOH, methanol–water), and the acids were separated by iodolactonization. Hydrogenation and degradation of the exo acid **43** afforded (+)-(1*S*,2*S*,4*R*)-2-norbornylamine (**3'**) of 95 ± 1% ee.

Nitrous Acid Deamination of the 2-Norbornylamines. A solution of 80 mg of amine in 80 mL of water was adjusted to pH 3.8 (glass electrode) with dilute perchloric acid. Sodium nitrite (0.25 g) was added and stirring was continued for 12 h at room temperature. The products were extracted with ether and analyzed by GC on optically active PPG. With the aid of authentic samples, the 2-norbornanol peaks were assigned as (+)-exo, (−)-exo, (+)-endo, and (−)-endo in the order of elution. Treatment of the reaction products with $LiAlH_4$ (to achieve reduction of nitrite esters) did not affect the composition and enantiomeric purity of the 2-norbornanols.

Deaminations in carboxylic acids (Table I) were performed with 0.10 g of amine and 0.25 g of sodium nitrite in 2 mL of acid (12 h at room temperature). The reaction mixture was stirred with 100 mL of saturated aqueous $NaHCO_3$, followed by extraction with ether. (Complete removal of 2-ethylhexanoic acid from the ether solution required several extractions with $NaHCO_3$.) The nitrate, carboxylate, and alcohol fractions (order of elution) were separated by HPLC with ether–hexane (1:1 for acetates, 2:3 for 2-ethylhexanoates). *exo*-2-Norbornyl nitrate was identified by comparison with an authentic sample.[38] Reduction of the

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nitrate with $LiAlH_4$ afforded 2-norbornanol whose enantiomeric purity was determined by GC. Hydrolysis of the esters was achieved with 0.5 g of potassium hydroxide in 2 mL of methanol (12 h at room temperature). $LiAlH_4$ reduction of the 2-norbornyl acetates led to inferior and irreproducible enantiomeric purities of *endo*-2-norbornanol. It appears that the predominant and largely racemic *exo*-2-norbornyl acetate produced a trace (<1%) of *endo*-2-norbornanol on $LiAlH_4$ reduction. The popular $LiAlH_4$ procedure for ester cleavage was therefore replaced by alkaline hydrolysis.

Correlation of Configurations. The absolute configurations of *exo*-2-norbornanol, (−)-(1*S*,2*S*,4*R*), and of *endo*-2-norbornanol, (+)-(1*S*,2*R*,4*R*), have been established by correlation with fenchone.[39] (+)-*exo*-2-Norbornanecarboxylic acid (**49**) has been correlated with (−)-*exo*-2-norbornanol by Baeyer–Villiger oxidation of the corresponding methyl ketone.[40] (+)-*exo*- and (+)-*endo*-2-norbornanecarboxylic acids are interconverted by epimerization. Consequently, the acids used in this work, the amines derived therefrom, and the (major) 2-norbornanols obtained by deamination were all members of the (1*S*,4*R*) series.

Preparation and Deamination of 2-Norbornylamines-*2-d*. Reduction of 2-norbornanone with $LiAlD_4$, brosylation of the resultant mixture of 2-norbornanols-*2-d*, and purification[1] afforded 73% of *endo*-2-norbornyl-*2-d* brosylate. The brosylate (20 g) was stirred with 16 g of sodium azide in 170 mL of dimethyl sulfoxide (80 °C, 21 h).[41] Addition of water and extraction with ether yielded 8.0 g (97%) of crude 2-norbornyl-*2-d* azide. The azide was reduced with $LiAlH_4$ (6.0 g) in ether to give 6.0 g (93%) of crude 2-norbornylamine-*2-d* which was purified by preparative GC (Carbowax + KOH). Comparison by GC (80-m glass capillary coated with PPG + KOH) with undeuterated samples indicated 97.8% of *exo*- and 2.2% of *endo*-2-norbornylamine-*2-d*. ^1H NMR spectroscopy (C_6D_6) revealed the complete (>98%) absence of 2 H, and the ^2H NMR spectrum showed a single peak for 2 D.

2-Norbornanone oxime[42] (5.8 g) and Adams catalyst (PtO_2, 0.25 g) in CH_3CO_2D (50 mL) were shaken with deuterium (1.1–1.2 atm) in a Parr apparatus (16 h at room temperature). The catalyst was removed by filtration, and 10 mL of concentrated hydrochloric acid was added. Evaporation under vacuum gave a residue which was dissolved in 50 mL of 4 N hydrochloric acid. After being washed 5 times with ether, the solution was made strongly alkaline by addition of solid sodium hydroxide and extracted continuously with ether for 15 h. Distillation of the organic layer afforded a 90% yield of crude amine which was purified by preparative GC. The product consisted of 93% *endo*- and 7% *exo*-2-norbornylamine-*2-d*. The ^1H NMR spectrum (C_6D_6) confirmed complete (>97%) deuteration at C-2. In addition of 2 D, the ^2H NMR spectrum showed ca. 0.2 D in other positions, but none at C-1.

Deaminations were run with 0.50 g of the deuterated amines and 0.85 g of sodium nitrite in 70 mL of dilute perchloric acid (pH 3.8, 12 h at room temperature). After being extracted with ether, *exo*-2-norbornanol was isolated by preparative GC (Carbowax + KOH) and purified by sublimation; cf. Table II for results of ^2H NMR spectroscopy.

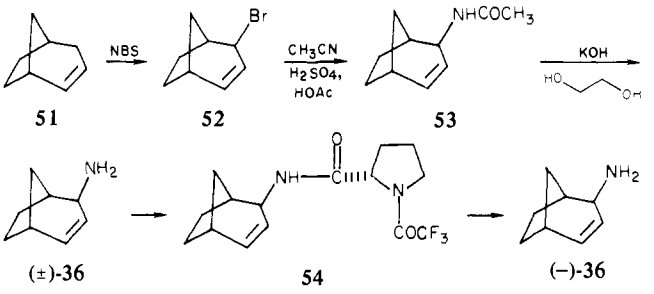
Preparation and Deamination of 2-Norbornylcarbamates. Methyl chloroformate (4.9 mL, 64 mmol) was added dropwise at 0–5 °C to 11 g (0.1 mol) of the appropriate amine in 25 mL of anhydrous ether. Additional 4.9 mL of methyl chloroformate and 5 g (0.125 mol) of sodium hydroxide in 7 mL of water were then added simultaneously. The mixture was warmed to room temperature and stirred for 1 h. The organic layer was separated, sufficient water was added to dissolve the solids, and the aqueous phase was extracted with ether. The combined organic layers were stirred with powdered potassium carbonate until residual methyl chloroformate had disappeared. The solution was concentrated and the product recrystallized from hexane.

Methyl *exo*-2-norbornylcarbamate: mp 86–87 °C, yield 92%; ^1H NMR (CCl_4) 1.05–1.35 (m, 4 H), 1.48 (m, 2 H), 1.78 (m, 2 H), 2.21 (s, br, 1 H), 2.25 (s, br, 1 H), 3.5 (m, 1 H), 3.65 (s, 3 H), 4.6 (s, br, 1 H). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.91; H, 9.05; N, 8.33.

Methyl *endo*-2-norbornylcarbamate: mp 89–91 °C, yield 42%; ^1H NMR (CCl_4) 0.70 (ddd, $J \sim 12, 4, 2$ Hz, 1 H), 1.1–1.6 (m, 2 H), 2.08 (m, 1 H), 2.20 (s, br, 1 H), 2.41 (s, br, 1 H), 3.67 (s, 3 H), 3.92 (m, 1 H), 4.7 (s, br 1 H). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.69; H, 8.76, N, 8.42.

The ^2H NMR spectra of the methyl 2-norbornylcarbamates-*2-d* were analogous to those of the corresponding amines.

Scheme VII



A solution of 1.0 g (5.9 mmol) of the appropriate carbamate in 60 mL of anhydrous ether was stirred at −10 °C with 1.0 g of anhydrous sodium acetate. A precooled (−30 °C) solution of 0.60 g of dinitrogen tetroxide in 30 mL of anhydrous ether was slowly added. After 30 min the reaction mixture was washed successively with cold water, cold aqueous $NaHCO_3$, and cold water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo below 0 °C. Complete evaporation of the ether may lead to spontaneous decomposition of the nitrosocarbamates. Concentrated solutions of the nitrosocarbamates were added to 30 mL of 0.3 M NaOCH_3 in CH_3OH. After being stirred for 30 min at room temperature the mixture was diluted with water and extracted with ether. The 2-methoxynorbornanes were isolated by preparative GC (Carbowax). GC separation of the epimers was achieved on 150-m glass capillaries coated with heptaglycol isononylphenyl ether (Marlophen provided by Chemische Werke Hüls). ^2H NMR spectra (Table II) were determined with the epimeric mixtures. The 2-D signals of *exo*- and *endo*-2-methoxynorbornane were cleanly resolved.

Preparation and Deamination of (−)-*exo*-Bicyclo[3.2.1]oct-3-en-2-amine (36) (Scheme VII). A solution of *exo*-2-bromobicyclo[3.2.1]-oct-2-ene (**52**)[43] (20 g, 0.11 mol, obtained by NBS bromination of bicyclo[3.2.1]oct-2-ene[44]) in 28 g (0.68 mol) of acetonitrile was added slowly to a mixture of concentrated sulfuric acid (11.2 g) and acetic acid (28 mL). The mixture was stirred at room temperature for 16 h, added to 200 mL of water, neutralized with saturated aqueous Na_2CO_3, and extracted with ether. The combined organic layers were washed with water and dried over potassium carbonate. The solvent was removed in vacuo to yield 17.3 g (98%) of crude bicyclo[3.2.1]oct-3-en-2-ylacetamide (**53**). Without purification, **53** was added to a solution of potassium hydroxide (20 g) in ethylene glycol (80 mL). The mixture was stirred at 160 °C for 16 h, added to water (500 mL), and extracted with ether (5 × 50 mL). The combined organic layers were washed with water, dried over potassium carbonate, and concentrated in vacuo. Short-path distillation yielded 8.0 g (62%) of **36**, 98% pure by GC. NMR ($CDCl_3$) 1.05 (s, NH_2), 1.1–1.8 (m, 6 H), 2.05 (m, 1 H), 2.3 (m, 1 H), 2.9 (m, 1 H), 5.45 (ddd, 1 H, J = 9.6, 3.8, 1.8 Hz), 5.9 (ddt, 1 H, 9.6, 7, 1.5 Hz).

Analytical GC (100-m glass capillary coated with Marlophen + KOH, 120 °C) indicated the absence of the endo isomer. The stereoselectivity of the Ritter reaction contrasts favorably with our attempts to convert **52** into **36** by azide displacement, followed by $LiAlH_4$ reduction. We obtained an exo:endo (2:1) mixture, contaminated with 6% of saturated amines.

To a stirred solution of **36** (8.7 g, 70 mmol) and pyridine (10.5 g) in 70 mL of anhydrous methylene chloride was added a solution of (−)-(*S*)-(trifluoroacetyl)prolyl chloride[37] (16.6 g, 77 mmol, ee 89%) in anhydrous methylene chloride (70 mL). After being stirred for 15 h, the mixture was washed successively with dilute hydrochloric acid, aqueous $NaHCO_3$, and water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 12.6 g (57%) of crude **54**. Three crystallizations from cyclohexane raised the melting point to 173–5 °C. GC (10-m glass capillary, coated with Carbowax, 160 °C) indicated a diastereomeric ratio of 84:16. Anal. Calcd for $C_{15}H_{19}F_3N_2O$: C, 56.95; H, 6.05; N, 8.86. Found: C, 56.97; H, 6.13; N, 8.96.

In a procedure exactly analogous to the alkaline hydrolysis of **53**, followed by preparative GC (Marlophen + KOH), **54** (3.45 g, 10.9 mmol) yielded 0.76 g (57%) of (−)-**36**, ee 63% (by GC of the (trifluoroacetyl)prolylamides), $[\alpha]^{20}_D$ −10.0° (neat), $[\alpha]^{20}_{546}$ −12.1° (neat).

The nitrous acid deamination procedures were followed as described for the norbornylamines. The major alcohol obtained in nonpolar solvents was (+)-bicyclo[3.2.1]oct-3-en-2-ol, as shown by comparison (GC on optically active PPG) with an authentic sample.[45] CD studies on **36**, **40**,

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and some of their derivatives suggest identical *R* configurations of (-)-**36** and (+)-**40**.[46]

Registry No. **3**-2-*d*, 84143-95-3; (+)-**3'**, 84235-33-6; **6**-2-*d*, 84143-96-4; (-)-**6'**, 84235-34-7; **9**, 38397-34-1; **10**-2-*d*, 84143-99-7; **12**-2-*d*, 84144-00-3; (-)-**36**, 84143-97-5; (±)-**36**, 84235-39-2; (±)-**40**, 84235-41-6; (-)-**41**, 4835-96-5; **42**, 84235-35-8; **43**, 67999-53-5; **44**, 84235-37-0; **45**, 84235-36-9; **46**, 58001-99-3; **47**, 72203-34-0; (-)-**48**, 84143-98-6; (±)-**52**, 84144-01-4; (±)-**53**, 84144-02-5; **54** (isomer 1), 84144-03-6; **54** (isomer 2), 84235-42-7; (±)-bicyclo[3.2.1]oct-2-ene, 823-02-9; [1*S*,-(1α,2β,4α)]methyl 2-norbornylcarbamate, 84144-04-7; [1*S*-(1α,2α,4α)]methyl 2-norbornylcarbamate, 84235-40-5; cyclopentadiene, 542-92-7; (±)-bicyclo[3.2.1]oct-2-ene, 84235-38-1.

(46) Snatzke, G., unpublished results. We are grateful to Professor Snatzke for communication of his preliminary data.

Photoreaction of Thymidine with Alkylamines. Application to Selective Removal of Thymine from DNA

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Abstract: A new type of photoreaction between thymidine (Thd) and alkylamines has been described. Irradiation of Thd and methylamine in $NaHCO_3$ aqueous solution at 0 °C provided ring-opened adduct **15** quantitatively, which on subsequent heating gave 1-methylthymine (**8**). High selectivity toward Thd has been observed when the photoreaction of a mixture of dAdo, dCyd, dGuo, and Thd with methylamine was carried out at 0 °C in the presence of diazabicyclo[2.2.2]octane (0.2 mM), and then the photolysate was kept at 20 °C after irradiation. Irradiation of calf thymus DNA and methylamine under the specified conditions followed by heating at 70 °C led to the efficient release of **8** from DNA. The extent of DNA modification is readily determined by the absorbance change at 300 nm, which corresponds to the amount of the ring-opened adduct between methylamine and thymine in DNA. Model experiments using thymidylyl(3'-5')-2'-deoxyadenosine demonstrate that the 3'-5' phosphodiester linkage is cleaved efficiently in this photoreaction. The present results indicate the irradiation of DNA with methylamine induces an exceedingly facile removal of thymine from DNA with the strand cleavage at the reacting thymine, providing a convenient and potentially useful method for thymine selective modification of DNA.

Chemical modification of nucleic acid components is one of the promising approaches for studying the structure and function of nucleic acids.[1] The developments of base-specific chemical reactions of nucleic acid constituents is extremely important for modification of nucleic acids. The most prominent example so far known for the use of base-specific chemical reaction is the Maxam-Gilbert method for sequencing DNA.[2] In our study exploring the chemical basis of UV-induced nucleic acid-protein cross-links,[3] we have found that photoexcited thymidine reacts with primary amines to produce a ring-opened adduct, which on subsequent heating is readily converted to N(1)-substituted thymine in high yields.[4] We felt that this novel type of photochemical conversion would be used for a specific modification of thymine moieties in DNA. In the present paper, we describe the details of the photochemistry of thymidine in the presence of amines and its application to selective removal of thymine from DNA.[5]

Photochemistry of nucleic acid bases has been studied extensively for many years in connection with photobiology of nucleic acids.[6] The formation of pyrimidine photodimers and photohydrates has been recognized as one of the major reactions induced by UV irradiation of nucleic acids.[6] In view of the importance of photo-cross-linking of biopolymers, especially nucleic acid-protein cross-links, photochemical reactions of nucleic acid components with a variety of compounds have also been thoroughly investigated.[7] Despite many approaches to pyrimidine photochemistry, very little is known about the photoreaction in the presence of amines.[7c] The only study in which products have been fully characterized is that of photoaddition of 1,3-dimethyluracil with *n*-propylamine,[8] although photoaddition of 4-thiouracils[3c] and free radial initiated reaction of purines[9] with alkylamines have previously been reported. This is surprising since basic amino groups on the side chains of lysine and arginine are suggested to be involved in the binding of proteins to the backbones of nucleic acids in nucleic acid-protein complexes such as histone-DNA complexes,[10] and hence photochemical reaction with amino groups is expected to play an important role in the cross-linking processes.[4a,11] We therefore investigated the photochemistry of nucleic acid bases in the presence of amines in detail in order to get a clearer picture of the molecular aspects of UV-induced nucleic acid-protein cross-linking.

Results and Discussion

Photoreaction of Thymidine with Alkylamines. We first examined the direct irradiation of nucleosides including 2'-deoxyadenosine (dAdo), 2'-deoxyguanosine (dGuo), 2'-deoxycytidine (dCyd), and thymidine (Thd) with 254-nm light in the presence

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