over a sequential Michael-type sequence for the following reasons: (1) high degree of stereospecificity, (2) absence of a noncyclized adduct, and (3) lack of precedence for an intramolecular Michael reaction in an exo-methylene ketone. Orbital symmetry rules predict that a concerted cycloaddition of the "W-type allyl anion" from our system would yield a product in which the thioaryl group and the bridgehead β-hydrogen were trans to one another. Additional experiments are in progress to rigorously test the generality of this stereochemical prediction.

The cycloadditions described not only constitute an efficient and highly specific synthesis of a new class of hydrindanones but they are a prototype of a potentially general pentannelation process which should allow for the fusion of five-membered rings to other cyclic ketones.

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Thermal Decomposition of N-Nitrosohydroxylamines. VII. Retention in the Combination of Optically Active 2-Butyl-tert-butoxy Radical Pairs

Sir:

We wish to report the results of our studies of the yields (Y) and optical purities (OP) of the 2-butyl tert-butyl ether (5), isolated from the rearrangement and subsequent homolysis of (S)-N-nitroso-N-(α-methyl)-butanoyl-O-tert-butylhydroxylamine (2, Scheme I), in

Scheme I[a]
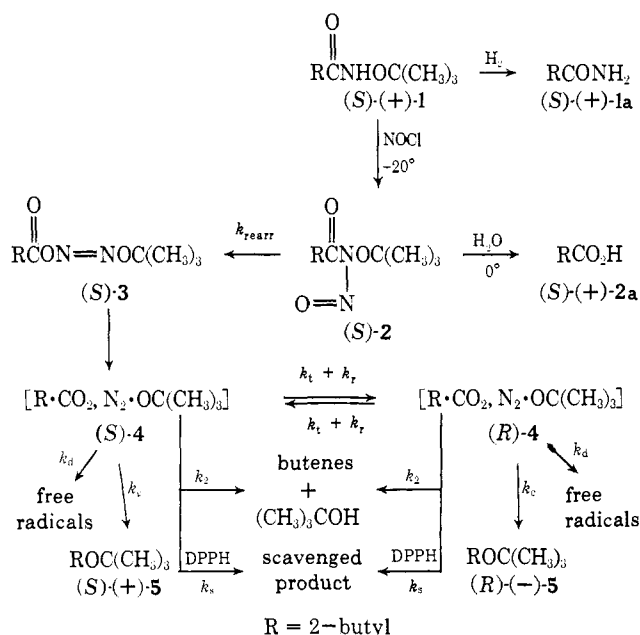
R = 2-butyl

[a] R = 2-butyl.

solvents of varying viscosity and the first experimental results on the response of the optical purity of a cage product to high concentrations of scavengers. The

Table I. Yields and Optical Purities from Decomposition of **2** at 30°

Solvent[a]	[DPPH], M	η (cP)	N_2[b]	CO_2	Y_{ether}	(OP)[c] ether
Pentane		0.260	0.99	0.96	0.113	0.013
Decane		0.809			0.182	0.019
Dodecane		1.184			0.203	0.023
Nujol		33.7	1.00	0.97	0.278	0.090
CHCl₃		0.555	(1.00)	0.99	0.158	(0.016)
CHCl₃	0.25	0.555	(1.00)	0.96	0.139	0.018
CHCl₃	0.50	0.555	(1.00)	0.97	0.123	0.020
CHCl₃	0.84	0.555	(1.00)	0.97	0.106	0.024

[a] Containing 10 volume % CCl_4. [b] Values in parentheses are assumed. [c] Corrected assuming 86.6 optical purity in the starting material.

results show a small but definite reduction of the combination efficiency of the deaminatively formed pair (4), compared to that recently reported from studies of the corresponding perester.[1] The effect of added DPPH is to reduce the yield and raise the optical purity of the ether product (5). These variations are consistent with a scheme which involves a single intermediate radical pair.

The O-tert-butyl hydroxamate (1, $[\alpha]^{23°}_{589}$ +15.15°, c 1.6, CCl_4) was prepared from the optically active acid chloride[1] and tert-butoxyamine.[2] It was purified by column chromatography, sublimation, and recrystallization to constant rotation. A sample of this material was hydrogenolyzed in acetic acid over platinium giving (S)-(+)-2-methylbutyramide (1a) of 88.7% optical purity ($[\alpha]^{23°}_{589}$ +16.24°, c 1.03, H_2O; lit.[3] $[\alpha]^{23°}_{589}$ +18.31, H_2O). A second sample of the hydroxamate (1) was nitrosated (in CCl_4) at −20° with nitrosyl chloride, and the resulting nitroso compound (2) was stirred at 0° with water yielding (S)-(+)-2-methylbutanoic acid (2a) of 87.6% optical purity. We thus conclude that the optical purity of the starting material (1) was 88 ± 1% and that no significant racemization of the nitroso compound (2) or the hyponitrite occurs during the reactions.[4]

The rearrangement of the nitroso compound to the hyponitrite is very rapid at room temperature but the rate could be estimated in carbon tetrachloride at −19° (k_{rearr} = 6.1 × 10⁻⁵ sec⁻¹).[5] The half-life for the decomposition of the hyponitrite is ca. 8 min in carbon tetrachloride at ambient temperature in the nmr (T-60) probe. The relative yields and optical purities of the ether (5) from solutions of varying fluidity and DPPH concentration were determined by the same methods used in the perester studies.[1] A common stock solution of nitroso compound (2) in CCl_4 was prepared at −20°, and aliquots of this solution were diluted (1:9) with the appropriate hydrocarbon to effect viscosity change. These solutions were degassed by freezing and warming to −30°. The reactions were carried out

(1) T. Koenig and J. M. Owens, *J. Amer. Chem. Soc.*, **95**, 8485 (1973).

(2) T. Koenig, M. Deinzer, and J. A. Hoobler, *J. Amer. Chem. Soc.*, **93**, 938 (1971).

(3) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **103**, 1923 (1913).

(4) The hydrolysis reaction occurs in competition with rearrangement of **2** and decomposition of **3**, both of which give the acid. Racemization of either **2** or **3** would be expected to show up in **2a**. The 12% racemic **1** was probably formed during the purification which was rather difficult.

(5) The rapid rate of rearrangement in this case means that the denitrosation of **2** is not a problem: T. Koenig, J. A. Hoobler, and W. R. Mabey, *J. Amer. Chem. Soc.*, **94**, 2514 (1972).

Table II. Rate Constants Derived[a] from Scheme I

Reaction	Constant	3, 32°	Perester 102°	E_a
Tumbling	k_t (1 cP)	$(1.1 \times 10^{11} \text{ sec}^{-1})^a$	$(1.5 \times 10^{11} \text{ sec}^{-1})^a$	0.0
Internal rotation	k_r	$5.8 \times 10^{10} \text{ sec}^{-1}$	$6.7 \times 10^{10} \text{ sec}^{-1}$	0.5 kcal/mol
Combination	k_c	$1.0 \times 10^9 \text{ sec}^{-1}$	$1.8 \times 10^9 \text{ sec}^{-1}$	0.0
Disproportionation	k_2	$2.4 \times 10^9 \text{ sec}^{-1}$	$3.8 \times 10^9 \text{ sec}^{-1}$	0.9
Scavenging	k_s(DPPH)	$3.6 \times 10^9 \text{ l./(mol sec)}$		
Diffusion	k_d (1 cP)	$2.0 \times 10^9 \text{ sec}^{-1}$	$2.7 \times 10^9 \text{ sec}^{-1}$	0
$r_{\text{diffusion}}{}^b$		3.3 Å	3.2 Å	
$\tau_{\text{combination}}{}^c$		$1.8 \times 10^{-10} \text{ sec}$	$1.2 \times 10^{-10} \text{ sec}$	
$\tau_{\text{retention}}{}^d$		$6.0 \times 10^{-12} \text{ sec}$	$4.5 \times 10^{-12} \text{ sec}$	

[a] Assuming 2.0 Å as the effective tumbling radius of the 2-butyl radical and the Debye–Stokes relationship. [b] The effective radius for diffusion using the Stokes–Einstein relationship and the derived k_d. [c] The lifetime for all pairs giving combination. [d] The lifetime of the pairs giving retention.

at 30°. The concentration of **2** in the CCl₄ stock solution was estimated by low temperature nmr, comparing the area of the aliphatic protons to that of added dioxane. The nitrogen and carbon dioxide yields were determined by gas chromatography using argon as an internal standard. The optical purities of **5** were also measured and found to be the same as the first run. The results for the DPPH solutions were based on nitrogen. All of these results are summarized in Table I. The ether yields increased with increasing viscosity and decreased with increasing DPPH concentration. We interpret the ether yields in terms of the competition between combination (k_c), disproportionation (k_2), diffusion (k_d), and scavenging (k_s) of **4**, formed directly from the hyponitrite (**3**). Equation 1, derived from Scheme I, allows a quantitative comparison with the perester results.

$$\frac{1}{Y} - 1 = \frac{k_2}{k_c} + \frac{k_d}{k_c} + \frac{k_s(\text{DPPH})}{k_c} \quad (1)$$

The reciprocal yield function appears to be linear with fluidity to the $^3/_4$ power as was observed at higher temperature for the perester[1] but with higher slope ($k_d/k_c = 1.96$ vs. 1.49[1]). The direction of this change is opposite to the temperature effect expected from a Stokes–Einstein model for diffusion coefficients but is consistent with a reduction in combination efficiency due to the additional intervening nitrogen molecule or a positive activation energy for the combination process. The smaller relative increase in the intercept ($k_2/k_c = 2.32$ vs. 2.10 for the perester[1]) compared to the slope indicates a nonzero activation energy for either the disproportionation or combination. The optical purities also increase with increasing viscosity. The optical purity function, derived from Scheme I, is given by eq 2,

$$\frac{1}{Y}\left(\frac{1 - (\text{OP})}{2(\text{OP})}\right) = \frac{k_r}{k_c} + \frac{k_t}{k_c} \quad (2)$$

where k_r is the rate constant for the internal rotation path to inverted ether and k_t is the rate constant for the tumbling of the 2-butyl radical with respect to its *tert*-butoxy partner.[6] A linear correlation is again obtained using fluidity to the $^3/_4$ power. The slope ($k_t/k_c = 122$ vs. 84 for the perester[1]) is increased, which provides an *independent* suggestion of a reduced k_c for the present case. Furthermore, the extent of reduction in

(6) During the course of this work Meakin and Krusic[7] have provided independent esr evidence for two rotational correlation times which are ascribed to a viscosity sensitive tumbling (k_t) and a viscosity insensitive internal rotation (k_r).

(7) P. Meakin and P. Krusic, *J. Amer. Chem. Soc.*, **95**, 8185 (1973).
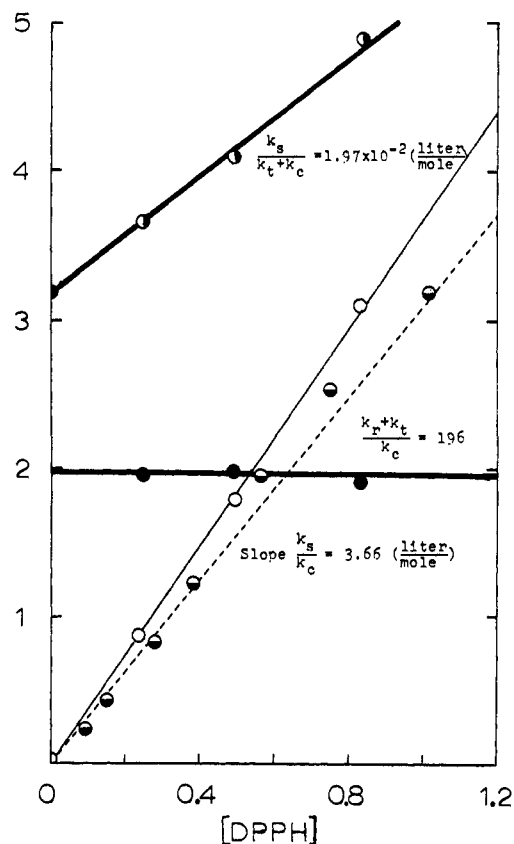
Figure 1. Scavenger effects: ◐, $(1/Y_{\text{DPPH}} - (1/Y_0, 1,1'$-dicyanobicyclohexyl, ref 9; ○, $(1/Y_{\text{DPPH}}) - (1/Y_0$, ether **5**; ●, $(1/2Y)(1 - (\text{OP})/(\text{OP})(10^{-2})$, ether **5**; ◑, $(2(\text{OP})/(1 - (\text{OP}))(10^2)$, ether **5**.

k_c required here is *identical* with that indicated by the diffusion result. The intercept increase is not in the same proportion as for the slopes ($k_r/k_c = 5.7$ vs. 3.7[1]) suggesting a smaller positive activation energy for k_r.

Figure 1 shows the sensitivity of the ether yield function to added DPPH. Equation 1a is chosen for this

$$\left(\frac{1}{Y}\right)_{\text{[DPPH]}} - \left(\frac{1}{Y}\right)_0 = \frac{k_s[\text{DPPH}]}{k_c} \quad (1a)$$

representation. The observed correlation is consistent with a simple pseudo-first-order scavenging reaction and the slope can be interpreted as the ratio of the rate constants ($k_s/k_c = 3.7$ mol/l.). Data of Waits and Hammond[8] for the formation of 1,1'-dicyanobicyclohexyl

(8) H. P. Waits and G. S. Hammond, *J. Amer. Chem. Soc.*, **86**, 1911 (1964).

from the corresponding ketenimine are included for comparison.

Scheme I implies two additional methods of assessing the effect of the scavenging path on optical purity. Equation 2a gives the function needed to obtain the

$$\left(\frac{2(OP)}{1-(OP)}\right)_{DPPH} = \frac{k_s[DPPH]}{k_t+k_r} + \left(\frac{2(OP)}{1-(OP)}\right)_0 \quad (2a)$$

scavenging to rotation–tumbling rates. Figure 1 contains a plot of the observed points which yields the ratio as 0.0197 (mol/l.). Alternatively, eq 2 predicts that the function on the left should be independent of DPPH. These points are also included in Figure 1.

The present data show a very high degree of internal consistency in the ratios of rate constants estimated by independent comparisons with effective translational and rotational motions. Table II summarizes these results in terms of absolute rate constants by setting k_t as the reciprocal of the Debye–Stokes rotational correlation time for a particle with a 2 Å effective rotational radius.

The present results are in accord with the original[9] cage model for combination, as distinct from the more frequently noted geminate effect model,[10] in that no evidence for distinct primary and secondary pairs is observed. The scavenging results demonstrate the feasibility of trapping species with lifetimes of the order of 10^{-10} sec. The choice between decreased entropy of activation for the deaminatively formed hyponitrite (implicitly assumed in Table II) and a positive activation energy for the combination must await results of variable temperature studies of the optically active perester.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this work.

(9) J. Frank and E. Rabinowitch, *Trans. Faraday Soc.*, **30**, 120 (1934); E. Rabinowitch and W. Wood, *ibid.*, **32**, 1381 (1936).

(10) Discussed in "Free Radicals," Vol. I, J. Kochi, Ed., Wiley, New York, N. Y., 1972.

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Studies on the Incorporation of $(2S,3R)$-$[4,4,4$-$^2H_3]$Valine and $(2S,3S)$-$[4,4,4$-$^2H_3]$Valine into β-Lactam Antibiotics

Sir:

Previous studies have clearly shown the asymmetric incorporation of $(2S,3S)$-$[4$-$^{13}C]$valine[1] and $(2S,3R)$-$[4$-$^{13}C]$valine[2] into β-lactam antibiotics. As a sequel, we have undertaken the synthesis of chirally labeled CD_3-valines[3] to examine the stereochemical fate of the isopropyl hydrogenes. The α,β-dehydrovaline derivative of a tripeptide[4,5] has been proposed as a possible common intermediate in the biosynthesis of penicillin and cephalosporin. This paper reports studies on the fate of the diastereotopic deuterium-labeled methyls

(1) H. Kluender, C. H. Bradley, C. J. Sih, P. Fawcett, and E. P. Abraham, *J. Amer. Chem. Soc.*, **95**, 6149 (1973).

(2) N. Neuss, C. H. Nash, J. E. Baldwin, P. A. Lemke, and J. B. Grutzner, *J. Amer. Chem. Soc.*, **95**, 3797 (1973).

(3) For other syntheses of chirally labeled CD_3-valines see R. K. Hill, S. Yan, and S. M. Arfin, *J. Amer. Chem. Soc.*, **95**, 7857 (1973); D. J. Aberhart and L. J. Lin, *ibid.*, **95**, 7859 (1973).

(4) E. P. Abraham and G. G. F. Newton, *Biochem. J.*, **79**, 377 (1961).

(5) A. L. Demain, *Trans. N. Y. Acad. Sci.*, **25**, 731 (1963).

of L-valine in the course of their incorporation into penicillin N and cephalosporin C.

The synthetic sequence employed for the preparation of $(2S,3S)$-$[4,4,4$-$^2H_3]$valine (1) parallels that used for the synthesis of $(2S,3S)$-$[4$-$^{13}C]$valine[1] except that CD_3I[6] was substituted for $^{13}CH_3I$. The trifluoroacetamide methyl ester derivative of $(2S,3R)$-methylaspartic acid (2) was used as the starting material for the preparation of $(2S,3R)$-$[4,4,4$-$^2H_3]$valine (5). The deuterium was
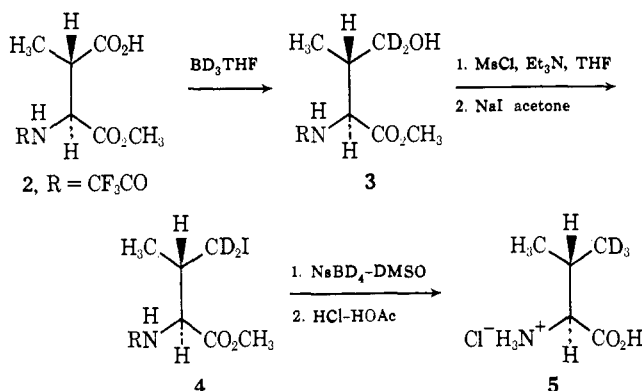
introduced *via* reduction of 2 with deuterated diborane yielding 3, which was converted to the iodide, 4, *via* mesylation followed by refluxing with sodium iodide in acetone. Reduction[7] of 4 with $NaBD_4$ in dimethyl sulfoxide followed by acidic hydrolysis afforded $(2S,3R)$-$[4,4,4$-$^2H_3]$valine (5) with a deuterium content of $78\% d_3$.

After incubation of 1 and 5 with washed cells of *Cephalosporium acremonium*, mutant C91,[8] for 10 hr, the resulting penicillin N and cephalosporin C were isolated,[1] converted into their respective N-acyl methyl ester derivatives,[9] and subjected to mass spectrometric analyses.[10] The results are summarized in Table I.

Consistent with our earlier incorporation experiments,[1] both penicillin N and cephalosporin C were enriched with deuterium to an extent of about 20–44%. Although several mass fragments[11] may be used in the calculation of isotopic ratios, the most intense of these are at m/e 174[12] for penicillin N and m/e 230 for cephalosporin C as shown in Table I. It is evident that the α-methyl of penicillin N derivative derived from 1 contained three deuteriums as clearly indicated by the very

(6) CD_3I (>99%) was a product of Aldrich. The final product, 1, had a deuterium content of >99%.

(7) Reduction of 4 using D_2 gas over 10% Pd/C at atmospheric pressure afforded valine with a deuterium content of only 51% d_3.

(8) B. Smith, S. C. Warren, G. G. F. Newton, and E. P. Abraham, *Biochem. J.*, **103**, 877 (1967).

(9) The crude penicillin N (79% pure by bioassay), isolated *via* the procedure previously described (ref 1), was treated with an excess of benzoyl chloride and potassium dibasic phosphate in acetone–water, followed by diazomethane. The N-benzylpenicillin N methyl ester was purified by tlc (pH 7.0 buffered silica gel) using ether–tetrahydrofuran (9:1) as the solvent system. The crude cephalosporin C was chromatographed on cellulose plates using 1-butanol–water–acetic acid (80:20:20); the purified cephalosporin C (90% pure by uv assay) was treated with acetic anhydride in phosphate buffer at pH 8–9. After the usual work-up, it was treated with diazomethane to yield N-acetylcephalosporin C methyl ester. In a control experiment, no isomerization of the Δ^3-cephem to the Δ^2-cephem derivative was observed under these conditions.

(10) Mass spectra were obtained with an AEI MS-9 mass spectrometer using direct probe introduction with an ion source temperature of 180–190°, electron potential of 70 eV and an ionizing current of 100 μA.

(11) Similar isotopic ratios of other fragments at m/e 485 and 366 for the cephalosporin C derivative and m/e 491 for the penicillin N were obtained.

(12) W. Richter and K. Biemann, *Monatsh. Chem.*, **95**, 766 (1964).