bond lengths[13] and reactivity.[1,2] (10) The optimal paths and conformations deduced from computations may be of particular interest in the study of enzyme reactions.

In a nonenzymatic hydrolysis reaction the most stable tetrahedral species is expected to form preferentially. However this thermodynamically preferred conformer may not be (and, in the present $CH(OH)_2NH_2$ case, is not) the kinetically most labile one.

In enzymatic hydrolysis the arrangement of the catalytic groups in the active site may be such as to impose upon the tetrahedral intermediate optimal stereoelectronic effects for fast and specific reaction. By making use of the enzyme-substrate binding forces, the active site may lock the tetrahedral intermediate in the conformation (3 in the present case, or perhaps one of the most closely related other forms) which is *not* the most stable one of the free species but which leads to *easiest* and most *selective* cleavage of the C–N bond in the case of amide hydrolysis. Such conformational locking can occur both in the substrate cleavage step and in the deacylation of the acyl enzyme. Conversely, from an independent knowledge of the optimal conformer it is possible to make inferences about the required geometry of the active site. A special class of nonproductive substrates would be those which bind and undergo reaction with the catalytic groups but lead to a tetrahedral species which favors C–O cleavage over C–N cleavage (as in 2, 4, or 5), thus reverting to the starting material.

The present and previous[7a] conclusions apply to neutral tetrahedral intermediates. Similar stereoelectronic effects should operate in the charged derivatives occurring in acid or base catalyzed reactions and in other species containing geminal heteroatoms (derived from imines, urea, etc.).

Theoretical studies which help uncover the requirements for optimal reactivity and/or specificity should have impact both on the understanding of enzyme catalysis and on the design of synthetic molecular catalysts.

(13) H. B. Bürgi, J. D. Dunitz, and E. Shefter, in preparation; H. B. Bürgi, private communication.
(14) E. R. A. 265 du C. N. R. S.

J. M. Lehn,* G. Wipff

Institut de Chimie, Université Louis Pasteur
*67-Strasbourg, France[14]*

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Cycloadditions of Allyl Anions. I. A Regiospecific and Stereospecific Pentannelation Reaction

Sir:

In recent years, the synthetic challenges posed by the much heralded prostaglandins have stimulated a flurry of activity in new syntheses for functionalized cyclopentanes. Despite many very elegant approaches to the aforementioned molecules,[1] there is still noticeably lacking a direct method for the construction of five-

(1) For recent reviews on Prostaglandin syntheses, see U. Axen, J. E. Pike, and W. P. Schneider in "The Total Synthesis of Natural Products," Vol. I, J. ApSimon, Ed., Wiley-Interscience, New York, N. Y., 1973, pp 81–142; N. M. Weinshenker and N. H. Anderson in "The Prostaglandins," Vol. I, P. W. Ramwell, Ed., Plenum Press, New York, N. Y., 1973, pp 5–82.

membered rings which would rival the generality and stereospecificity of the Diels–Alder reaction. The timely formulation and predictions of the Woodward–Hoffmann rules[2] have clearly delineated the possibility for concerted cycloadditions of allyl anions with unsaturated systems to produce cyclopentyl anions. To date, the symmetry allowed concerted process of the type $_\pi 2_s + _\pi 4_s$ has not been clearly demonstrated for allyl anions.[3] We have been involved in the preparation and utilization of allyl anion synthons of the general type 1, with the objective of cycloadding these four-electron systems to unsaturated molecules (A=B).

1   2
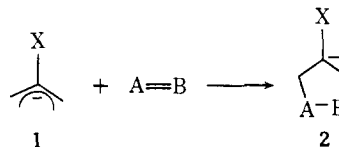
Our approach to the synthesis of cyclopentanoids requires that our allyl anion synthons meet the following criteria: (1) that the allyl anion can be rapidly generated under irreversible conditions, (2) that the stability of the allyl anion is not so great as to diminish the nucleophilicity of the carbanion, and (3) that an electron-withdrawing X moiety be cross-conjugated with the allyl system in order to stabilize the resulting cyclopentyl anion. While these requirements are not inherent for a concerted $_\pi 2_s + _\pi 4_s$ process, we did not expect them to perturb the "concertedness" of the cycloaddition, and in fact we anticipated that they would provide maximum driving force for the cycloadditions. A final point of definition in the design of our allyl synthons needs some elaboration. Substituents at the extremities of the allyl anion must be arranged in such a manner as to prevent formation of an allyl anion which is conjugated with the X group. This objective may be met if an anion directing moiety resides at one end of the allyl system.

In this communication we wish to report on one example of the above approach which promises to be the prototype for a general regiospecific and *stereospecific pentannelation*[4] process. The present system contains a cyclic ketone function as the electron-withdrawing X group, while the allyl anion is derived from a vinyl sulfide. Over a decade ago, Ireland and Marshall[5] introduced the exo-thiobutylmethylene moiety as a protecting group for the α position of cyclic ketones. Synthetically, this allowed for specific substitution at the other α positions. We have revived this functionality and transformed it from a protecting group to an activating group. Instead of n-butylthiol, we have used p-chlorobenzenethiol to form the exo-methylene sulfide for the following reasons: (1) to enhance the crystallinity of the products, (2) to facilitate allyl anion formation and stabilize the resulting anion, and (3) to ensure the unidirectional deprotonation of the vinyl sulfide.

(2) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.
(3) Kauffmann has stereoselectively trapped the 1,3-diphenyl-2-azaallyl anion (T. Kauffman, *Angew. Chem., Int. Ed., Engl.*, 11, 290 (1972)) and has reported one instance of the cycloaddition of 2-phenyl allyl anion to stilbene (*Angew. Chem.*, 84, 292 (1972)). For a summary of allyl anion formations from cyclopropyl anion openings, see W. T. Ford and M. Newcomb, *J. Amer. Chem. Soc.*, 95, 6277 (1973); R. Huisgen and P. Eberhard, *ibid.*, 94, 1346 (1972).
(4) The term pentannelation is defined as the annulation of a five-membered ring to another ring of any size in one synthetic operation.
(5) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, 27, 1615 (1962).

To implement our plans for cycloadditions, 2,2-dimethyl-6-(p-chlorothiophenylmethylene)cyclohexanone[6] (4) was prepared in high yield and by standard procedures[5,7] as outlined in Scheme I. The gem-

Scheme I

3

4

Ar = p-ClPh
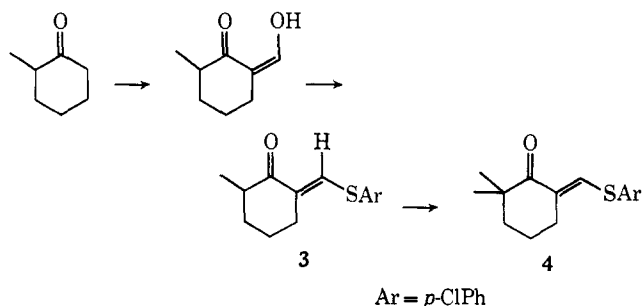
dimethyl groups were chosen as convenient blocking groups for the other acidic sites. Since the vinyl sulfide also acts as a protecting moiety, many other functionalities and substituents could replace the present dimethyl groups and their introduction into the molecule could come from several directions. We have found that vinyl sulfide 3 was best prepared (>85%) from the pure vinyl alcohol by treatment first with tosyl chloride in pyridine at 0° and then addition of the thiol at 0°. The crystalline dimethyl derivative 4 (mp 104–105°)[6] was prepared according to Ireland's procedure[5] and was shown to be the trans isomer from the downfield position of the vinyl hydrogen.[8]

When the allyl anion synthon 4 was treated at −78° with 1 equiv of lithium diisopropylamide in THF for 1–2 hr and at −30° for 3–4 hr, a deep yellow-orange color developed.[9] At −78°, 2 equiv of an α,β-unsaturated ester 5 was added very slowly in a THF solution. The reaction mixture was kept at −78° for several hours and then allowed to warm to room temperature overnight. With ethyl acrylate 5a as the trap, a 65% (95% based on recovered starting material) yield of a crystalline cycloadduct 6a (mp 131–134°) was obtained. When the allyl anion was trapped by diethyl fumarate, 5b, once again a single diastereomer 6b (mp 134–135°) was isolated along with some starting vinyl sulfide. We tentatively have assigned the stereochemistry of this cycloadduct with the two ester groups trans. An attempt to prepare the cis-diester cycloadduct from diethyl maleate resulted in the production of the same isomer 6b isolated from the fumarate reaction. Apparently the diethyl maleate isomerized to the fumarate under the reaction conditions, before the cycloaddition. This was substantiated by the isolation of only diethyl fumarate from the maleate mother liquors.[10]

In assigning the relative stereochemistry of the groups in the cyclopentane ring, we have assumed initially that the cis-fused hydrindanone is the thermodynami-

4

5

R

6a, R = H
b, R = CO₂Et
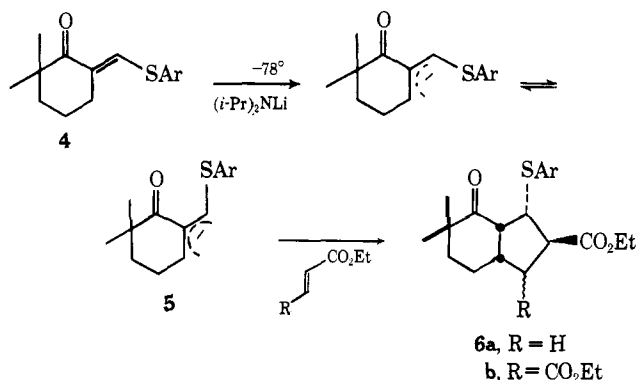
cally more stable isomer.[11] When the cycloadduct 6a from ethyl acrylate was oxidized with 1 equiv of m-chloroperbenzoic acid, two crystalline sulfoxides, A (mp 157–158°) and B (mp 166–168°), were produced in a ratio of 2:1. Furthermore, the nmr spectrum of sulfoxide B exhibited a shielded methyl resonance at δ 0.65 instead of the usual methyl chemical shift.[12] We have interpreted the diastereomeric sulfoxides A and B as arising only from the endo sulfide 6a, since no conformation of an exo-sulfide would yield two different sulfoxides, one of which displays a significant shielding of one of the gem-methyls. The nmr spectrum of 6a was most consistent for a trans arrangement between the –SAr and the carbethoxy groups.[13] The regiospecificity of adduct 6a was more rigorously shown by first oxidation of sulfoxides A and B separately, with excess trifluoroperacetic acid in methylene chloride. These oxidations yielded an identical hydroxysulfone, 7, which was easily converted to the decarboxylated dione 8 when treated with potassium hydroxide in refluxing chloroform. The formation of the hydroxysulfone

A + B

7

8
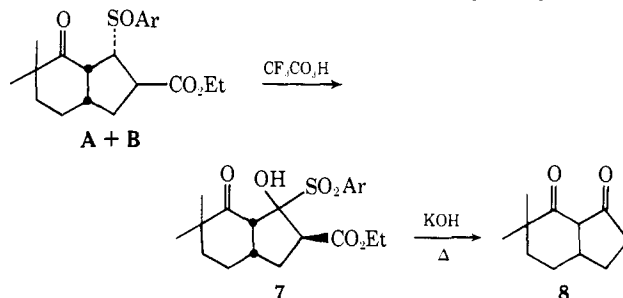
7 can easily be accounted for by an initial Pummerer reaction followed by oxidation of the resulting hydroxysulfide. The subsequent nonhydrolytic ketone generation and decarboxylation also represents a novel transformation of an aryl sulfoxide.[14]

Mechanistically, we envisage the above pentannelations as a concerted $_\pi 2_s + {}_\pi 4_s$ cycloaddition of the W form of the allyl anion.[15] We favor a concerted reaction

(6) All new compounds gave satisfactory elemental analyses.

(7) C. Ainsworth, "Organic Synthesis," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 536.

(8) The chemical shift of the vinyl hydrogen is δ 7.5 (CDCl₃). A. Hassner and T. C. Mead, Tetrahedron, 20, 2201 (1964), found the vinyl hydrogen absorption for the cis and trans isomers of 2,2-diphenyl-6-benzylidenecyclohexanone at δ 6.33 and 7.0–7.5, respectively.

(9) The color developed at −78° during the first hour and was reproducible.

(10) E. B. Milovskaya, O. V. Soklova, and B. L. Erusalimskii, Zh. Obshch. Khim., 32, 621 (1962). These workers found that Me₂NH isomerized maleate esters to fumarates very rapidly and completely at room temperature.

(11) E. L. Eliel in "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, New York, N. Y., 1962, p 276.

(12) The chemical shifts for the gem-dimethyl groups are: 6a (CDCl₃), δ 0.90, 1.03; sulfoxide A, 0.90 and 1.05; sulfoxide B, 0.65 and 1.00.

(13) The HA100 nmr spectrum in CDCl₃ was most consistent for the regiospecificity shown for 6a and the trans relationship for the SAr and CO₂Et groups. The proton α to the SAr group was a doublet of doublets centered at δ 3.25 (J = 4.7 and J = 9.2 Hz).

(14) More details on the conversion of aryl sulfoxides to ketones under nonhydrolysis conditions will be reported elsewhere.

(15) Kaufmann (ref 3) has shown that the 1,3-diphenyl-2-azallyl anion prefers the trans-trans or W-form conformation in its cycloadditions. Also see H. H. Freedman, V. R. Sandel, and B. P. Thill, J. Amer. Chem. Soc., 89, 1762 (1967), for a discussion of the geometric stability of 1,3-diphenylallyllithium.

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.

J. P. Marino,* Wm. B. Mesbergen

*Department of Chemistry, University of Michigan
Ann Arbor, Michigan 48104*
Received November 1, 1973

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]
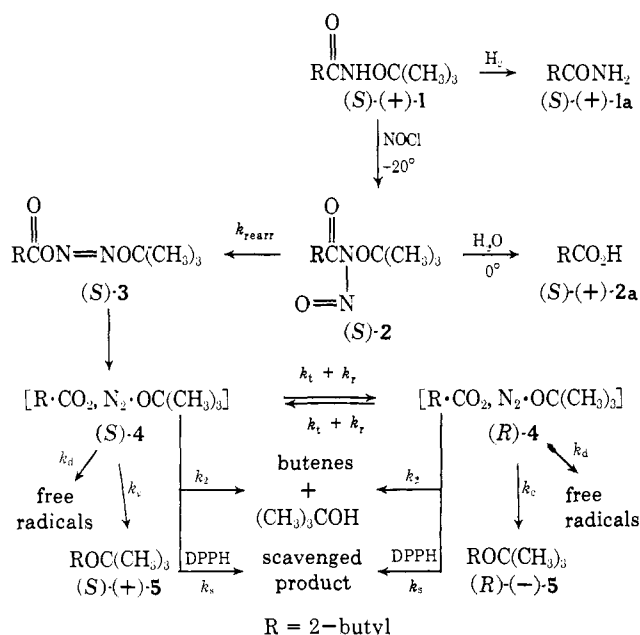
R = 2—butyl

[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
CHCl$_3$		0.555	(1.00)	0.99	0.158	(0.016)
CHCl$_3$	0.25	0.555	(1.00)	0.96	0.139	0.018
CHCl$_3$	0.50	0.555	(1.00)	0.97	0.123	0.020
CHCl$_3$	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$_2$O; lit.[3] $[\alpha]^{23°}_{589}$ +18.31, H$_2$O). 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).