from the initial slope of experiments in which $[S_0] >> K_m$. The constant k_{cat} was then calculated using the equation $V_{max} = k_{cat}[E_0]$. The cinnamoylimidazole titration was used to determine $[E_0]$.[9] Figure 2 (curve B) shows a plot of k_{cat} as a function of pH.

We interpret these data as follows. (1) The results of Figure 2 show that k_{cat} and k_{obsd} have the same pH dependency and that k_{cat} and k_{obsd} are approximately equal. (As expected from eq 3, if $k_2/k_3 \neq \infty$, k_{cat} is slightly less than k_3.) This implies that the intermediate formed from the acid at low pH is the kinetically important intermediate in the turnover reaction of the ester (*i.e.*, $k_{obsd} = k_3$) and, furthermore, that this intermediate does not contain the alcohol moiety of the original substrate since it (the intermediate) can be prepared from a species (the acid) in which the leaving group is only water. (2) Only one process is observable in Figure 1. No other intermediate is seen. No nonrandom deviations from first-order kinetics can be observed in either the initial or the final stages of the deacylation reaction. This result argues against theories which involve a rate-determining transfer of the acyl group from one enzyme residue to another. (3) The constant k_3 applies to a first-order process, but k_{cat} is calculated by dividing a zero-order velocity by the enzyme concentration. The agreement of these two constants indicates that the cinnamoylimidazole titration and the other titration procedures[8] really do measure the absolute concentration of those active sites which are involved in the hydrolysis of specific substrates.

These results indicate that in the steady-state hydrolysis of a specific ester substrate there is one kinetically important intermediate (other than an enzyme–substrate complex).[10] The fact that this intermediate is formed at low pH in equilibrium with the acid and the free enzyme strongly suggests that it is an acyl-enzyme although it does not directly identify the enzyme residue which is acylated. Our results do not, of course, exclude the possibility that other steps (such as changes in the conformation of the enzyme) may occur on the reaction pathway. They do indicate, however, that the rates of these steps, if they occur, must be considerably greater than that of the rate-determining step.

We believe that these experiments not only give strong support to the hypothesis that at neutral pH there is on the stopped-flow time scale (milliseconds) one kinetically important intermediate (other than an enzyme–substrate complex) in chymotrypsin-catalyzed hydrolyses of specific ester substrates; they also indicate that this intermediate is an acyl-enzyme.

(9) M. L. Bender, M. L. Begue-Canton, R. L. Blakeley, L. J. Brubacher, J. Feder, C. R. Gunter, F. J. Kézdy, J. V. Killheffer, Jr., T. H. Marshall, C. G. Miller, R. W. Roeske, and J. K. Stoops, *J. Am. Chem. Soc.*, 88, 5890 (1966).

(10) T. E. Barman and H. Gutfreund (*Biochem. J.*, **101**, 411 (1966)) have argued that the results of their study of the rate of ethanol release in the reaction of chymotrypsin and N-(furyl)acryloyl-L-tyrosine ethyl ester demand the inclusion of intermediates other than those indicated in eq 1. A. Himoe and G. P. Hess (*Biochem. Biophys. Res. Commum.*, 27, 494 (1967)), however, have shown that these results can be satisfactorily accounted for by eq 1.

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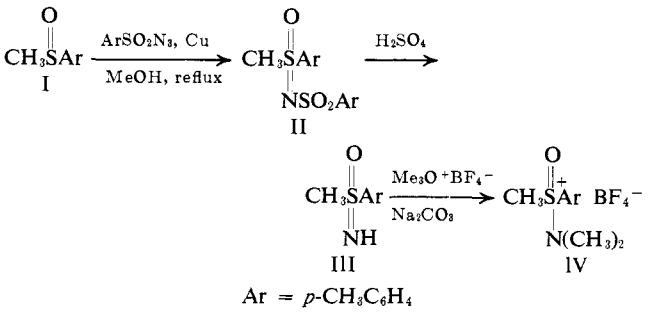
Synthesis of Optically Active Cyclopropanes and Oxiranes Using an Optically Active Oxosulfonium Methylide[1,2]

Sir:

Oxosulfonium ylides derived from salts of sulfoximines were shown in an earlier report to be convenient reagents for the synthesis of oxiranes and cyclopropanes. It was suggested that optically active ylides in this series might be useful in asymmetric synthesis.[3] We have found that optically active N,N-dimethylamino-*p*-tolyloxosulfonium methylide is capable of transferring its methylene in an asymmetric manner to suitably substituted electrophilic double bonds.

Beginning with the optically active sulfoxide I,[4] the salt, (*R*)-(−)-(N,N-dimethylamino)methyl-*p*-tolyloxosulfonium fluoroborate (IV), was prepared (Scheme I).

Scheme I



Ar = *p*-$CH_3C_6H_4$

For the preparation of *dl*-sulfoximine III it was found convenient to react the *dl*-sulfoxide I with hydrazoic acid (sodium azide, sulfuric acid, chloroform); it was found, however, that these conditions lead to racemization of the optically active sulfoxide prior to conversion to sulfoximine. The problem was readily circumvented by the use of the copper-catalyzed decomposition of *p*-toluenesulfonyl azide[5] followed by acid hydrolysis.[6] The over-all yield for the sequence I → IV was 71%. The optical rotations for the various sulfur compounds are given in Table I.

Table I. Characteristics of Sulfur Compounds

Compd	Absolute configuration	$[\alpha]_D$, deg	Mp, °C
I	*R*	+149.1[a,c]	74–76
II	*R*	−144.0[a,d]	158–161
III	*R*	−33.8[a,e]	58–62
IV	*R*	−4.6[a]	65–67
VI	*R*	−165.9[b,f]	64–66

[a] Acetone. [b] Ethanol. [c] Optical purity 96% based on 155° reported by M. A. Sabol, R. W. Davenport, and K. K. Andersen, *Tetrahedron Letters*, 2159 (1968). [d] $[\alpha]_{546}$ −174.6° compared to −172.5° reported by D. R. Rayner, D. M. von Schriltz, J. Day, and D. J. Cram, *J. Am. Chem. Soc.*, **90**, 2721 (1968). [e] $[\alpha]_{546}$ −41.5° compared to −39.9° (reported by Cram)[d]. [f] Lit.[9] for *S* compound, +157°.

(1) (a) Chemistry of Sulfoxides and Related Compounds. XV. (b) Part XIV: C. R. Johnson and W. G. Phillips, *J. Am. Chem. Soc.*, in press.

(2) We gratefully acknowledge support by the National Science Foundation (Grant No. GP-5944).

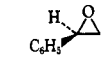
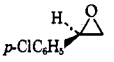
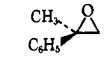
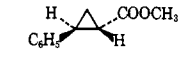
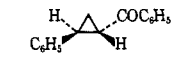
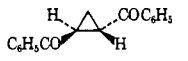
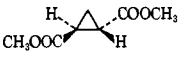
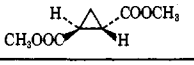
(3) C. R. Johnson, E. R. Janiga, and M. Haake, *J. Am. Chem. Soc.*, **90**, 3890 (1968).

(4) (a) K. K. Andersen, *Tetrahedron Letters*, 93 (1962); (b) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternary, Jr., *J. Am. Chem. Soc.*, 87, 1958 (1965).

(5) H. Kwart and A. A. Kahn, *ibid.*, **89**, 1950 (1967).

(6) H. R. Bently and J. K. Whitehead, *J. Chem. Soc.*, 2081 (1950).

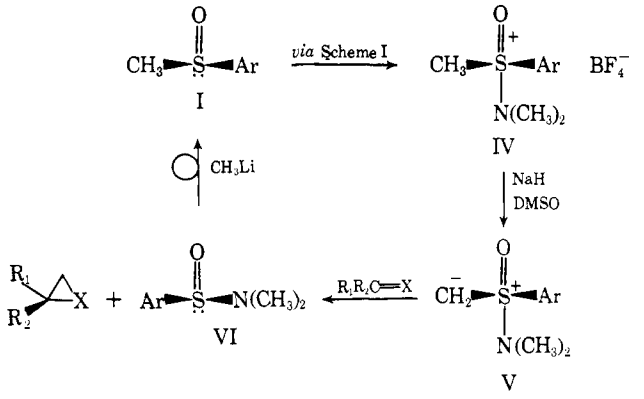
Table II. Reactions of Optically Active Ylide V

Substrate	Product	Yield, %	$[\alpha]_D$, deg (acetone)	Optical purity, %	Absolute configuration[a]
Benzaldehyde		60	+1.56	5[b]	*R*
p-Chlorobenzaldehyde		74	+0.60		(*R*)
Acetophenone		38	+1.90		(*R*)
trans-Methyl cinnamate		76	+95.0	30.4[c]	1*S*:2*S*
trans-Chalcone		94	+137.7	35.3[d]	(1*S*:2*S*)
trans-1,4-Diphenyl-2-buten-1,4-dione		76	+46.9		(1*S*:2*S*)
Dimethyl fumarate		60	+30.4	15.2[e]	1*S*:2*S*
Dimethyl maleate		56	+35.7	17.8[e]	1*S*:2*S*

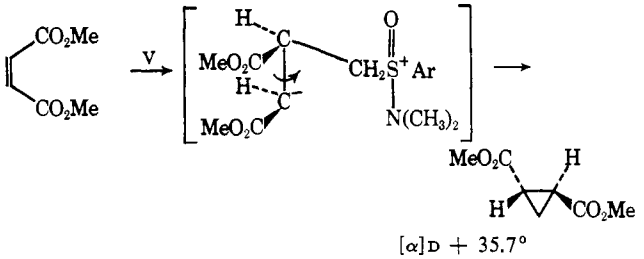
[a] Absolute configurations shown in parentheses are tentative assignments and based solely on analogy to the established configurations of related products produced by reaction with ylide V. [b] Based on $[\alpha]_{max}$ +31°.[8b] [c] Based on $[\alpha]_{max}$ +311° (Y. Inouye, T. Sugita, and H. M. Walborsky, *Tetrahedron*, **20**, 1965 (1964)). [d] Based on $[\alpha]_{max}$ +390.5° (obtained by resolution by fractional crystallization). [e] Based on $[\alpha]_{max}$ +200°.[8d]

The optically active ylide V, formed by treating salt IV with sodium hydride, is generated and reacted at room temperature in dimethyl sulfoxide. Reaction of the ylide in dimethyl sulfoxide with aldehydes or ketones produces optically active oxiranes, whereas reaction with electrophilic olefins yields optically active cyclopropanes (Scheme II). For example, when ylide V was

Scheme II



allowed to react with methyl cinnamate the product, (1*S*,2*S*)-(+)-*trans*-methyl 2-phenylcyclopropanecarboxylate, was obtained in 76% yield with an optical purity of 30.4%. Evidence that such reactions proceed through an intermediate betaine is found in the case of addition to dimethyl maleate. The only product



obtained is the *trans* adduct; the formation of the *trans* product is rationalized by suggesting that rotation about a single bond of the betaine adduct occurs. Apparently formation of the betaine is a reversible reaction; control experiments indicate that the ylide is capable of isomerizing dimethyl maleate to dimethyl fumarate.

A summary of examples of asymmetric syntheses employing ylide V is provided in Table II. *In all cases where comparative data are available,*[7,8] *the optical purity obtained is the highest reported to date for a direct asymmetric synthesis.*

The by-product of these reactions, (*R*)-(−)-N,N-dimethyl-*p*-toluenesulfinamide (VI), was isolated and found to have $[\alpha]_D$ −165.9°. Treatment of the sulfinamide VI with methyllithium in ether afforded the sulfoxide I ($[\alpha]_D$ +125.1°, optical purity 81%) of configuration identical with that employed at the start of Scheme I. This latter reaction must proceed by inversion of configuration,[9,10] since by analysis of the reactions at the sulfur atom in the conversion of I to VI an inversion of the chirality at the sulfur atom must occur.[11] The regeneration of the starting sulfoxide I

(7) Optically active oxiranes have been produced by asymmetric epoxidations: (a) R. C. Ewins, H. B. Henbest, and M. A. McKervey, *Chem. Commum.*, 1085 (1967); (b) H. B. Henbest, "Organic Reaction Mechanisms," Special Publication No. 19, The Chemical Society, London, 1965; (c) G. V. Pigulevskii and G. V. Markina, *Dokl. Akad. Nauk SSSR*, **63**, 6277 (1948); (d) R. M. Bowman, J. F. Collins, and M. F. Grundon, *Chem. Commum.*, 1131 (1967).

(8) Optically active cyclopropanes have been produced in asymmetric syntheses by (a) the base-catalyzed condensation of (−)-menthyl chloroacetate with ethyl acrylate [H. M. Walborsky and C. G. Pitt, *J. Am. Chem. Soc.*, **84**, 4831 (1962)] and related reactions [Y. Inouye, S. Inamasu, and H. Horiike, *Chem. Ind.* (London), 1293 (1967)]; (b) condensation of *C*-(−)-menthyl-P,P-diethyl-2-phosphonopropionate with epoxides [I. Tomoskozi, *Tetrahedron*, **22**, 179 (1966)]; (c) condensation of sulfonium methylides with (−)-menthyl or (+)-bornyl β-arylacrylates [H. Nozaki, H. Ito, D. Tunemoto, and K. Kondo, *ibid.*, **22**, 441 (1966)]; (d) the Simmons–Smith reaction with (−)-menthyl esters of unsaturated acids [S. Sawada, K. Takehana, and Y. Inouye, *J. Org. Chem.* **33**, 1767 (1968)] or in the presence of (−)-menthyl [S. Sawade, J. Oda, and Y. Inouye, *ibid.*, **33**, 2141 (1968)].

(9) S. Colonna, R. Giovine, and F. Montanari, *Chem. Commun.*, 865 (1968).

(10) J. Jacobus and K. Mislow, *ibid.*, 253 (1968).

(11) It is amusing to note that, although neither the sequence I → IV (addition of the dimethylamino group) nor the sequence IV → VI (loss of methyl) can be associated with an inversion of configuration at the sulfur atom, the combination of the sequences (I → VI) does result in the inversion of configuration at the sulfur atom. The over-all

allows the effective asymmetric reagent to be cycled, eliminating the need for a new resolution step with each asymmetric synthesis. Extensive studies of these seemingly versatile ylides as well as the properties of optically active products of the type reported here continue in our laboratories.[12,12a]

effect of the conversion of I to VI is to interchange the position of a substituent on sulfur and the free electron pair. Note that the configuration label remains *R* throughout the series although the sulfur atom of the sulfinamide and sulfoxide has the opposite chirality.

(12) M. E. Munk and J. L. Horvath, Jr., have recently resolved a sulfonium salt suitable for the generation of an optically active methylide (private communication, Professor Munk, Arizona State University).

(12a) NOTE ADDED IN PROOF. D. Darwish and R. L. Tomilson [*J. Am. Chem. Soc.* **90**, 5938 (1968)] have recently reported on the preparation and racemization of an optically active sulfonium ylide.

(13) (a) Alfred P. Sloan Research Fellow, 1965–1968; (b) National Science Foundation Graduate Trainee, 1967–1968.

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The Titanium–Naphthalene-Catalyzed Synthesis of Sodium Hydride from the Elements at Room Temperature and Atmospheric Pressure

Sir:

Recent endeavors in this laboratory have been concerned with effecting normally difficult reductions, *e.g.*, molecular nitrogen to ammonia,[1-3] under mild conditions by employing selected transition metal coordinating species along with suitable electron sources. An issue of this program is the high-yield room-temperature–atmospheric pressure synthesis of sodium hydride from molecular hydrogen and metallic sodium, described herein. Traditionally an uncatalyzed reaction requiring several hundred degree temperatures,[4] such ready and complete combination of these elements can be achieved in a matter of minutes by addition of catalytic amounts of titanium tetraisopropoxide and naphthalene to the reaction medium.

The general procedure involves vigorously stirring a mixture of sodium chunks and naphthalene in dry THF (80–100 ml) at room temperature under 1 atm of hydrogen (passed through a P_2O_5 drying tower and then a solution of sodium benzophenone ketyl in tetraglyme) while adding dropwise a solution of $(i\text{-PrO})_4\text{Ti}$ in tetrahydrofuran (THF) (10^{-1} to 10^{-4} *M*) fast enough to maintain a maximum rate of hydrogen absorption. The total amount of $(i\text{-PrO})_4\text{Ti}$ used was 0.1–1 mole % of the sodium. The gas volume changes were measured with a gas buret system connected to the reaction flask. As the reaction neared completion, the dark green mixture took on a brown coloration and finally reached a red-brown to brown color, depending upon the relative amounts of reactants used. The amount of hydrogen absorbed corresponded to 90–100% of that required for sodium hydride formation.

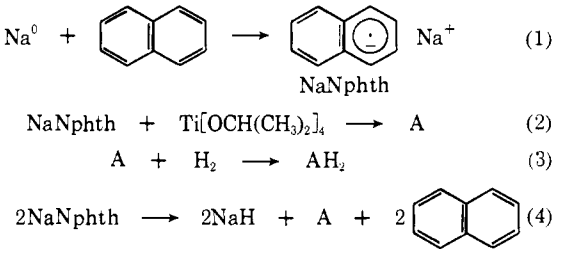
Hydrolysis of a typical reaction product mixture gave 1.9 moles of gas per mole of hydrogen absorbed. That the gas evolved was hydrogen was demonstrated by its utility in the quantitative conversion of maleic acid to succinic acid in the presence of PtO_2.

The role of $(i\text{-PrO})_4\text{Ti}$ was demonstrated by stirring a room-temperature THF solution of sodium naphthalide (50 mmoles) under hydrogen and observing only very slow hydrogen absorption.[5] Upon commencement of addition of 0.1 mole % $(i\text{-PrO})_4\text{Ti}$, the absorption rate increased sharply and the reaction was complete in 47 min.

Naphthalene is a required catalytic constituent of the reaction. No hydrogen absorption was observed during 25 min by a mixture of sodium dispersion (50 mg-atoms) in THF and $(i\text{-PrO})_4\text{Ti}$ (0.1 g-atom % of sodium). Upon addition of naphthalene (5 mole % based on sodium) and further amounts (0.2 mole % based on sodium) of $(i\text{-PrO})_4\text{Ti}$, hydrogen absorption commenced and was complete in 29 hr. In a similar run on a slightly larger scale (65 mg-atoms of sodium) the naphthalene was present in 20 mole % (based on sodium), and the reaction was over in 3 hr. The naphthalene can be recovered quantitatively from a hydrolyzed reaction mixture.

To demonstrate that the product is indeed sodium hydride, the flask content at the end of a reaction was centrifuged, providing a gray substance contaminated with small quantities of a white solid. A sample of gray material was hydrolyzed to give the theoretical (based on sodium hydride) amount of hydrogen and 89% of the theoretical amount of sodium hydroxide. Two samples each containing some white material gave a ratio of H_2:NaOH = 0.98 and 0.95, respectively.

Although the entire catalytic sequence cannot be delineated unequivocally at this time, the phenomena featured in eq 1–4 seem likely (A = lower valent titanium species).[2,6]



Acknowledgment. The authors are grateful to National Institutes of Health for financial support (Grant GM-13797).

(1) E. E. van Tamelen, G. Boche, S. W. Ela, and R. B. Fechter, *J. Am. Chem. Soc.*, **89**, 5707 (1967).

(2) E. E. van Tamelen, G. Boche, and R. Greeley, *ibid.*, **90**, 1677 (1968).

(3) E. E. van Tamelen and B. Åkermark, *ibid.*, **90**, 4492 (1968).

(4) G. W. Matson and T. P. Whaley, *Inorg. Syn.*, **5**, 10 (1957).

(5) The use of sodium naphthalide in the noncatalytic reduction of molecular nitrogen has been disclosed.[1] Its stoichiometric reaction with molecular hydrogen also had been observed in this laboratory and was recently published by S. Bank and T. A. Lois, *J. Am. Chem. Soc.*, **90**, 4505 (1968).

(6) The nature of the actual titanium catalyst in this and related fixation–reduction reactions will be the subject of a future publication.

(7) NIH Postdoctoral Fellow.

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The Molecular Structure of a Thiocarbonyl Oxide[1]

Sir:

Although numerous compounds with the thiocarbonyl oxide grouping have been prepared, generally

(1) Abstracted from the Ph.D. Thesis of G. A. Wolfe, University of Arizona, 1968.