Addition of Aromatic Thiols to Conjugated Cycloalkenones, Catalyzed by Chiral β-Hydroxy Amines. A Mechanistic Study on Homogeneous Catalytic Asymmetric Synthesis[1]

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Abstract: Reactions between aromatic thiols and conjugated cycloalkenones afford optically active 3-arylthiocycloalkanones, when chiral bases are used as catalysts. This paper reports a detailed investigation into the mechanism of this catalytic asymmetric synthesis. The reaction has been performed under a variety of conditions. Catalysts containing the β-hydroxy amine moiety (cinchona and ephedra alkaloids) give higher reaction rates and higher enantiomeric excesses (ee's) (up to 75%) than catalysts without a hydroxyl function. Polar solvents, concentrated reaction solutions, and the presence of tetra-*n*-butylammonium salts lower the ee's substantially. Kinetic measurements on a quinine-catalyzed reaction in toluene solution point to a third-order reaction, first order in each of the reactants. Activation enthalpies are very low (~0 kcal/mol) and activation entropies highly negative (~−62 cal/(mol K)). Models of the transition-state complexes of the thiol addition reactions are proposed, which account well for the experimental data on reaction rate, ee, and absolute configuration. The erythro cinchona and ephedra alkaloids catalyze the reaction via tight transition-state complexes, composed of three species: thiol, enone, and catalyst. Important for the geometry of these complexes are three stabilizing interactions: an electrostatic interaction between the thiol anion and the ammonium cation, a hydrogen bond between the catalyst hydroxyl group and the enone carbonyl group, and a dispersion interaction between the catalyst aromatic ring system and the thiol anion. Different steric conditions cause a free-energy difference between two possible orientations of the enone, resulting in formation of unequal amounts of *R* and *S* products. The threo cinchona alkaloids and the catalysts without a hydroxyl group lack at least one of the stabilizing interactions, leading to less structured transition states and consequently lower ee's. The suggestion is made that these mechanisms of asymmetric catalysis also hold for other reaction types, catalyzed by cinchona and ephedra alkaloids. The alkaloids having the erythro β-hydroxy amine configuration can be viewed as bifunctional catalysts. The value of such chiral catalysts in catalytic asymmetric synthesis is discussed.

Catalytic asymmetric synthesis is the most attractive method for the preparation of pure enantiomers, using achiral starting materials. The amount of the chiral reagent is small compared to the number of molecules synthesized, and the desired chiral product is obtained free from any chiral auxiliary substance.[2] Furthermore, a catalytic asymmetric reaction may be studied as a primitive enzyme model. Enzymes are structurally the most ideal chiral catalysts, and they are successfully applied in organic synthesis.[3,4] However, their utility is limited and application has not yet become a standard method. Considerable progress has been made during the last decade in developing chiral metal complexes as homogeneous catalysts for a variety of asymmetric reactions, and ee's above 90% have been obtained in selected cases.[5] Surprisingly, much less attention has been paid to the exploration of the utility of chiral amines in base-catalyzed asymmetric reactions, although chiral amines are often more stable and accessible than chiral metal complexes; furthermore, amine-catalyzed reactions are often easily performed.

Some base-catalyzed addition reactions to carbonyl groups and carbon–carbon double bonds have proved to be suitable systems for catalytic asymmetric synthesis. Important examples are the cyanohydrin formation, catalyzed by cinchona alkaloids (ee's up to 25%),[6] the chiral amine-catalyzed addition of methanol[7a,b] and chloral[7c] to ketenes (ee's up to about 70%), and the intramolecular aldol condensation catalyzed by chiral amino acids (ee 95%).[8,9] In conjugate addition reactions considerable asymmetric induction has been found in the Michael reaction[10,11] and in the thiol[12,13] and selenol[14] addition reaction, catalyzed by chiral amines (ee's up to 70%). Polymeric amines have also been used as chiral catalyst for some of these reactions.[15]

For the ee of an asymmetric synthesis to be improved, knowledge of the structures of both transition-state complexes of the configuration-determining step (one leading to the *R* enantiomer and one leading to the *S* enantiomer) is essential. This knowledge permits rational synthesis of improved catalysts. Studies toward a detailed mechanism of a catalytic asymmetric reaction, including elucidation of transition-state geometries, are difficult in view of the very small free-energy differences involved; only few systematic studies of this kind have been published.[6,7b,16] The choice of a chiral catalyst is still mostly a matter of trial and error.

The discovery that high ee's are obtained when carbon acids, thiols, and selenols are added to α,β-unsaturated ketones in the presence of cinchona alkaloids as catalysts[11,13,14] prompted us to subject this type of asymmetric synthesis to a comprehensive

(1) Abstracted from the doctor's dissertation of H. H. Groningen, 1980.
(2) Recent reviews on asymmetric synthesis: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175; (b) ApSimon, J. W.; Seguin, R. P. *Tetrahedron* **1979**, *35*, 2797; (c) Pearce, R. *Catalysis (London)* **1978**, *2*, 176.
(3) Jones, J. B.; Beck, J. F. In "Application of Biochemical Systems in Organic Chemistry"; Jones, J. B., Sih, C. J., Perlman, E., Eds.; Wiley: New York, 1976; Part I, p 107.
(4) Davies, J.; Jones, J. B. *J. Am. Chem. Soc.* **1979**, *101*, 5405.
(5) (a) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5496. (b) Fryzuk, M. D.; Bosnich, B. *Ibid.* **1977**, *99*, 6262. (c) Nakamura, A.; Konishi, A.; Tatsuno, Y.; Otsuka, S. *Ibid.* **1978**, *100*, 3443.
(6) Prelog, V.; Wilhelm, H. *Helv. Chim. Acta* **1954**, *37*, 1634.
(7) (a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9. (b) Pracejus, H.; Kohl, G. *Ibid.* **1969**, *722*, 1. (c) Borrmann, D.; Wegler, R. *Chem. Ber.* **1967**, *100*, 1575.
(8) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.
(9) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412.
(10) Långström, B.; Bergson, G. *Acta Chem. Scand.* **1973**, *27*, 3118.
(11) (a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057. (b) Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 1508. (c) Hermann, K.; Wynberg, H. *Ibid.* **1979**, *44*, 2238. (d) Trost, B. M.; Shuey, C. D.; DiNinno, F., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 1284.
(12) Pracejus, H.; Wilcke, F.-W.; Hanemann, K. *J. Prakt. Chem.* **1977**, *319*, 219.
(13) Helder, R.; Arends, R.; Bolt, W.; Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2181.
(14) Pluim, H.; Wynberg, H. *Tetrahedron Lett.* **1979**, 1215.
(15) (a) Ueyanagi, K.; Inoue, S. *Makromol. Chem.* **1977**, *178*, 375. (b) Yamashita, T.; Yasueda, H.; Miyauchi, Y.; Nakamura, N. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1532. (c) Kobayashi, N.; Iway, K. *J. Am. Chem. Soc.* **1978**, *100*, 7071.
(16) Glaser, R.; Geresh, S.; Twaik, M.; Benoiton, N. L. *Tetrahedron* **1978**, *34*, 3617 and previous papers.

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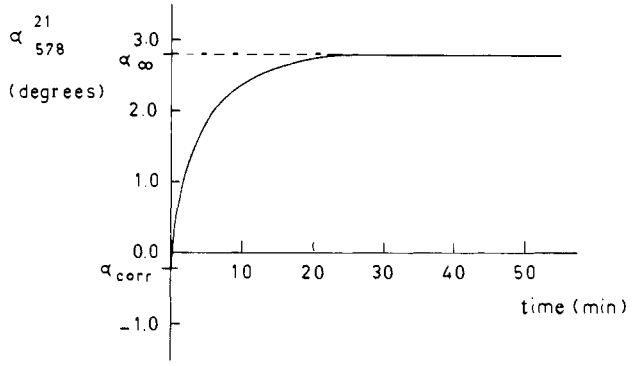
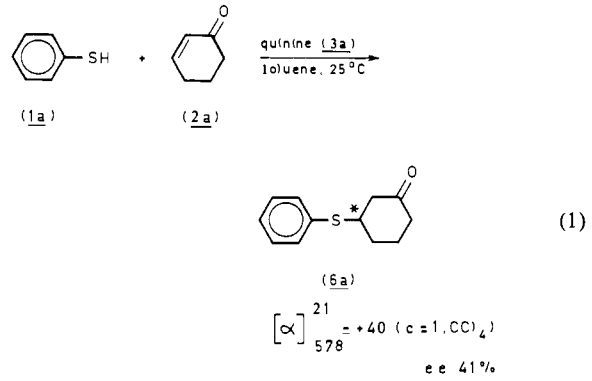


Figure 1. Rotation of the reaction mixture as a function of time for the addition of thiophenol to 2-cyclohexen-1-one, catalyzed by quinine (eq 1).

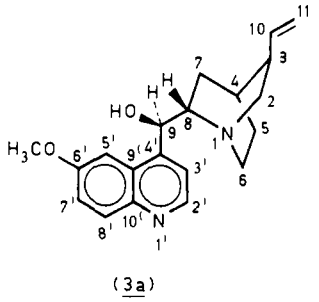
investigation. In this paper the results are reported of a study of the addition of arenethiols (**1a–g**) to 2-cycloalken-1-ones (**2a–i**; e.g., eq 1).[13]



(1)

The Thiol Addition Reaction. The base-catalyzed addition of thiols to α,β-unsaturated ketones is a typical 1,4-addition (or conjugate addition) reaction. The general mechanistic feature is base-catalyzed formation of an anion which adds to a specific position of an electron-poor olefin, followed by proton transfer. The thiol addition is a well-known reaction,[17] important in biochemical processes[18] as well as in synthesis.[19] The above-mentioned structural types of substrates were chosen for two main reasons. Aromatic thiols (**1**) and cyclic α,β-unsaturated ketones (**2**) have known conformations, and small structural changes can easily be introduced. Both points facilitate the systematic study of the mechanism and the transition-state geometry. As chiral catalysts we used cinchona (**3**,**4**) and ephedra (**5**) alkaloids and synthetic derivatives of these natural products.[20] These groups of bases have frequently been applied in asymmetric synthesis as the source of chirality.[2,21] They are easily available in pure form, are stable, and consist of a number of molecules of similar structures. Furthermore, the chemistry of these compounds has been studied thoroughly.[20]

The ee of the thiol addition reaction was determined as a function of substrate and catalysis structure, temperature, solvent, concentration of reactants, and presence of salts. Further insight in the reaction mechanism was gained from kinetic measurements. Utilizing these experimental results enabled us to elaborate a detailed description of the course of the asymmetric thiol addition. The implication of these results will be discussed in relation to catalytic asymmetric synthesis in general.



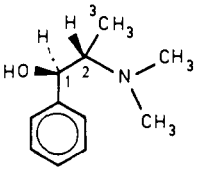


Figure 2. Structure and numbering of quinine (**3a**) and (−)-*N*-methylephedrine (**5a**).

Results

When the addition of thiophenol (**1a**) to 2-cyclohexen-1-one (**2a**) was carried out in the presence of a catalytic amount of quinine (**3a**) in toluene solution at 25 °C, the optically active product **6a** was formed in quantitative chemical yield and in 41% ee (eq 1).[13]

Reaction Features. In addition to the relatively high ee this asymmetric reaction had a number of other favorable properties. The reaction was easy to carry out. To a mixture of thiophenol and about 0.01 M equiv of quinine in toluene was added about 0.9 M equiv of 2-cyclohexen-1-one. It was essential that reactants and solvents were pure, since small changes in the polarity of the reaction solution influenced the ee. When the solution was left standing, e.g., 1–10 h (depending on the concentration of the reactants), the reaction was complete and was worked up in a simple manner as described in the Experimental Section. The course of the reaction could be followed by continuously measuring the rotation of the reaction mixture. The reaction as a function of time for eq 1 is given in Figure 1. At the beginning of the reaction the catalyst caused a negative rotation of the reaction mixture. Formation of the addition product raised the rotation to a constant value of +2.8° after about 40 min. This means that the formation of the product is kinetically controlled and that the product is optically stable under the reaction conditions.

The ^{1}H NMR spectrum of the reaction mixture after 40 min showed that cyclohexenone had been consumed completely and that the addition product had been formed quantitatively. In a control experiment without catalyst, the product could not be detected after 2 h; thus the contribution of the uncatalyzed reaction to product formation was negligible. The above-mentioned reaction characteristics, quantitative chemical yield, kinetically controlled product formation, no racemization, and no uncatalyzed reaction, are important factors that enabled us to subject the asymmetric thiol addition to an extensive study (including kinetic measurements) without undue experimental or kinetic complexities.

Standard Reaction. As standard reaction to determine the dependence of the ee's on reaction conditions and reagent and catalyst structure, we chose the addition of *p-tert*-butylthiophenol[22] (**1b**, 1.81 mmol) to 2-cyclohexen-1-one (**2a**, 1.56 mmol) in benzene (3.0 mL) at room temperature (22 °C) with cinchonidine (**3b**, 0.015 mmol) as catalyst (eq 2). A slight excess of the thiol compared to the unsaturated ketone was convenient in connection with the isolation of the product. Under these standard conditions an ee of 62% was obtained.

Influence of Catalyst Structure. In Figure 2 the structures of quinine (**3a**) and (−)-*N*-methylephedrine (**5a**) are represented to show the general numbering of both types of bases. Figure 3 lists all of the catalysts that have been used in the standard reaction (eq 2). The results are summarized in Table I. All reactions showed quantitative yields on standing overnight. Reactions with

(17) For the first extensive study of this reaction see: Hurd, C. D.; Gershbein, L. L. *J. Am. Chem. Soc.* **1947**, *69*, 2328.

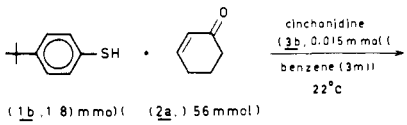
(18) See, e.g.: (a) Fluharty, A. L. In "The Chemistry of the Thiol group"; Patai, S., Ed.; Wiley: New York, 1974; Part 2, p 589. (b) Fujita, E.; Nagao, Y. J. *Bioorg. Chem.* **1977**, *6*, 287.

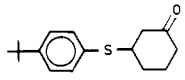
(19) See, e.g.: (a) Julia, M.; Badet, B. *Bull. Soc. Chim. Fr.* **1975**, 1363; (b) Trost, B. M.; Keeley, D. E. *J. Org. Chem.* **1975**, *40*, 2013. (c) Chang, Y.-H.; Pinnick, H. W. *Ibid.* **1978**, *43*, 373; (d) Shono, T.; Matsumura, Y.; Kashimura, S.; Hatanaka, K. *J. Am. Chem. Soc.* **1979**, *101*, 4752.

(20) See, e.g.: Pelletier, S. W., Ed. "Chemistry of the Alkaloids"; Van Nostrand-Reinhold: New York, 1970, p 24 for ephedra and p 301 for cinchona alkaloids.

(21) See, e.g.: Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; Prentice Hall: Englewood Cliffs, N.J., 1971.

(22) *p-tert*-Butylthiophenol was chosen because its odor is less repugnant than that of the remaining thiophenols.





(7a) (2)

$[\alpha]^{21}_{578} = +47$ ($c = 1$, CCl_4)

ee 62%

catalysts lacking the hydroxyl group (**3e–g**, **5b**) proceeded more slowly than reactions with OH-containing catalysts, so that in the former case less solvent was used in order to have a complete reaction within about 10 h. It appeared (entries 2 and 3 in Table I) that the concentration of reactants had a large influence on the ee. This relation was therefore examined separately (Figure 4).

Influence of Reaction Medium. The standard reaction (eq 2) was carried out in 17 solvents, varying from cyclohexane to ethanol. Chemical yields were quantitative in all solvents. The solvents, their dielectric constants, and the ee's are given in Table II. It is evident that the ee's are strongly dependent upon the nature of the solvent.

Table II also shows the remarkable influence of the presence of ammonium salts on the ee of the thiol addition reaction. The standard reaction (eq 2) was carried out with different quantities of tetra-*n*-butylammonium chloride and iodide. Chemical yields were quantitative.

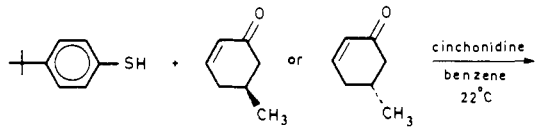
The standard reaction (eq 2) was also carried out in different quantities of the solvents benzene, dioxane, acetone, and ethanol and without any solvent. The ee's as a function of the quantity of the solvent are graphically represented in Figure 4. When no solvent was used, an ee of 23% was obtained. Addition of solvent gave a gradual change of the ee to a constant value, when about 3 mL of solvent was present (values in Table II).

Influence of Temperature. The standard reaction was carried out in toluene solution at five different temperatures varying from −22 °C to +60.5 °C. Higher reaction temperatures gave slow racemization during the reaction, while at lower reaction temperatures the reaction was incomplete upon standing 1 night. Temperatures and ee values for the standard reaction (eq 2) were respectively: −22 °C, 59%; +3.0 °C, 60%; +22.0 °C, 62%; +40.0 °C, 62%; +60.5 °C, 59% ee. The *R* enantiomer was always formed in excess. ee's are thus almost entirely insensitive to temperature changes.

Influence of Substrate Structure. Table III shows the results of the reaction of eq 2, performed with seven aromatic thiols (**1a–g**) and nine conjugated cycloalkenones (**2a–i**). Chemical yields were in all cases nearly quantitative. **2e** reacted so slowly that a complete reaction could only be achieved by using little solvent.

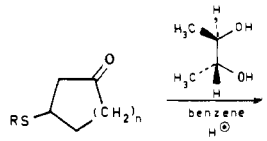
The reaction between *p-tert*-butylthiophenol and excess racemic 5-methyl-2-cyclohexen-1-one (**2k**), catalyzed by cinchonidine (eq 3), was carried out to determine the relative reactivity of both enantiomers of **2k**. When a mole ratio of enone to thiol of 2.0 was used, the remaining enone, separated from the addition product by distillation, had an optical purity of 36% with the *S* enantiomer in excess.[23] Thus the *R* enantiomer of **2k** reacts faster than the *S* enantiomer in a cinchonidine-catalyzed thiol addition reaction (eq 3).

Enantiomeric Excess Determination. All thiol addition products were unknown compounds except for racemic **6a**.[24] A new method was developed for the determination of the ee's. This technique[25]



products (3)

consists of conversion of the optically active ketone into a mixture of diastereomeric acetals, using (2*R*,3*R*)-butane-2,3-diol (eq 4),



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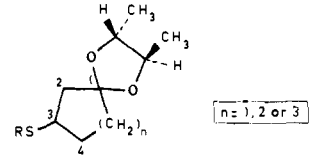


(4)

followed by determination of the ratio of these acetals with the aid of ^{13}C NMR spectroscopy. This method, although somewhat laborious, worked very well and was applied in all cases except for **7b**, **7c**, and **7h** (Table III). The use of the chiral shift reagent $Eu(dcm)_3$[26] in ^1H NMR spectroscopy appeared to be an appropriate method for the determination of the ee for these latter three compounds. Some addition products could easily be crystallized to enantiomeric purity (see Experimental Section). The product **7a** of our standard reaction (eq 2, $[\alpha]^{21}_{578} = +47°$) could be purified to enantiomerical purity ($[\alpha]^{21}_{578} = +77°$ (c 1, CCl_4)) via three recrystallizations from pentane. This absolute rotation value was used to calculate the optical yields of all of the addition reactions of **1b** to **2a** (Tables I and II, Figure 4).[27]

Absolute Configuration Determination. We determined the absolute configurations of the addition products from their circular dichroism spectra by using the Octant Rule.[28] This will be the subject of a separate paper.[29] We only want to remark here that the absolute configurations of the cyclohexanones could be established with certainty. Application of the Octant Rule to five- and seven-membered rings is more difficult, and Table III shows the most probable absolute configuration for **7f–i**.[30]

Kinetic Measurements. The kinetics of the addition of thiophenol (**1a**) to 5,5-dimethyl-2-cyclohexen-1-one (**2c**), catalyzed by quinine (**3a**) in toluene solution, was considered first (eq 5). Enone **2c** was chosen because of the high asymmetric induction obtained with this compound. Quinine was used instead of cinchonidine on account of the better solubility in toluene. The concentration of the product as a function of time was determined by measuring the rotation of the reaction mixture at certain intervals (see Figure 1 for a plot of the rotation of the reaction mixture against time). It was assumed that the product concentration is directly proportional to the corrected rotation of the reaction mixture.[31] This correction in the rotation consisted of subtracting from the observed rotation the small and constant

(23) Chirally catalyzed thiol addition to an excess of a racemic conjugated enone is of course a method for obtaining optically active enones (kinetic resolution).

(24) Chamberlain, P.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 2* **1972**, 130.

(25) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183.

(26) McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038.

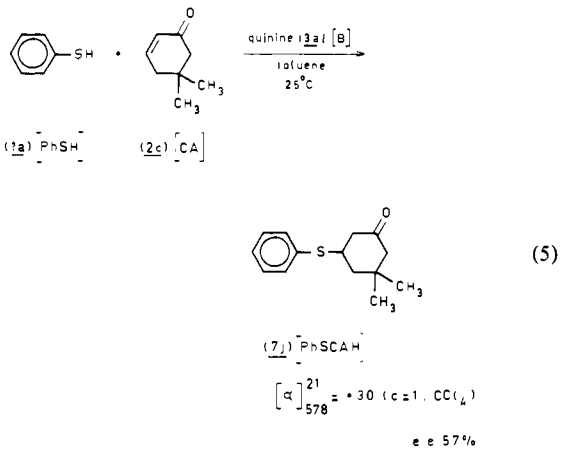
(27) Although in principle values for ee and optical yield of the same material can be different, these quantities were assumed to be equal.

(28) Moffitt, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi, C. *J. Am. Chem. Soc.* **1961**, *83*, 4013.

(29) Hiemstra, H.; Pluim, H.; Bühre, W.; Wynberg, H., to be submitted for publication.

(30) See, e.g.: (a) Legrand, M.; Rougier, M. J. In "Stereochemistry, Fundamentals and Methods"; Kagan, H. B., Ed.; Thieme: Stuttgart, 1977; Vol. 2, p 103. (b) Kirk, D. N. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 2122 and previous papers.

(31) The best check for the correctness of this far-reaching assumption is the reproducibility of the results and the independence of the rate constants on different initial concentrations of reactants.



(5)

rotation value of the catalyst. This is the only other substance contributing to the total rotation of the reaction solution, assuming immeasurably small concentrations of chiral intermediates. This correction value (α_{cor}, Figure 1) was determined by extrapolating the rotation to time zero. When the theoretical final concentration of the product was divided by the corrected value of the final rotation (α_∞, Figure 1), the proportionality constant was obtained for the conversion of the rotation data into concentration values.

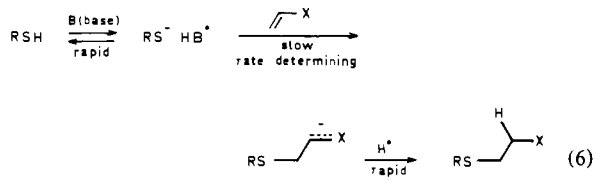
An excellent correlation was found between the concentration of the product and time, when second-order rate equations were used. These second-order rate equations, utilized for the determination of the rate constants, could be derived straightforwardly and are given in the Experimental Section. Figure 5 shows a typical plot for the determination of the observed rate constant k_{obsd}. The initial rates and rate constants for six runs with different initial concentrations of reactants are given in Table IV. In all cases straight lines were obtained in second-order plots.[32] The data in Table IV show that the thiol addition reaction is first order in thiol, alkenone, and catalyst. The total order is therefore three, but since the base concentration is essentially constant, the reaction is pseudo-second order.

Temperature Dependence of Rate Constants. Table V shows the variation of the rate constants with temperature for the addition of thiophenol to **2a** and **2c**, catalyzed by quinine in toluene. All runs exhibited second-order kinetics.[32] At 75.0 °C the rotation values decreased at the end of the measurements; however, this occurred so slowly that the accuracy of the rate constants was not influenced. The Eyring equation was used to determine enthalpy and entropy of activation. The Eyring plots for both reactions are given in Figure 6. In both cases only the points between 35 and 75 °C lie reasonably well on a straight line. Table VI contains the $\Delta H^\ddagger$ and $\Delta S^\ddagger$ values, belonging to the two lines.

The addition of thiophenol to **2a** was also kinetically studied in dioxane with quinine as catalyst and in toluene with acetylquinine (**3e**) as catalyst. Both reactions were again nicely second order.[32] All kinetic results are summarized in Table VI. In the runs with **3e** as catalyst a much higher base concentration was necessary to maintain a convenient reaction rate.

Discussion

A number of mechanistic studies have appeared in the literature dealing with base-catalyzed addition of thiols to electron-poor olefins.[33-38] Equation 6 gives a representation of the generally



(6)

(32) About ten data points (until 80% conversion) were used to determine the best lines (least-squares correlation coefficients generally higher than 0.98).

(33) Dmuchovsky, B.; Vineyard, B. D.; Zienty, F. B. *J. Am. Chem. Soc.* **1964**, *86*, 2874.

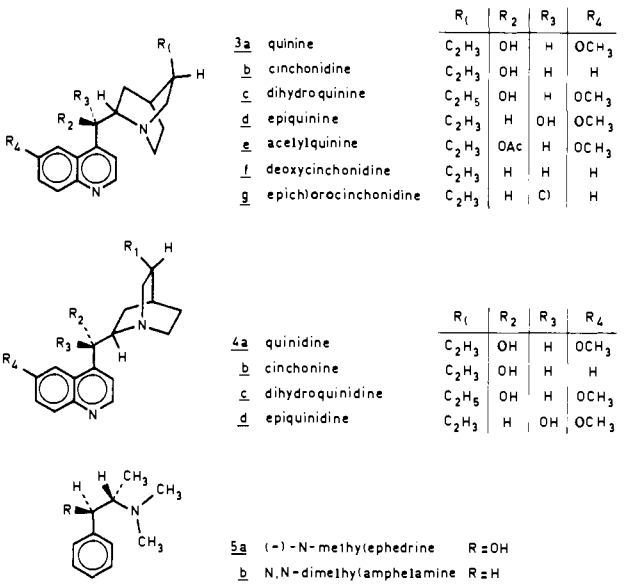


Figure 3. Structures of the catalysts, used in the asymmetric thiol addition.

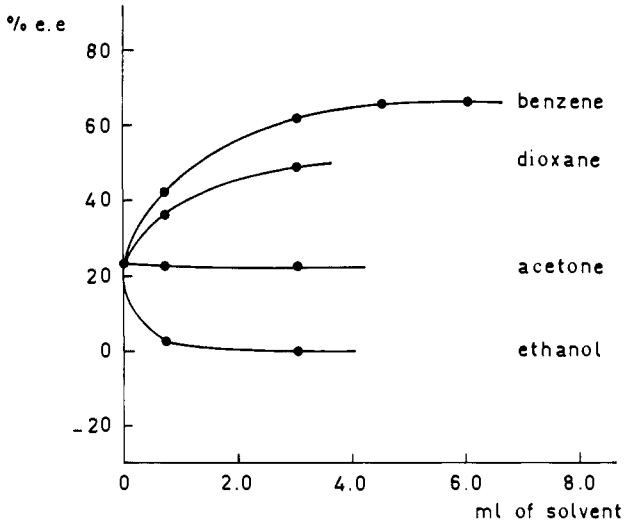


Figure 4. Dependence of the ee of the standard reaction (eq 2) on the quantity of the solvent. ee data are averages from two or three experiments.

Table I. Results of the Standard Reaction (Equation 2) as a Function of the Structure of the Catalyst

	catalyst				product	
		abs conf				
entry	no.[b]	C8	C9	quant of solv, mL	ee,[a] ±2%	abs conf
1	**3a**	*S*	*R*	3.0	44	*R*
2	**3b**	*S*	*R*	3.0	62	*R*
3	**3b**	*S*	*R*	0.375	36	*R*
4	**3c**	*S*	*R*	3.0	35	*R*
5	**3d**	*S*	*S*	3.0	18	*R*
6	**3e**	*S*	*R*	0.375	7	*R*
7	**3f**	*S*		0.375	4	*R*
8	**3g**	*S*	*S*	0.375	3	*S*
9	4a	*R*	*S*	3.0	55	*S*
10	4b	*R*	*S*	3.0	67	*S*
11	4c	*R*	*S*	3.0	44	*S*
12	4d	*R*	*R*	3.0	10	*S*
13	5a	*S*(C2)	*R*(C1)	3.0	29	*R*
14	5b	*S*(C2)	(C1)	0.375	0	

[a] Data are averages from two or three experiments. [b] See Figure 3.

accepted mechanism of the reaction. The formation of the carbon–sulfur bond always appears to be the rate-determining step.

Table II. Result of the Standard Reaction (Equation 2) as a Function of the Nature of the Reaction Medium

entry	solv	ϵ (25 °C)	salt	molar ratio of salt: cinchonidine	ee,[a] ±2%	abs conf
1	cyclohexane	2.01			46	*R*
2	carbon tetrachloride	2.22			60	*R*
3	benzene	2.27			62	*R*
4	toluene	2.37			62	*R*
5	carbon disulfide	2.63			58	*R*
6	thiophene	2.76			60	*R*
7	chloroform	4.64			55	*R*
8	dichloromethane	8.9			55	*R*
9	1,4-dioxane	2.21			48	*R*
10	ethyl ether	4.2			52	*R*
11	ethyl acetate	6.0			47	*R*
12	tetrahydrofuran	7.4			39	*R*
13	acetone	20.7			23	*R*
14	acetonitrile	36.2			15	*R*
15	pyridine	12.3			3	*R*
16	*tert*-butyl alcohol	12.2			16	*R*
17	ethanol	24.3			0	
18	benzene		$(n\text{-Bu})_4N^+Cl^-$	24.0	0	
19	benzene		$(n\text{-Bu})_4N^+Cl^-$	1.0	2	*S*
20	benzene		$(n\text{-Bu})_4N^+Cl^-$	0.24	2	*S*
21	benzene		$(n\text{-Bu})_4N^+I^-$	24.0	1	*R*
22	benzene		$(n\text{-Bu})_4N^+I^-$	1.0	7	*R*
23	benzene		$(n\text{-Bu})_4N^+I^-$	0.24	17	*R*

[a] Data are averages from two or three experiments.

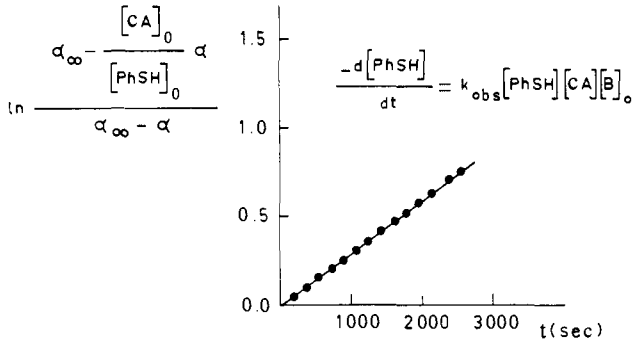
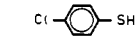
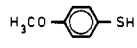
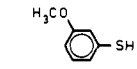
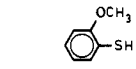
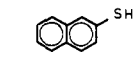
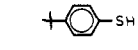
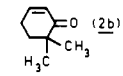
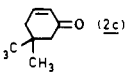
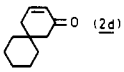
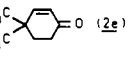
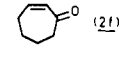
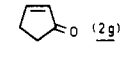
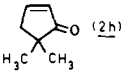
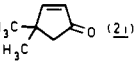


Figure 5. Second-order plot of thiol addition eq 5.

In solvents like water or water–alcohol mixtures the thiolate anion serves as the only reactive species attacking the double bond. The reaction obeys second-order kinetics, first order both in thiolate anion and in olefin.[34,36,38] In nonhydroxylic, less polar solvents an unstable 1:1 complex of thiol and base is formed first in an equilibrium reaction.[33,34] This complex then reacts with the olefin in the rate-determining step. Zienty et al. studied the addition of thiols to maleic anhydride in xylene, catalyzed by 1,4-diazabicyclo[2.2.2]octane, and found third-order kinetics, first order in each of the reactants.[33] Dvorko et al., investigating a similar reaction, namely, the addition of thiophenols to diethyl maleate in toluene, catalyzed by triethylamine, found fourth-order kinetics, second-order in thiophenol.[34] Apparently another molecule of thiophenol is necessary to reach the transition state for this reaction. From these two studies it is far from clear which factors determine the number of molecules present in the transition-state complex. Knowledge of this number is of course essential in order

Table III. Influence of the Structure of Thiol and Enone on the Course of the Asymmetric Thiol Addition Reaction (Equation 2)

entry	thiol	enone	addition product No	$[\alpha]_{578}^{21}$ (c≈1, CCl_4)	ee[a] (%, ±2)	abs conf
1	(1a)	(2a)	6a	+53	54	R
2	 (1c)		6c	+31	35	R
3	 (1d)		6d	+43	50	R
4	 (1e)		6e	+40	52	R
5	 (1f)		6f	+42	50	R
6	 (1g)		6g	+32	37	R
7	 (1b)		7a	+47	62	R
8		 (2b)	7b	+67	62	R
9		 (2c)	7c	+35	75	R
10		 (2d)	7d	+33	71	R
11		 (2e)	7e	+42[b]	41[b]	S
12		 (2f)	7f	+20	65	R
13		 (2g)	7g	+04	5	R
14		 (2h)	7h	+35	49	R
15		 (2i)	7i	+68	35	S

[a] Most data are averages from two to three experiments. [b] Reaction carried out in 0.375 mL of benzene.

Table IV. Effect of the Initial Concentrations on the Rate of the Thiol Addition Equation 5

$[PhSH]_0$, mol/kg	$[CA]_0$, mol/kg	$[B]_0$, mol/kg	initial rate, mol/(kg s)	k_{obsd} ± 0.02 $kg^2/(mol^2\ s)$
0.516	0.512	0.002 87	0.000 110	0.21
0.522	0.524	0.001 45	0.000 063	0.20
1.018	0.522	0.002 90	0.000 224	0.21
0.505	1.027	0.002 86	0.000 199	0.18
0.313	0.313	0.001 74	0.000 029	0.21
1.225	0.608	0.004 44	0.000 381	0.19

(34) Klimenko, L. P.; Solodushenkov, S. M.; Dvorko, G. F. *Dopov. Akad. Nauk Ukr. RSR, Ser. B: Geol., Geofiz., Khim. Biol.* **1974**, *36*; *Chem. Abstr.* **1975**, *82*, 85933.
(35) Tanchuk, Y. V.; Kornienko, A. A. *Zh. Org. Chim.* **1976**, *12*, 2057; *Chem. Abstr.* **1977**, *86*, 54656.
(36) Semenow-Garwood, D. *J. Org. Chem.* **1972**, *37*, 3797.
(37) Medvedev, A. I.; Ignatov, V. A.; Romanchenko, T. S. *Tezisy Dokl. Nauchn. Sess. Khim. Teknol. Org. Soedin. Sery Sernistykh Neftei* **1974**, *13*, 232; *Chem. Abstr.* **1977**, *86*, 29134.
(38) De Maria, P.; Fini, A. *J. Chem. Soc. B* **1971**, 2335.

Table V. Effect of the Temperature on the Rate Constants for the Additions of Thiophenol in Toluene, Catalyzed by Quinine

	k_{obsd}, kg²/(mol² s) for addtn of 1a	
T, ±0.1 °C	2c	2a
13.5	0.13	
17.2		0.93
17.5	0.16	
25.0	0.20	1.02
37.5	0.24	1.04
50.1	0.25	0.99
62.5	0.26	0.95
75.0	0.26	0.90

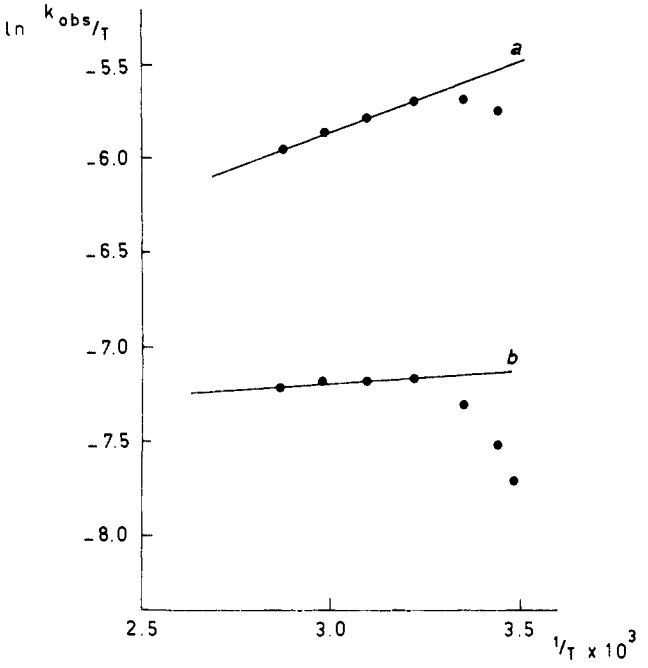


Figure 6. Eyring plots for the addition of 1a to 2a (a) and 2c (b) (see Table V).

to gain insight into the stereochemical features of the thiol addition.

Kinetics. This paper reports the first kinetic measurements of the addition of thiols to α,β-unsaturated ketones as far as we know. Our results point to a pseudo-second-order reaction, first order in thiol, cycloalkenone, and catalyst, corresponding with the kinetic equation 7 (see also eq 5; $[B]_0$ denotes the initial (and constant) catalyst concentration).

$$d[PhSCAH]/dt = k_{obsd}[PhSH][CA][B]_0 \quad (7)$$

It is reasonable to assume a thiol–base complex (PhSHB) as intermediate in a steady-state concentration, which then reacts with the cycloalkenone (eq 8; in analogy to the proposals of

$$PhSH + B \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} PhSHB \xrightarrow[k_s]{CA} PhSCAH + B \quad (8)$$

Zienty[33]). Assuming that the concentration of the intermediate thiol–base complex is small and constant, we obtain eq 9. With

$$d[PhSHB]/dt = 0 = k_1[PhSH][B] - k_{-1}[PhSHB] - k_s[PhSHB][CA] \quad (9)$$

$[B] = [B]_0 - [PhSHB]$ the concentration of the thiol–base complex is given by eq 10. The reaction rate can then be written as eq

$$[PhSHB] = k_1[PhSH][B]_0/(k_1[PhSH] + k_{-1} + k_s[CA]) \quad (10)$$

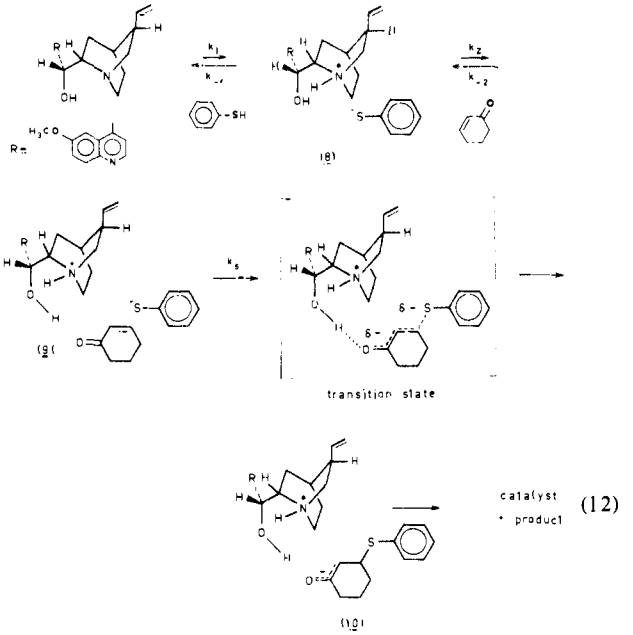
11. If $k_{-1} \gg k_1[PhSH]$ and $k_{-1} \gg k_s[CA]$, eq 11 changes into

$$\text{rate} = d[PhSCAH]/dt = k_1k_s[PhSH][B]_0[CA]/(k_1[PhSH] + k_{-1} + k_s[CA]) \quad (11)$$

eq 7, the experimental rate equation, with $k_{obsd} = k_1k_s/k_{-1}$. This means that in our thiol addition reaction the equilibrium between thiol and base lies far to the left. Furthermore, the second step, the addition to the enone, is rate-determining.

Thiol–Base Ion Pair. The first step of the thiol addition reaction is the formation of an unstable thiol–base complex (eq 8). Zienty[33] was able to detect an interaction between thiol and the base 1,4-diazabicyclo[2.2.2]octane. The infrared spectrum of a 1:1 mixture of these compounds in xylene showed an absorption at 3253 cm^{-1}, attributed to a nonhydrogen bonded ^+N–H and pointing to the presence of an ion pair. We recorded the infrared spectrum of a concentrated 4:1 mixture (by weight) of thiophenol and quinine in CH_2Cl_2 (the solubility of quinine in toluene was too low) but did not observe a sharp signal near 3250 cm^{-1} (this region was, however, somewhat obscured by a broad band, centered at about 2950 cm^{-1}). Perhaps the equilibrium between thiol and base in our case is so unfavorable that the absorption is too weak to be seen or the ^+N–H is hydrogen bonded (either intramolecularly or intermolecularly).

To what extent interactions between amines and thiols lead to either ion pairs or hydrogen-bonded complexes is not clear from the literature. Sandorfy[39] in an infrared study of such interactions as well as Crampton[40] in a review about hydrogen bonding and acidity of thiols does not even mention the existence of ion pairs, whereas DeTar estimates the equilibrium constant between thiophenol and quinuclidine in propionitrile as solvent to be as high as 25 mol^{-1} in favor of the ion pair.[41] According to the kinetics of our thiol addition reaction, the equilibrium constant of the ion-pair formation must be $\ll 1$. At any rate we assume that the ion pair **8** (eq 12), consisting of the thiophenoxide anion



(12)

and the protonated base (protonation occurs at the quinuclidine nitrogen, which is much more basic than the quinoline nitrogen), is the reactive intermediate in our thiol addition reaction, when being carried out in apolar solvents like toluene.

Hydrogen Bond between Enone and Catalyst. The ion pair **8** (eq 12) then reacts with the conjugated enone in the rate-determining step. If this reaction takes place in the usual manner as shown in eq 6, an enolate anion arises, which then takes up a proton to give the product. The transition state will thus possess some enolate character. The formation of an enolate anion is very unfavorable in an apolar nonhydrogen-bonding solvent. In the case of quinine catalysis, however, this process can be facilitated

(39) Bicca de Alencastro, R.; Sandorfy, C. *Can J. Chem.* **1973**, *51*, 985.
(40) Crampton, M. R. In "The Chemistry of the Thiol Group"; Patai, S., Ed.; Wiley: New York, 1974; Part 1, p 379.
(41) DeTar, D. F.; Coates, D. M. *J. Am. Chem. Soc.* **1974**, *96*, 942.

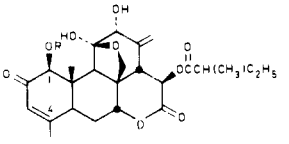
Table VI. Kinetic Data of the Addition of 1a to 2a and 2c in Toluene or Dioxane, Catalyzed by 3a or 3e[a]

$[PhSH]_0$, mol/kg	$[CA]_0$, mol/kg	$[B]_0$, mol/kg	solv	k_{obsd}, kg²/(mol² s) (25 °C)	$\Delta G^{\ddagger}$, kcal/mol (25 °C)	ee, % (25 °C)	$\Delta\Delta G^{\ddagger}$, kcal/mol (25 °C)	$\Delta H^{\ddagger}$, kcal/mol (35–75 °C)	$\Delta S^{\ddagger}$, cal/(mol K) (35–75 °C)
1a, 1.2	**2**c, 0.6	**3**a, 0.0045	toluene	0.20 (±0.02)	18.4 (±0.1)	57 (±2)	0.77	−0.2 (±0.6)	−62 (±2)
1a, 0.6	2a, 0.3	**3**a, 0.0060	toluene	1.02 (±0.02)	17.4 (±0.1)	41 (±2)	0.52	−1.5 (±0.5)	−63 (±2)
1a, 0.6	**2**a, 0.3	**3**a, 0.0060	dioxane	0.48 (±0.02)	17.9 (±0.1)	17 (±2)	0.20		
1a, 1.1	**2**a, 0.4	**3e**, 0.106	toluene	0.0039 (±0.0002)	20.7 (±0.1)	10 (±2)	0.12		

[a] Given concentration data are averages of the initial concentrations of at least two runs.

by the presence of a hydrogen bond between the hydroxyl group of quinine and the enolate oxygen, originating from the enone. In this way the negative charge is better spread out and the free energy of the transition state is lowered. The assumption that the hydroxyl function of the catalyst has a catalytic function in our thiol addition reactions offers the explanation for the large rate differences between reactions catalyzed by quinine and acetylquinine (a factor of about 250, Table VI) and in general between reactions catalyzed by bases with and without a hydroxyl group (Table I).

Catalysis by hydroxyl groups in the conjugate addition of thiols to α,β-unsaturated ketones has been proposed earlier in biological chemistry.[18b,42] For instance, Kupchan et al. attribute much larger physiological (antileukemic) activity of **11a** compared to **11b** to a catalytic effect of the hydroxyl group at carbon 1 in **11a**. Formation of a hydrogen bond to the α,β-unsaturated carbonyl group is supposed to facilitate addition of biological nucleophiles (e.g., thiol groups) at carbon atom 4.

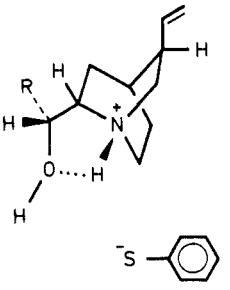


11a R = H
11b R = CH_3

Equation 12 shows the mechanism proposed by us for the addition of thiophenol to cyclohexenone in the presence of a hydroxyl-containing catalyst, i.e., quinine. In two preequilibria thiol, as well as cyclohexenone, is attached to the catalyst. Both equilibria lie far to the left in order to be in agreement with the kinetics (see below). In complex **9** (eq 12) thiophenol has been made more nucleophilic by deprotonation and cyclohexenone has been made more electrophilic, because the hydrogen bond introduces an additional polarization into the π system. For the transition state to be reached, the negative charge on sulfur partly shifts to the oxygen of the original cyclohexenone. The hydrogen bond facilitates the development of charge on this oxygen compared to the case in which no hydrogen bond is present. The assumption of an additional preequilibrium (compare eq 8) does not conflict with the kinetics of the reactions catalyzed by quinine. Two rate constants k_2 and k_{-2} are added to k_{obsd}, giving $k_{obsd} = k_1k_2k_s/k_{-1}k_{-2}$, if k_{-1}, $k_{-2} \gg k_1$[PhSH], k_2[CA], k_s apply. The sequence of ion-pair formation and hydrogen bonding, i.e., the first two steps of eq 12, is essentially arbitrary.

Ion pair **10** (eq 12) once formed most probably transforms rapidly to product and free catalyst by hydrogen transfer. Finally, the hydrogen bond between catalyst and product (a saturated ketone) is probably less stable than the hydrogen bond between catalyst and cyclohexenone,[43] thus, the catalyst can continue its job by preferentially binding the next substrate molecule.

Are there any other possible explanations for the rate difference between the thiol addition reactions catalyzed by quinine and acetylquinine? One may argue that the ion pair **8** (eq 12) can be stabilized by a hydrogen bond between the hydroxyl group of the catalyst and the $^{+}$N–H (**12**), increasing k_1/k_{-1} and thus k_{obsd}. Structure **12** requires a close proximity of the OH and the quinuclidine nitrogen. This is only possible for the threo bases (**3d**, **4d**) and not for the erythro ones (**3a**, **3b**, **3c**, **4a**, **4b**, **4c**).[44-46] Therefore, a hydrogen bond as depicted in **12** cannot explain the above-mentioned rate difference.



(12)

It may be possible that steric hindrance of the acetyl group causes the rate difference between the thiol addition reactions catalyzed by quinine and acetylquinine. However, the catalytic activities of **3f** and **3g** were also much less than that of quinine, showing that the presence of a hydroxyl group is important. Finally, it seems highly improbable that the difference in base strength between quinine and acetylquinine is large enough to cause the rate difference.

Mechanism and Thermodynamic Parameters. The quinine catalyzed reactions in Table VI have small negative enthalpies of activation. This is a result of the fact that the preequilibria have negative equilibrium enthalpies (compatible with literature data[47]). The entropies of activation are highly negative. Usual $\Delta S^{\ddagger}$ values for third-order reactions are about −30 to −40 cal/(mol K).[48] That $\Delta S^{\ddagger}$ for our thiol addition is even more negative (−62 cal/(mol K); Table VI) is probably caused by the process of charge separation in an apolar solvent, which requires much entropy.[48] At any rate the large $\Delta S^{\ddagger}$ value points to a highly structured transition state.

Reactions with transition states that are more polar than the starting compounds usually give a rate increase when being carried out in a more polar solvent. For instance, the Menschutkin reaction has a larger rate in dioxane than in benzene.[49] The reverse is true for the quinine-catalyzed thiol addition (Table VI), which is slower in dioxane than in toluene. A plausible explanation is that in dioxane a hydrogen bond is formed between the OH of quinine and the solvent. It now will cost more free energy to make the OH free to form a hydrogen bond to cyclohexenone. Stated otherwise, quinine is more strongly solvated in dioxane than in toluene.

Temperature Effect. The strong curvature of the Eyring plots at temperatures below 35 °C (Table V, Figure 6) can be explained as resulting from dimerization of the catalyst. Equilibrium constants for dimerization of bifunctional catalysts in solvents like

(42) Kupchan, S. M.; Lacadie, J. A. *J. Org. Chem.* **1975**, *40*, 654.
(43) Nakano, M.; Nakano, N. I.; Higuchi, T. *J. Phys. Chem.* **1967**, *71*, 3954.
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(49) Wiberg, K. B. "Physical Organic Chemistry"; Wiley: New York, 1964; p 379 ff.

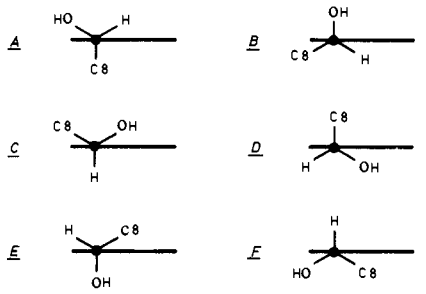


Figure 7. Conformations of quinine around the C9C4′ bond. The thick line represents the quinoline nucleus, perpendicular with respect to the plane of the paper and behind C9.

toluene can be large[47] (for benzoic acid in benzene at 25 °C, $K \simeq 500$ mol^{-1}). Hydrogen-bonding interactions between quinine molecules can also lead to dimers or larger complexes, although the equilibrium constants will be much lower than in the case of benzoic acid because of less favorable electronic and steric conditions. The ^{1}H NMR spectrum (in $CDCl_3$) of enantiomerically impure dihydroquinine (**3c**), recorded by Uskokovič et al.,[50] showed separate signals for each enantiomer, which was strong evidence for the presence of specific intermolecular interactions.[50,51] We obtained additional proof by measuring the average molecular weight of quinine, dissolved in toluene, by using vapor-phase osmometry.[52] At 37 °C we measured an average molecular weight of 395 ± 15 for a quinine concentration of 0.018 mol/kg, indicating that particles larger than monomeric quinine (M_r = 324.5) were present. At the concentrations used in the kinetic measurements (<0.005 mol/kg) quinine appeared to be >95% monomeric at 37 °C. Complex formation becomes more favorable, however, at lower temperatures and will then most probably affect the concentration of free quinine.

Another explanation might be dimerization or other types of complexation of thiophenol.[53] More experiments like temperature studies in other solvents or with acetylquinine are necessary to elucidate the low-temperature effect on the reaction rate.

Dimerization of the base as explanation for the rapid rate decrease at low temperature is compatible with the temperature influence in the ee. The insensitivity of the ee to temperature changes is an indication that the pertinent mechanism of the thiol addition does not change. Furthermore, it means that $\Delta\Delta G^{\ddagger}$ mainly originates from $\Delta\Delta S^{\ddagger}$ and that $\Delta\Delta H^{\ddagger}$ is very small. This is of course not surprising, since $\Delta H^{\ddagger}$ itself is small (Table VI).

Elaboration of Transition-State Geometries. Kinetic measurements have shown that our asymmetric thiol addition is kinetically controlled and that the configuration-determining step is the rate-determining step. The ee of such a reaction is determined by the free-energy difference ($\Delta\Delta G^{\ddagger}$) between the two transition states of the configuration-determining step, one leading to *R* and one leading to *S* product. An ee of about 70% requires only 1.0 kcal/mol in $\Delta\Delta G^{\ddagger}$ (at 25 °C). Thus when elaborating the structural differences of both transition-state complexes, one has to find explanations for very small free-energy differences, which often makes conclusions doubtful. However, it is the only manner in which an asymmetric synthesis can be optimized systematically. In this paper ee values larger than 25% ($\Delta\Delta G^{\ddagger}$ > 0.3 kcal/mol, 25 °C) are considered to permit conclusions concerning transition-state geometries.

The transition state of the configuration-determining step is a complex of three species as depicted in eq 12: protonated quinine, thiophenoxide ion, and enone. The interactions, resulting from the relative orientations of these components, determine the free-energy content of each transition state and thus the ee. Our analysis of the structures of the transition-state complexes is based upon the concept of steric approach control.[54,55]

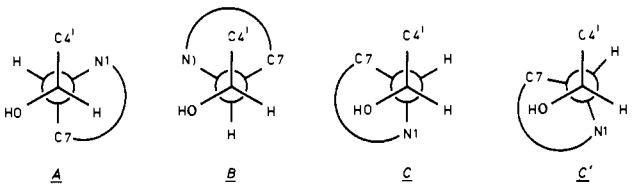


Figure 8. Conformations of quinine around the C9C8 bond.

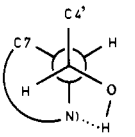


Figure 9. Preferred conformation of epiquinine around the C9C8 bond.

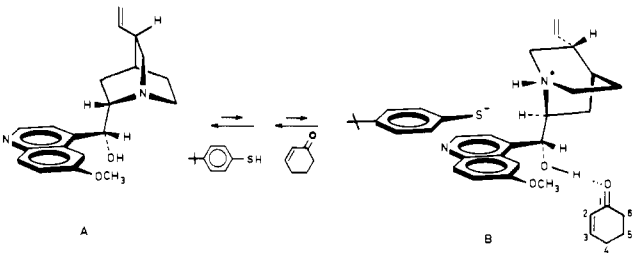


Figure 10. Preferred conformation of free quinine (A) and of quinine as complex with thiophenol and cyclohexenone (B).

Conformation of Quinine. We will discuss the reaction between *p-tert*-butylthiophenol (**1b**) and 2-cyclohexen-1-one (**2a**), catalyzed by quinine (**3a**) in toluene (eq 2). The structures of thiol and enone are rather rigid, and their conformations need no further comment for the present.

Prelog and Wilhelm[6] and Meurling[56] have discussed the conformations of the cinchona alkaloids. In quinine (**3a**) the two pertinent bonds permitting a certain degree of free rotation are the C9C4′ and the C9C8 bonds (see Figure 2). In Figure 7 the six possible rotamers around the C9C4′ bond are shown. The C8 substituent of C9 is by far the largest group and needs the most space, followed by the OH substituent. In this study conformation A is therefore regarded as the conformation of lowest free energy. Prelog[6] and Meurling[56] estimated conformations A and B to be about equally favorable. However, consideration of either A or B makes no difference in the following discussion.

Surprisingly, the conformations around the C9C8 bond have not been discussed by the above-mentioned authors. Figure 8 shows the three staggered projections (A–C). Consideration of the size of the different groups attached to C8 and C9 leads to the supposition that conformation A will be the most stable one. In this conformation an intramolecular hydrogen bond (between N1 and OH) is not possible. The absence of such a hydrogen bond in quinine has been proved with infrared spectroscopy.[44] For comparison we also assessed the most stable conformation of epiquinine (**3d**), which is shown in Figure 9. IR spectroscopy has proved the presence of an intramolecular hydrogen bond in this compound.[44,45]

We turned to ^{1}H NMR spectroscopy (solvent $CDCl_3$) to obtain more evidence concerning the preferred conformation around the C8C9 bond. The H8H9 vicinal coupling constant in epiquinine is 9.5 Hz, corresponding with an angle close to 180° (Karplus–Conroy curve) and in agreement with the conformation of Figure 9. For quinine a $^3J_{H8H9}$ of only 4.0 Hz was found. This means that conformation A cannot be the only one, since for this con-

(50) Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871.
(51) Kabachnik, M. I.; Mastryukova, T. A.; Fedin, E. I.; Vaisberg, M. S.; Morozov, L. L.; Petrovskii, P. V.; Shipov, A. E. *Russ. Chem. Rev.* (*Engl. Transl.*) **1978**, *47*, 821.
(52) We are indebted to H. Draayer, H. Pluim, and E. J. R. Sudhölter for carrying out and discussing these measurements.
(53) See, e.g.: Bicca de Alencastro, R.; Sandorfy, C. *Can. J. Chem.* **1972**, *50*, 3594.
(54) Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579.
(55) See, e.g.: Pracejus, H. *Fortschr. Chem. Forsch.* **1967**, *8*, 493.
(56) Meurling, L. *Chem. Scr.* **1975**, *7*, 90.

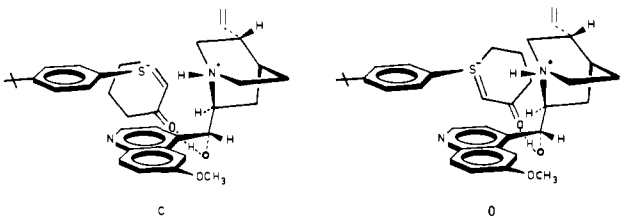


Figure 11. The two possible orientations of cyclohexenone in the transition state of the thiol addition reaction.

formation a $^3J_{H8H9}$ of about 9.5 Hz is expected. Inspection of space-filling models revealed that conformation B is not possible but that C might be reasonably stable. Furthermore, a dihedral angle between H8 and H9 of about 80–90° in C seemed to furnish the most stable arrangement, because the bulky groups C4′ and C7 are then farther apart. In such a conformation (C′) with a dihedral angle between OH and N1 of 80–90° an intramolecular hydrogen bond is not feasible. For C′ a $^3J_{H8H9}$ of about 0–3 Hz can be expected. Thus, most probably both conformations A and C′ occur with C′ as the preferred one. This argument is supported by the magnitude of $^3J_{H8H9}$ in acetylquinine (**3e**), being 7.5 Hz. Increasing the size of the substituent at C9 favors A compared to C′. The most stable conformation of quinine proposed here has been drawn in Figure 10A.[57]

Transition-State Complexes. *p-tert*-Butylthiophenol and 2-cyclohexen-1-one should be attached to quinine in such a manner that the most favorable transition-state complexes are formed. The route to the transition state will lead via the termolecular complex **9** (eq 12), which will have similar features to those of the transition-state complex. We propose that in complex **9** (eq 12) the C8C9 bond of quinine exists preferably as a rotamer A of Figure 8. In this conformation the thiophenoxide ion can be close to the electron cloud of the quinoline ring system, giving a weak but favorable interaction. Figure 10B shows the conformation of the ion pair proposed by us. If quinine in this ion pair had a conformation as depicted in Figure 10A, the anion could not be above the quinoline nucleus and more solvent molecules (toluene) needed to be correctly oriented in order to permit the anion to exist. The formation of such an arrangement would thus cost more entropy. That an aromatic ring can stabilize charge is evident, for instance, from the solvent effect on the reaction rate of the quaternary ammonium iodide formation from triethylamine and ethyl iodide: in benzene the rate is about 80 times as large as in hexane.[49]

Another reason to choose conformation A (Figure 8) for quinine in complex B (Figure 10) emerges from model studies of the transition-state complexes. In the case of conformation A the two possible orientations of cyclohexenone have clearly different stabilities (see the following discussion; Figure 11). If quinine adopted conformation C′ (Figure 8) in complex B, it would be more difficult to account for the ee.

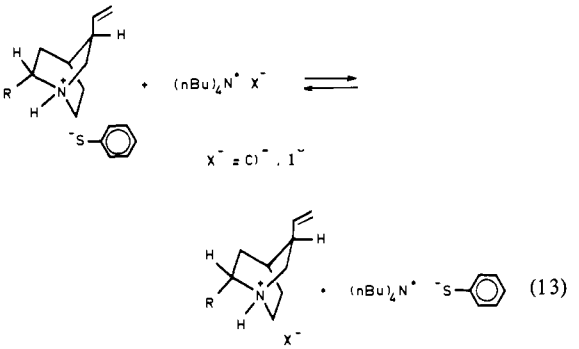
Although convincing evidence concerning the conformation of quinine in the transition-state complex is lacking, we assume that it is as shown in Figure 10B. To reach the transition state starting from the situation of Figure 10B, the π orbital of C3 of 2-cyclohexen-1-one has to come into interaction with the sulfur of the thiophenoxide ion, without breaking the three favorable interactions (hydrogen bond, electrostatic interaction in the ion pair, and the dispersion force between the thiophenoxide ion and the quinoline ring). The negative sulfur atom has to approach perpendicularly to the plane of the carbon atoms 1, 2, and 3 in order to get the best interaction with the π orbital on carbon 3. There are two possibilities, represented in Figure 11. Transition-state C leads to a product with absolute configuration *R* and D leads to *S*. From the drawings it can be anticipated that C is more favorable than D because of the severe steric hindrance in D between the carbon atoms 4, 5, and 6 of 2-cyclohexen-1-one and carbon atom 2 of quinine. Inspection of models confirms this conclusion. Thus one would expect the *R* enantiomer to be formed in excess, which is borne out by the experimental result (Table I).

The discussion about the structure of the transition state, which leads to a prediction of the correct enantiomer formed in excess, must have predictive value to be of use. Also, experimental confirmation of predictions, based on our model, can be construed as support for the correctness of this model. We will now evaluate the results of all experiments in view of these considerations.

Medium Effects on ee. The solvent effects on the ee (Table II) can readily be explained with the mechanism proposed. The first eight solvents in the table are inert solvents that do not affect the structures of transition states as depicted in Figure 11, giving rise to similar ee's. The hydrogen-bond accepting solvents (entries 9–14, Table II) show a decrease in ee with an increase in dielectric constant. This phenomenon can be ascribed to the fact that the strength of an ionic bond is correlated with the polarity of the medium.[48] Qualitatively, higher polarity gives a weakening of the ionic interaction and thus a larger distance between anion and cation in the transition state. The transition-state complexes (Figure 11) become looser, and the difference in free energy between both is reduced.

The solvents of entries 15, 16, and 17 (Table II) can break up the important interactions in the transition states, at least to a large extent. Pyridine as solvent apparently replaces the base as catalyst. Alcohols form a hydrogen bond to the carbonyl group of the cyclohexenone, thus taking over the other function of the catalyst. Consequently ee's are low in these solvents.

The large change in ee upon increasing the concentrations of the reactants (Figure 4) is linked up with participation of solute molecules in the solvent effect. It leads to higher or lower ee's dependent upon the behavior of the original solvent itself. The even more drastic changes in ee on addition of tetraalkylammonium salts (Table II, entries 18–23) can be explained as the result of exchange of the ions of both ion pairs, the added ammonium salt, and the catalyst thiol ion pair (eq 13). Reaction



(13)

of the tetra-*n*-butylammonium thiophenoxide ion pair gives of course no asymmetric induction, unless the reacting cyclohexenone remains hydrogen bonded to the chiral catalyst. This explains the formation of the S enantiomer in excess in some cases (Table II, entries 19 and 20). The ammonium chloride acts more efficiently than the iodide in reducing the ee. The theory of hard and soft ions can provide the explanation. The relatively hard Cl^-, compared to I^-, is more strongly bound to the relatively hard cinchonidine ammonium ion, compared to the $(n\text{-}Bu)_4N^+$ ion. The exchange equilibrium (eq 13) is thus shifted further to the right-hand side for chloride than for iodide.

Substrate Structure and ee. Only aromatic thiols were employed in the asymmetric addition reaction. Therefore, we cannot deduce anything about the role of the aromatic part of the thiols in this process. The influence of substituents in the aromatic moiety of the thiols on the ee (Table III, entries 1–7) is difficult to understand. All thiols used gave the same enantiomer in excess, showing that the mechanistic picture of Figure 11 holds in all cases. The structures of the transition-state complexes (Figure 11)

(57) Our discussion concerning the preferred conformations of quinine and epiquinine bears resemblance to studies of the conformations of ephedrines and related compounds: (a) Hine, J. B. *Can. J. Chem.* **1961**, *39*, 2536; (b) Testa, B. *Pharm. Acta Helv.* **1973**, *48*, 389; (c) Dangoumau, J.; Barrans, Y.; Cotrait, M. *J. Pharmacol.* **1973**, *4*, 5.

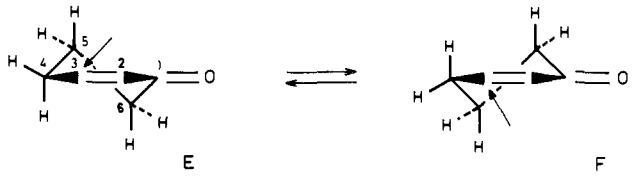


Figure 12. Conformations of 2-cyclohexen-1-one (the arrows indicate the preferred side of nucleophilic attack on C3).

suggest that the size of the para substituent ought not to have a large influence on the ee. The data in Table III indeed do not show a clear relation between size of substituent and ee. There appears to be no clear relation between the acidities of the thiols and the ee either.

All cycloalkenones listed in Table III (entries 7–15) afforded those enantiomers in excess that resulted from attack of the thiophenoxide ion on the same side of the conjugated system, showing again that conformation C is more favorable than D (Figure 11) in all cases. The first six cycloalkenones in Table III (entries 7–12) gave ee's between 60 and 80% (extrapolation of the ee for **2e** to 3 mL of solvent results in about 70% ee, see Figure 4). Introduction of substituents at the 5-position of **2a** (**2c**, **2d**) had a positive influence on the ee compared to **2a** itself, probably because transition-state structure Figure 11D becomes still more unfavorable. Cyclopentenone (**2g**) gave only a very small ee, whereas introduction of methyl groups (**2h**, **2i**) raised the ee considerably. A reasonable explanation is that the steric hindrance in the complex of Figure 11D is less for a five-membered ring than for larger rings. Methyl groups in the five ring again cause more hindrance.

So far, we have ignored the conformational mobility of the cycloalkenones. Conjugated six-membered-ring enones have been studied in detail. They exist in two enantiomeric half-chair conformations (E and F), separated by low-energy barriers, permitting rapid interconversion at room temperature (Figure 12).[58] A number of studies have been published, dealing with the stereochemistry of the addition of nucleophiles to electron-poor double bonds, incorporated in six-membered rings.[24,59,60] In all cases a strong preference was found for antiparallel attack, indicated with arrows in Figure 12 (antiparallel refers to the relation between the incoming reagent and the axial hydrogen on the adjacent carbon). For the conformations of the reacting molecules in the transition-state complexes (Figure 11) antiparallel attack of the nucleophile means that cyclohexenone reacts in conformation F (Figure 12) in transition-state Figure 11C and in conformation E (Figure 12) in transition-state Figure 11D. Cyclohexenone will thus mainly react when existing in conformation F (Figure 12), since the transition-state complex C is more favorable than D (Figure 11).[61]

The results of the reaction between p-*tert*-butylthiophenol and excess racemic 5-methyl-2-cyclohexen-1-one (**2k**), catalyzed by cinchonidine in benzene (eq 3), provide additional evidence for our model of the transition state (Figure 11), assuming antiparallel attack is preferred. Figure 13 shows the conformations of both enantiomers of **2k**.[62] Because an axial methyl group shields the double bond from antiparallel attack on conformations H and M,[59] reaction will take place preferably when the enone exists in conformations G and L. It is now easily predicted that *R*-**2k** (conformation L) will react more rapidly than *S*-**2k** (conformation G), by using the same arguments as with 2-cyclohexen-1-one itself (Figure 12). This prediction is indeed confirmed by the experimental results.

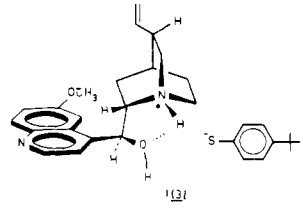
Catalyst Structure and ee. Catalysts without a hydroxyl group cannot form a hydrogen bond with the carbonyl group of **2a**. This leads to a less structured transition state without specific orientation of **2a**. Comparison of entries 6, 7, 8, and 14 in Table I with entry 3 (the same reaction conditions) shows indeed the expected decrease in ee. It will be clear that the erythro bases (**3a–c**, **4a–c**) do not owe their usefulness as chiral catalyst in the thiol addition only to the diminished number of possible conformations of the transition-state complex. Also, the rate enhancement, caused by the presence of a hydroxyl group, is very important, since hydroxyl-bearing catalysts can be used in more dilute solutions, leading to an additional increase in ee (Figure 4).

The dual function of the hydroxyl group (enhancement of both reaction rate and ee) has been reported to be operative in other conjugate addition reactions also. In the addition of thiols to α-phthalimidoacrylic acid methyl ester (solvent toluene)[12] and in the Michael addition of methyl 2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate to methyl vinyl ketone (solvent CCl_4)[11c] quinine appeared to be superior as a catalyst compared with acetylquinine. In these instances the transition-state complexes will most probably have features similar to our case.

Cinchonidine (**3b**), dihydroquinine (**3c**), and (−)-*N*-methylephedrine (**5a**) gave an excess of the *R* enantiomer (Table I). These catalysts possess the same absolute configuration in the β-hydroxy amine part of the molecules as quinine and will therefore react via transition states resembling those of quinine as depicted in Figure 11. Even (−)-*N*-methylephedrine gave almost 30% ee despite its less rigid structure. Apparently the bicyclic rigid structure of quinuclidine does not play a crucial role, nor does the quinoline ring, compared to that of a phenyl ring.[63] We do not want to speculate at this time about the reasons for the influences of the methoxy group in the quinoline ring and the ethyl or vinyl group attached to the quinuclidine on the ee's, although the effects were considerable.[64]

The absolute configuration of the β-hydroxy amine part of **4a–c** is the opposite from that in quinine. This explains the opposite absolute configuration of the enantiomers formed in excess when using these catalysts. ee's in the quinidine series (**4a–c**) are somewhat higher than in the quinine series (**3a–c**) which must be a consequence of the opposite orientation of the vinyl substituent with respect to the C8C9 configuration.

The threo bases (**3d** and **4d**) have an intramolecular hydrogen bond in their most stable ground-state conformation when being dissolved in an apolar solvent like benzene[44-46] (Figure 9). We confirmed this with ^{1}H NMR spectroscopy, as was discussed earlier in this paper. We propose that reaction with thiophenol leads to an ion pair which stabilizes itself via an intramolecular hydrogen bond between the OH and the $^+$N–H (structure **13**).



Structural reasons now prevent the thiophenoxide ion from being above the plane of the quinoline ring. The anion is located somewhere close to the positive nitrogen atom. Whether cyclohexenone is hydrogen bonded to OH in the transition-state complex or not, inspection of models does not reveal any specific transition-state structure which clearly seems more stable than others. This can be the explanation for the low ee's obtained with the epibases.[65]

(58) Barieux, J.-J.; Gore, J.; Richer, J.-C. *Bull. Soc. Chim. Fr.* **1974**, 1020.
(59) Allinger, N. L.; Riew, C. K. *Tetrahedron Lett.* **1966**, 1269.
(60) Abramovitch, R. A.; Rogić, M. M.; Singer, S. S.; Venkateswaran, N. *J. Org. Chem.* **1972**, *37*, 3577. (b) Abramovitch, R. A.; Singer, S. S. *J. Org. Chem.* **1976**, *41*, 1712.
(61) Consideration of the real (half-chair) conformations of cyclohexenones does not alter our previous conclusions regarding the relative stability of the transition states C and D (Figure 11).
(62) See also: Barieux, J.-J.; Gore, J.; Subit, M. *Tetrahedron Lett.* **1975**, 1835.
(63) The finding of Pracejus that the use of (−)-*N*-methylephedrine as catalyst in a similar thiol addition reaction furnished the opposite enantiomer as when quinine was used[12] is difficult to understand.
(64) Prelog[6] and Meurling[56] made use of the influences of the methoxy substituent in order to elucidate the stereochemical couse of their reactions.
(65) We assume that the epibases catalyze according to the same overall mechanism as quinine (three molecules in the transition-state complex).

The catalytic behavior of the different cinchona alkaloids in our thiol addition shows similarity to their action in other asymmetric reactions. (*S*)-C8,(*R*)-C9 catalysts (**3a–c**) and (*R*)-C8,(*S*)-C9 catalysts (**4a–c**) produce in most cases the opposite enantiomers in about equally high ee's.[6,11c,12,56,66,67] The less frequently used threo bases always show lower asymmetric induction.[6,12] There exists, therefore, a certain consistency in the action of these bases independent of the reaction type. It seems reasonable to suppose that the mechanism of catalysis put forward for the thiol addition has a more general meaning. This mechanism can be summarized as follows. Reaction between a cinchona base and a substrate leads to an ion pair which in the case of an erythro base stabilizes itself by positioning the anion above the aromatic part of the catalyst. The number of ways of approach of the molecule that has to react with the anion are limited, because the anion is shielded at one side, resulting in high stereospecificity. In the case of a threo base, the ion pair can stabilize itself by an intramolecular hydrogen bond, leaving the anion more open to react indiscriminately. More experiments are necessary, however, to settle this theory.

Bifunctional Catalysis. The erythro cinchona and ephedra alkaloids can be regarded as bifunctional catalysts for the thiol addition to α,β-unsaturated ketones. They activate the thiol via ion-pair formation and the enone via hydrogen bonding. Litvinenko and Oleinik differentiated bifunctional catalysts in tautomeric bifunctional catalysts, covalent bifunctional catalysts, and bifunctional solvation catalysts.[68] The β-hydroxy amines belong to the third type, defined as "catalysts that activate via cyclic transition states certain sections of the reactants, either as a result of the formation of hydrogen bonds or as a result of electrostatic, dispersion, and other forces". β-Hydroxy amines can exert this behavior as bifunctional solvation catalysts in many other addition reactions to polarized double bonds. Their bifunctional character is most probably the main reason for the success gained with compounds like quinine and ephedrine as the source of chirality in asymmetric synthesis.

Conclusions and Prospects. For our standard reaction, the addition of *p-tert*-butylthiophenol to 2-cyclohexen-1-one, catalyzed by cinchonidine, the experimental conditions to obtain the highest ee demanded that the reaction was carried out as dilute as compatible with a reasonable reaction rate in an apolar solvent at room temperature. The inescapable conclusion is that still higher ee's in this particular reaction can only be achieved by modification of the structure of the catalyst. The choice of cinchonidine is more or less fortuitous, and better catalysts must exist. Knowledge of the structures of the transition-state complexes should serve as a guide for the development of better catalysts. The result of each new catalyst deepens the insight in the reaction mechanism. Because of the complexity of the reaction and the small energy differences, the mechanisms proposed must be considered a working hypothesis rather than a final comprehensive theory.

This study shows the importance of examining in great detail one suitable reaction. It furthermore shows the advantages of bifunctional (or polyfunctional) catalysis in the preparation of enantiomers by catalytic chiral synthesis. A great number of reactions can be catalyzed bifunctionally.[68,69] In the (multistep) synthesis of a chiral compound such a reaction is very suitable for the introduction of chirality.[11d]

The scope of the utility of hydroxy amines can perhaps be extended by constructing a catalyst containing a stronger base or a better hydrogen bond donor. Examples are introduction of bases like DBN (1,5-diazabicyclo[4.3.0]non-5-ene) or phenolic hydroxyl groups. Perhaps other Michael reactions can then be performed which are not possible with bases like quinine.[11c]

Not only are hydroxy amines capable of exerting bifunctional catalysis but also other combinations of functional groups can in principle exhibit such behavior. The development of new chiral catalysts with the principle of multifunctional catalysis in mind will certainly enhance the importance of catalytic chiral synthesis as a method for obtaining optically active substances. This catalytic mechanism is of course not novel. It is utilized by enzymes as one of their means to be the best chiral catalysts of all.[70]

Table VII. Physical Data of the Catalysts Used

catalyst[a]	mp, °C	$[\alpha]^{22}_D$, deg
3a	173–174.5	−162 (*c* 1.1, EtOH)
3b	203–206	−109 (*c* 0.96, EtOH)
3c	171–172.5	−143 (*c* 0.97, EtOH)
3d	oil	+43.4 (*c* 1.0, EtOH)
3e	117.5–119	−50.4 (*c* 0.90, EtOH)
3f	106–108	+95.5 (*c* 1.7, $CHCl_3$)
3g	58–58.5	−14.4 (*c* 0.80, $CHCl_3$)
4a	173.5–174	+261 (*c* 0.80, EtOH)
4b	263–264	+225 (*c* 0.41, EtOH)
4c	166–167.5	+220 (*c* 0.99, EtOH)
4d	oil	+96.0 (*c* 1.3, EtOH)
5a	86.5–87.5	−24.0 (*c* 1.9, EtOH)
5b	oil	+2.6 (neat)

[a] See Figure 3.

Experimental Section

Instrumentation. Melting points were determined on a Mettler FP2 melting point apparatus. All melting and boiling points are uncorrected. IR spectra were measured on a Unicam (SP-200) spectrophotometer. ^{1}H NMR spectra were recorded either at 60 MHz (Varian A-60 or JEOL C-60 HL) or 100 MHz (Varian XL-100). ^{1}H chemical shifts are reported in δ units (ppm) relative to internal Me_4Si (δ 0). ^{13}C NMR spectra were recorded at 25 MHz (Varian XL-100), and ^{13}C chemical shifts are denoted in δ units (ppm) relative to the solvent $CDCl_3$ (δ 77.0). Mass spectra were recorded on an AEI MS-902 spectrometer. Elemental analyses were performed in the microanalytical section of this department. Optical rotations were measured on a Perkin-Elmer 241 polarimeter; tetrachloromethane was used as solvent (concentration about 1.0 g/100 mL) unless otherwise stated. For the kinetic measurements the polarimeter was equipped with a Lauda thermostat, maintaining the temperature within ±0.1 °C. Reactions for kinetic measurements were carried out in a 1-dm jacketed cell and optical rotations automatically printed at certain intervals by using a Perkin-Elmer timer and printer.

Solvents. All solvents used for the thiol addition reactions were purified according to standard procedures and kept over molecular sieves.

Catalysts. The chemical homogeneity of the commercially available bases **3a**, **3b**, **3d**, **4a**, **4b**, and **4d** (**3d** and **4d** were obtained from their mono HCl salts, ACF chemiefarma, Amsterdam) was checked by using ^{13}C NMR spectroscopy.[71] All compounds were >97% pure except for **3a** and **4a** which contained considerable amounts of **3c** and **4c**, respectively. These were removed by using a known procedure.[72] **3c** and **4c** were obtained from the corresponding vinyl bases by catalytic hydrogenation in 96% EtOH (catalyst 5% Pd/C, 3 atm of H_2 pressure). **3e** (from purified quinine), **3f** and **3g** were synthesized according to known procedures.[73,74] **5a** and **5b** were prepared from the commercially available bases (−)-ephedrine and *N*-methylamphetamine via methylation with formaldehyde.[75] All catalysts were thoroughly dried before use. Physical constants of the catalysts are given in Table VII.

Aromatic Thiols (see Table III). All thiols except **1b** were obtained commercially and recrystallized or distilled before use.

***p-tert*-Butylbenzenesulfonyl Chloride.** The known procedure for the synthesis of this compound was slightly modified.[76a] To a stirred solution of 67 g (0.5 mol) of *tert*-butylbenzene in 150 mL of chloroform was carefully added at −5 to 0 °C over 30 min 175 g (1.5 mol) of chloro-

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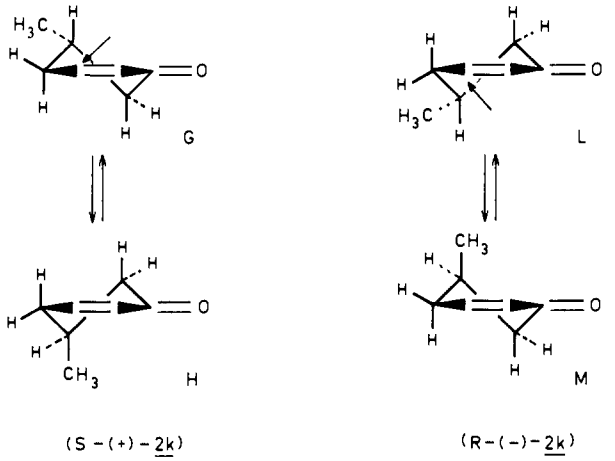
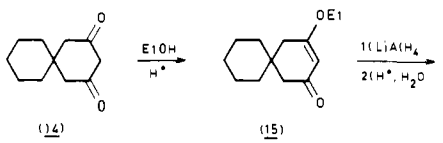


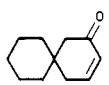
Figure 13. Conformations of 5-methyl-2-cyclohexen-1-one (**2k**).

sulfonic acid. After being left standing 1 night (during which the temperature of the mixture slowly reached room temperature), the reaction mixture was poured out onto excess ice (about 1 kg). The chloroform layer was separated and the water layer extracted with 80 mL of chloroform. The combined organic layers were washed with Na_2CO_3 solution (200 mL). The chloroform was removed together with some water at atmospheric pressure and the residue vacuum distilled (bp 84–85 °C (0.08mmHg)). Crystallization of the distillate from hexane afforded 86 g of white crystals (0.37 mol, 74%, mp 81.5–83.5 °C).

***p*-*tert*-Butylthiophenol (1b).** From 81 g of *p*-*tert*-butylbenzenesulfonyl chloride 47 g of **1b** (bp 120 °C (22mmHg); 81%) was obtained by applying the usual procedure.[76b] IR (liquid film): 2960, 2555 (S–H), 1120, 1015, 820 cm^{-1}. ^1H NMR (100 MHz, CCl_4): δ 1.25 (s, 9 H), 3.14 (s, 1 H), 7.12 (m, 4 H). The meta isomer could not be detected.[77]

Conjugated Cycloalkenones (see Table III). The unsubstituted enones **2a**, **2f** and **2g** were obtained commercially and were distilled before use. The enones **2b**,[79] **2c**,[80] **2e**,[81] **2h**,[82] and **2i**[83] and racemic **2k**[84] were synthesized according to literature procedures. Enone **2d** was prepared from spiro[5.5]undecane-2,4-dione (**14**)[85] as shown in eq 14.





(14)

(2d)

4-Ethoxyspiro[5.5]-3-undecen-2-one (15). A mixture of 22.8 g (0.127 mol) of spirodiketone **14**, 50 mL of absolute ethanol, 1.0 g of *p*-toluenesulfonic acid, and 300 mL of benzene was heated under reflux during 10 h in a Dean–Stark apparatus. The reaction solution was extracted twice with 100 mL of a Na_2CO_3 solution, dried ($MgSO_4$), and evaporated to leave a colorless oil, which was crystallized from pentane at –20 °C, to afford 20.9 of white crystals (0.100 mol, 79%, mp 44–45 °C). IR (liquid film): 1660 (C=O), 1615 cm^{-1} (C=C). ^1H NMR (60 MHz, $CDCl_3$): δ 5.23 (s, 1 H), 3.83 (q, 2 H), 2.29 (s, 2 H), 2.25 (s, 2 H), 1.43 (br s, 10 H), 1.34 (t, 3 H). Anal. ($C_{13}H_{20}O_2$): C, H.

Spiro[5.5]-3-undecen-2-one (2d). To a stirred solution of 20.0 g (0.096 mol) of enol ether **15** in 150 mL of ether was slowly added over 20 min 1.2 g (0.032 mol) of $LiAlH_4$, so that the reaction mixture gently refluxed. After being stirred 1 h at room temperature, the reaction mixture was hydrolyzed at 0 °C with 30 mL of H_2O followed by a mixture of 3 mL of concentrated H_2SO_4 and 30 mL of H_2O. After another 30 min of stirring at room temperature, the organic layer was separated and the water layer extracted with 50 mL of ether. The combined ether layers were washed with water and brine, dried (Na_2SO_4), and evaporated. The residual oil was distilled (bp 77–80 °C (0.1mmHg)) to give 13.8 g of a colorless liquid (0.084 mol, 88%). IR (liquid film): 1680 (C=O), 1625 (C=C) cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 6.69 (dxt, J = 10.0, 4.4 Hz, 1 H), 5.78 (dxt, J = 10.0, 1.9 Hz, 1 H), 2.27 (s, 2 H), 2.23 (dxd, J = 4.4, 1.9 Hz, 2 H), 1.40 (s, 10 H). Anal. ($C_{11}H_{16}O$): C, H.

General Procedure for the Thiol Addition Reactions. To 0.015 mmol of the catalyst was added 1.81 mmol of the thiophenol followed by 3.0 mL of the solvent. To this mixture was then added 1.56 mmol of the conjugated alkenone. The flask was stoppered, shaken well, and put aside. The reaction mixtures were not always homogeneous owing to the low solubility of some catalysts in some solvents. It was however established that the ee's were not influenced by small changes in the (always very low) catalyst concentrations. Reactions were not carried out under an inert atmosphere because air oxidation of the thiols hardly occurred. The reaction mixture was worked up after about 15 h by adding 20 mL of benzene and extracting the benzene solution successively twice with 20 mL of 2 N HCl, twice with 10 mL of 2 N KOH, and twice with 10 mL of saturated NaCl solution. The benzene solution was dried ($MgSO_4$) and the solvent evaporated completely under diminished pressure (50–60 °C (±15mmHg)) to afford the addition product. IR and ^1H NMR spectroscopy were used to determine whether the reaction was complete. If not, the reaction was repeated with less solvent. If complete, the yields always amounted to 80–98% of chemically virtually pure product, 2–20% being lost by the workup procedure. The rotation of the crude product was determined (in CCl_4; c 1) and compared with the rotation of enantiomerically pure material, if known, to determine the optical yield. When the rotation of enantiomerically pure material was unknown, the crude product was either studied with ^1H NMR spectroscopy with the chircal shift reagent Eu(dcm)$_3$[26] or converted into a mixture of diasteromeric acetals,[25] in order to determine the enantiomeric purity.

Diastereomeric Acetals for ee Determinations. A mixture of 1.0 mmol of the crude optically active thiol addition product, 135 mg (1.5 mmol) of enantiomerically pure (–)-(2*R*,3*R*)-butane-2,3-diol ($[\alpha]^{21}_{578}$ –13.4° (neat)), 10 mg of *p*-toluenesulfonic acid, and 25 mL of benzene was heated under reflux in a Dean–Stark apparatus for 5 h. After the solution was cooled, Na_2CO_3 (1.0 g) was added followed by H_2O (20 mL). The benzene layer was separated and washed with a saturated Na_2CO_3 solution (20 mL) and brine (20 mL). After the benzene solution was dried ($MgSO_4$) the solvent was evaporated, leaving a colorless oil in quantitative yield. This oil, being a mixture of two diastereomeric acetals, was subjected to ^{13}C NMR spectroscopy without further purification, in order to determine the ratio of the acetals which is equal to the ee of the original ketone.[25]

Thiol Addition Products and Their ee's. In the following section all of the thiol addition products, obtained by using the standard conditions (eq 2), are enumerated, including the most important spectral data. Details are given about the method for the determination of the ee for each compound. Of the ^{13}C NMR spectra of the mixtures of diastereomeric acetals (measured in $CDCl_3$ solution) only the chemical shifts of the cycloalkane ring carbon atoms and of the carbons of alkyl substituents attached to the cycloalkane ring are reported (see eq 4 for the numbering of the atoms). Most of these carbon atoms showed separate signals for both diastereomers. The former of the chemical shift values listed belongs to the preponderant diastereomer. Only nicely separated signals were utilized for the determination of the ee.[25]

3-(Phenylthio)cyclohexanone (6a): oil; $[\alpha]^{21}_{578}$ +53°; spectral data were in accord with literature data.[24] Diastereomeric acetals: ^{13}C NMR δ 107.5 (C1), 42.5 and 43.6 (C2), 43.3 and 42.7 (C3), 32.1 (C4), 22.4 and 22.8 (C5), 36.2 and 35.2 (C6); ee 54%.

3-((*p*-*tert*-Butylphenyl)thio)cyclohexanone (7a): slowly solidifying oil; $[\alpha]^{21}_{578}$ +47°; IR (liquid film) 1710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.26 (s, 4 H), 3.22 (m, 1 H), 1.4–2.8 (m, 8 H), 1.30 (s, 9 H). Diastereomeric acetals: ^{13}C NMR δ 107.4 (C1), 42.6 and 43.6 (C2), 43.3 and 42.8 (C3), 32.3 (C4), 22.3 and 22.7 (C5), 36.2 and 35.2 (C6); ee 60%. When the crude ketone was recrystallized three times from pentane, white crystals were obtained: mp 63.5–64.5 °C; $[\alpha]^{21}_{578}$ +77°.

(77) In a similar preparation of *p*-*tert*-butylthiophenol the meta isomer appeared to be present in about 10%.[78] We were not able to detect this isomer in our reaction product.

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These values did not change upon further recrystallization. Anal. ($C_{16}H_{22}OS$): C, H, S. The ^{13}C NMR ee determination as well as the crystallization experiments indicated that the material with $[\alpha]^{21}_{578}$ +77° is a pure enantiomer. The absolute rotation value was used for the determination of the optical yield of all the addition reactions of *p-tert*-butylthiophenol to 2-cyclohexen-1-one (eq 2).

3-((*p*-Chlorophenyl)thio)cyclohexanone (6c): white crystalline solid; $[\alpha]^{21}_{578}$ +31°; IR (Nujol suspension) 1700 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 7.31 (m, 4 H), 3.37 (m, 1 H), 1.5–2.8 (m, 8 H). Exact mass: calcd for $C_{12}H_{13}ClOS$, 240.038; found, 240.035. Diastereomeric acetals: ^{13}C NMR δ 107.4 (C1), 42.4 and 43.5 (C2), 43.5 and 43.0 (C3), 32.0 and 31.9 (C4), 22.4 and 22.8 (C5), 36.2 and 35.2 (C6); ee 35%.

3-((*p*-Methoxyphenyl)thio)cyclohexanone (6d): slowly solidifying oil; $[\alpha]^{21}_{578}$ +43°; IR (liquid film) 1710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.8–7.8 (m, 4 H), 3.87 (s, 3 H), 3.25 (m, 1 H), 1.3–2.8 (m, 8 H). Exact mass: calcd for $C_{13}H_{16}O_2S$, 236.087; found, 236.086. Diastereomeric acetals: ^{13}C NMR δ 107.5 (C1), 42.5 and 43.5 (C2), 44.2 and 43.8 (C3), 32.0 (C4), 22.2 and 22.6 (C5), 36.0 and 35.0 (C6); ee 50%.

3-((*m*-Methoxyphenyl)thio)cyclohexanone (6e): oil; $[\alpha]^{21}_{578}$ +40°; IR (liquid film) 1710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.8–7.6 (m, 4 H), 3.85 (s, 3 H), 3.47 (m, 1 H), 1.3–2.9 (m, 8 H). Exact mass: calcd for $C_{13}H_{16}O_2S$, 236.087; found, 236.085. Diastereomeric acetals: ^{13}C NMR δ 107.4 (C1), 42.5 and 43.5 (C2), 43.0 and 42.5 (C3), 32.1 (C4), 22.4 and 22.8 (C5), 36.2 and 35.2 (C6); ee 52%.

3-((*o*-Methoxyphenyl)thio)cyclohexanone (6f): oil; $[\alpha]^{21}_{578}$ +42°; IR (liquid film) 1710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.8–7.7 (m, 4 H), 3.93 (s, 3 H), 3.60 (m, 1 H), 1.3–2.9 (m, 8 H). Exact mass: calcd for $C_{13}H_{16}O_2S$, 236.087; found, 236.087. Diastereomeric acetals: ^{13}C NMR δ 107.4 (C1), 42.3 and 43.3 (C2), 41.2 and 40.6 (C3), 31.8 (C4), 22.3 and 22.7 (C5), 36.1 and 35.2 (C6); ee 50%.

3-(β-Naphthylthio)cyclohexanone (6g): slowly solidifying oil; $[\alpha]^{21}_{578}$ +32°; IR (liquid film) 1710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.1–7.9 (m, 7 H), 3.39 (m, 1 H), 1.3–2.9 (m, 8 H). Exact mass: calcd for $C_{16}H_{16}OS$, 256.092; found, 256.095. Diastereomeric acetals: ^{13}C NMR δ 107.6 (C1), 42.6 and 43.7 (C2), 43.3 and 42.6 (C3), 32.2 and 32.0 (C4), 22.3 and 22.7 (C5), 36.3 and 35.3 (C6); ee 37%.

3-((*p-tert*-Butylphenyl)thio)-6,6-dimethylcyclohexanone (7b): oil; $[\alpha]^{21}_{578}$ +67°; IR (liquid film) 1710 cm^{-1}; ^1H NMR (100 MHz, CCl_4) δ 7.27 (s, 4 H), 3.26 (m, 1 H), 2.50 (m, 2 H), 1.4–2.1 (m, 4 H), 1.30 (s, 9 H), 1.10 (s, 3 H), 1.02 (s, 3 H). Addition of $Eu(dcm)_3$ to the ^1H NMR sample gave splitting of the signals of both methyl groups attached to the cyclohexanone ring: ee 62%. Via a number of recrystallizations from pentane at −40 °C enantiomerically pure material ($[\alpha]^{21}_{578}$ +109, mp <0 °C) could be separated from the racemic ketone (mp 51.5–53 °C. Anal. ($C_{18}H_{26}OS$) C, H, S).

3-((*p-tert*-Butylphenyl)thio)-5,5-dimethylcyclohexanone (7c): slowly solidifying oil; $[\alpha]^{21}_{578}$ +35°; IR (liquid film) 1705 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 7.27 (s, 4 H), 3.45 (txt, 1 H), 2.65 (dxdxt, 1 H), 1.8–2.4 (m, 4 H), 1.68 (dxd, 1 H), 1.30 (s, 9 H), 1.07 (s, 3 H), 0.90 (s, 3 H). Addition of $Eu(dcm)_3$ gave splitting of the signals of both methyl groups: ee 75%. Recrystallization from pentane (three times) furnished enantiomerically pure ketone: $[\alpha]^{21}_{578}$ +47°; mp 70–70.5 °C. Anal. ($C_{18}H_{26}OS$): C, H, S.

2-((*p-tert*-Butylphenyl)thio)spiro[5.5]undecan-4-one (7d): slowly solidifying oil; $[\alpha]^{21}_{578}$ +33°; IR (liquid film) 1705 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.26 (s, 4 H), 3.36 (m, 1 H), 1.5–2.8 (m, 6 H), 1.37 (br m, 10 H), 1.29 (s, 9 H). Diastereomeric acetals: ^{13}C NMR δ 108.3 and 108.1 (C1), 43.2 (C2), 39.1 and 38.7 (C3), 44.1 (C4), 34.9 and 35.1 (C5), 45.3 (C6), 41.8, 33.2, 26.3, and 21.5 (carbon atoms of the C5 substituents); ee 71%. Recrystallization of the crude ketone from pentane furnished white crystals of enantiomerically pure material: $[\alpha]^{21}_{578}$ +47; mp 80–82 °C. Anal. ($C_{21}H_{30}OS$): C, H, S.

3-((*p-tert*-Butylphenyl)thio)-4,4-dimethylcyclohexanone (7e). When the standard conditions were used for the synthesis of this compound, only about 50% had been formed upon standing overnight. With 0.375 mL of benzene instead of 3.0 mL, reaction was complete within this time period. The product was isolated as slowly solidifying oil: $[\alpha]^{21}_{578}$ +42°; IR (liquid film) 1710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.31 (s, 4 H), 3.10 (dxd, 1 H), 1.4–2.8 (m, 6 H), 1.30 (s, 12 H), 1.18 (s, 3 H). Exact mass: calcd for $C_{18}H_{26}OS$, 290.170; found, 290.175. Diastereomeric acetals: ^{13}C NMR δ 107.6 (C1), 40.6 and 41.0 (C2), 54.6 and 54.1 (C3), 34.3 (C4), 37.7 and 38.1 (C5), 32.9 and 32.2 (C6), 30.1 and 19.2 (methyl carbon atoms); ee 41%.

3-((*p-tert*-Butylphenyl)thio)cycloheptanone (7f): oil; $[\alpha]^{21}_{578}$ +20°; IR (liquid film) 1695 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.26 (s, 4 H), 3.23 (m, 1 H), 2.3–2.8 (m, 4 H), 1.3–2.1 (m, 6 H), 1.31 (s, 9 H). Exact mass: calcd for $C_{17}H_{24}OS$, 276.155; found, 276.158. Diastereomeric acetals: ^{13}C NMR δ 110.0 and 109.6 (C1), 45.3 and 45.6 (C2), 42.2 and 41.5 (C3), 35.5 and 34.7 (C4), 28.6 and 26.6 (C5), 21.9 (C6), 40.7 (C7); ee 65%.

3-((*p-tert*-Butylphenyl)thio)cyclopentanone (7g). The reaction mixture turned somewhat cloudy upon addition of 2-cyclopenten-1-one. Workup furnished about 80% of the chemically almost pure adduct as slightly yellow oil: $[\alpha]^{21}_{578}$ 0.4°; IR (liquid film) 1740 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.26 (s, 4 H), 3.76 (m, 1 H), 1.8–2.6 (m, 6 H), 1.30 (s, 9 H). Exact mass: calcd for $C_{15}H_{20}OS$, 248.123; found, 248.123. Diastereomeric acetals: ^{13}C NMR δ 115.9 and 115.7 (C1), 45.2 and 45.0 (C2), 43.4 and 43.3 (C3), 30.9 and 31.2 (C4), 37.0 and 36.6 (C5); ee 5%.

3-((*p-tert*-Butylphenyl)thio)-5,5-dimethylcyclopentanone (7h): oil; $[\alpha]^{21}_{578}$ +35°; IR (liquid film) 1730 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 7.26 (s, 4 H), 3.65 (txt, 1 H), 2.70 (dxdxd, 1 H), 2.22 (dxd, 1 H), 2.20 (dxdxd, 1 H), 1.78 (dxd, 1 H), 1.31 (s, 9 H), 1.10 (s, 3 H), 0.99 (s, 3 H). Exact mass: calcd for $C_{17}H_{24}OS$, 276.155; found, 276.158. Addition of $Eu(dcm)_3$ to the ^1H NMR sample gave rise to the splitting of both methyl signals: ee 49%.

3-((*p-tert*-Butylphenyl)thio)-4,4-dimethylcyclopentanone (7i): quickly solidifying oil: $[\alpha]^{21}_{578}$ +68°; IR (liquid film) 1740 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 7.28 (s, 4 H), 3.42 (dxd, 1 H), 2.61 (dxd, 1 H), 2.34 (dxd, 1 H), 2.24 (d, 1 H), 2.02 (d, 1 H), 1.30 (s, 9 H), 1.26 (s, 3 H), 1.14 (s, 3 H). Exact mass: calcd for $C_{17}H_{24}OS$, 276.155; found, 276.158. Diastereomeric acetals: ^{13}C NMR δ 113.7 and 113.8 (C1), 46.9 and 47.0 (C2), 56.4 (C3), 41.2 and 41.1 (C4), 53.7 (C5), 27.8 and 28.1 (CH_3), 22.6 and 23.3 (CH_3); ee 35%.

Reaction of 1b with Racemic 2k (Equation 3). To a mixture of 664 mg (4.0 mmol) of **1b**, 21 mg (0.07 mmol) of **3b** and 14 mL of benzene was added 880 mg (8.0 mmol) of **2k**. After the solution was left standing overnight, more benzene was added (25 mL). The mixture was extracted twice with 25 mL of 2 N HCl, twice with 25 mL of water, and once with 25 mL of a concentrated NaCl solution. After drying ($MgSO_4$) of the benzene solution and evaporation of the solvent the resulting oil was Kugelrohr distilled. A 330-mg (3.0-mmol, 80%) sample of chemically pure **2k** was obtained: $[\alpha]^{21}_{578}$ +29° (*c* 0.4, CCl_4). Enantiomerically pure *R*-**2k**[86] has $[\alpha]^{21}_{578}$ −80° (*c* 0.6, CCl_4). Thus, our kinetic resolution has led to **2k**, enriched in the *S* enantiomer, with an optical purity of 36%.

Kinetic Measurements. Two reactions were kinetically studied: the addition of thiophenol to **2a** and to **2c**. The product of the former reaction has already been described. The product of the latter (eq 5), 3-(phenylthio)-5,5-dimethylcyclohexanone (**7j**), was an oil with $[\alpha]^{21}_{578}$ +30°, when quinine was used as catalyst: IR (liquid film) 1710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.1–7.5 (m, 5 H), 3.38 (txt, 1 H), 1.3–2.8 (m, 6 H), 1.05, (s, 3 H), 0.87 (s, 3 H). Exact mass: calcd for $C_{14}H_{18}OS$, 234.108; found, 234.108. Addition of $Eu(dcm)_3$ to the ^1H NMR sample gave splitting of both methyl signals: ee 57%.

Kinetic Procedure. Two flasks A and B, A containing a mixture of weighed quantities of thiophenol and a stock solution of the catalyst (quinine or acetylquinine) in the solvent (toluene or dioxane) and **B** containing a known quantity of the cyclohexanone (**2a** or **2c**), were placed in the thermostated bath, in order to reach the reaction temperature. The jacketed polarimeter cell was also connected to the thermostat. Then in a period as short as possible the contents of A were added to **B**, the resulting mixture was shaken well, the cell was filled with the reaction mixture, the cell was placed in the polarimeter, and the rotation measurements were started. All these actions took less than 2 min. The small quantity that had remained in flask A was then weighed to determine the precise concentrations of the reaction components. During the first 5–10 min of the reaction the rotation was measured each 15 s. At the end of the reaction intervals of 15 min were chosen, and the reaction was stopped when the rotation remained constant.

Determination of Initial Rates and Rate Constants. The rotation values, so obtained as a function of time, were corrected for the rotation of the catalyst. The correction value α_{cor} was assumed to be equal to the rotation at $t = 0$, determined by extrapolation of the graph of the rotation against time to $t = 0$. The corrected rotation values were used for the calculation of the initial rates and rate constants. The initial rates were obtained from eq 15, in which $[PhSCAH]_\infty$ is the theoretical final concentration of the product, α_∞ the final rotation, and $d\alpha/dt$ the slope of the line, representing the relation between rotation and time at the very beginning of the reaction (about 6 data points). Equations 16 and 17 are

$$\text{initial rate} = d[PhSCAH]/dt = ([PhSCAH]_\infty/\alpha_\infty)\,(d\alpha/dt) \quad (15)$$

$$k_{obsd} = (t[B]_0[PhSH]_0)^{-1}\alpha/(\alpha_\infty - \alpha) \quad (16)$$

$$k_{obsd} = [t[B]_0([PhSH]_0 - [CA]_0)]^{-1} \ln\,(\alpha_\infty - \alpha[CA]_0/[PhSH]_0)/(\alpha_\infty - \alpha) \quad (17)$$

(86) Allinger, N. L.; Riew, C. K. *J. Org. Chem.* **1975**, *40*, 1316.

the relations utilized for the determination of the rate constants (eq 16 in cases where $[PhSH]_0 = [CA]_0$ and eq 17 when $[PhSH]_0 > [CA]_0$; $[B]_0$, $[CA]_0$, and $[PhSH]_0$ are the initial base, cycloalkenone and thiol concentrations). About 10 data points were used for each run, lying between about 10% and 80% completion of the reaction. Correlation coefficients of the lines (least squares) were generally >0.98. Estimated errors in the thermodynamic parameters are given in the tables.

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Kinetic Isotope Effect Study on Methyl Participation in Solvolysis of Neopentyl-Type Arenesulfonates[1,2]

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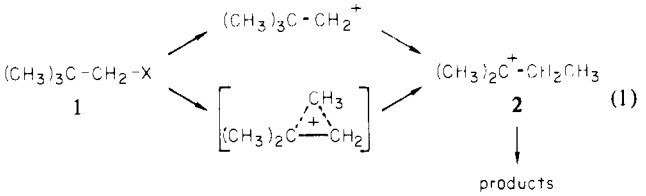
Abstract: Carbon-14 and deuterium kinetic isotope effects at various positions have been measured in the solvolysis of neopentyl arenesulfonates. In the acetolysis of neopentyl nosylate (**6**) at 100 °C, carbon isotope effects (k^{12}/k^{14}) are 1.073 at α, 1.019 at β, and 1.046 at γ. Deuterium effects (k_H/k_D) are 1.187 at α (D_2) and 1.016 at γ (D_9). In the trifluoroacetolysis of neopentyl brosylate (**7**) at 65 °C, k^{12}/k^{14} are 1.073 at α, 1.023 at β, and 1.026 at γ and k_H/k_D are 1.190 at α (D_2) and 1.012 at γ (D_9). These positive isotope effects at all the positions are compatible with the concerted nature of the solvolytic rearrangement. Kinetic isotope effects of only a migrating methyl group have been measured in the solvolysis of 2-methyl-2-adamantanemethyl brosylate (**9**), a model system of neopentyl solvolysis; k^{12}/k^{14} and k_H/k_D (D_3) are 1.037 and 1.123 in the acetolysis at 100 °C, 1.037 and 1.135 in the trifluoroacetolysis at 25 °C, and 1.035 and 1.12 in the trifluoroacetolysis at 45 °C, respectively. Combination of the results for **6** and **7** with those for **9** revealed that the carbon-14 isotope effects at γ primarily arise from the migrating methyl group and that the negligibly small D_9 effect at γ is brought about by cancellation of a normal effect of the migrating methyl group and inverse effects of the two nonmigrating methyl groups. The nature of σ participation as a composite of two formally conflicting modes, namely, hyperconjugation and bridging, is discussed on the basis of these results.

Neighboring group participation is usually classified into *n*-, π-, and σ-types depending on the nature of electrons used to interact with the reaction center in the same molecule.[3] A nonbonding pair of electrons is most effective in stabilizing a developing charge in nucleophilic substitution. Most of the phenomena called intramolecular catalysis belong to this category. π-Electrons of an aromatic ring or a double bond are moderately nucleophilic; their participation to an electron-deficient center has been well established.[4] σ-Electrons of a carbon–carbon or a carbon–hydrogen single bond are the least nucleophilic; participation by them is the most subtle phenomenon. The subtleness of the phenomenon is easily understandable when one regards that σ participation in the transition state corresponds to the so-called "nonclassical ion" in the intermediate. As the nonclassical ion problem has been the matter of long debate, so has the σ participation been.

Neopentyl solvolysis is the simplest among the problem systems. Neopentyl derivatives **1**, having a fully substituted carbon atom next to the reaction center, usually give rise to substitution and elimination products derived from the rearranged *tert*-amyl cation **2** under solvolytic conditions (eq 1). The timing of this rearrangement, concerted or stepwise, has been the subject of controversy.

Rate enhancement associated with the rearrangement is, if anything, too small in the usual solvents to establish methyl participation in the rate-determining transition state. Kinetic evidence for and against methyl participation has been accumulated.[5-11] Stereochemical studies favor participation,[12] and even a bridged intermediate has been claimed.[13] However, an alternative explanation by means of a tight ion pair may not be ruled out at least in solvolysis.



(1)

Kinetic isotope effects are known to be the most effective tool in studying such a subtle phenomenon. However, even this tool has so far been ineffective. Negligible intermolecular isotope effects in the hydrolysis[14] and the trifluoroacetolysis[15] of neopentyl-γ-d_9 derivatives and large intramolecular migrating ratios in the trifluoroacetolysis ($k_{CH_3}^{CD_3}/k_{CD_3}^{CH_3}$ = 1.22–1.31) led Schubert and Henson to conclude that the rearrangement occurs

(1) Neighboring group participation in solvolysis. 12. For Part 11, see: Yukawa, Y.; Kim, S.-G.; Yamataka, H.; Matsuda, K.; Ando, T. *J. Am. Chem. Soc.*, submitted for publication.

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