Synthesis, Structure, and Stereoselective Reaction of a Chiral Hydroxy-Stabilized Metal-Free Enolate

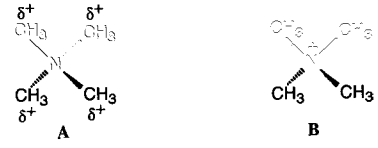
Manfred T. Reetz,* Stephan Hütte, Richard Goddard, and Chantal Robyr

Abstract: The reaction of acetophenone with tetrabutylammonium hydroxide affords the tetrabutylammonium enolate of phenyl (2-hydroxy-2-phenyl)propyl ketone. The crystal structure of this chiral enolate shows intramolecular hydrogen bonding between the hydroxyl group and the enolate oxygen atom. Furthermore, the α-methylene units of the ammonium counterion form hydrogen bonds to the basic enolate C and O atoms and to the O atom of the hydroxy group. This three-point bonding occurs selectively on the *Re,Re* side, a phenomenon which may be responsible for the direction of diastereoselectivity in the epoxide-forming reaction of the enolate with *N*-bromosuccinimide.

Keywords
asymmetric synthesis · chirality · enolates · hydrogen bonds · structure elucidation

Enolates constitute a synthetically important class of reagents used in aldol, Michael, alkylation, bromination and amination reactions.[1] The vast amount of research that has been invested in the development of stereoselective variations of such reactions[2] has stimulated interest in the structure and aggregation state of the compounds.[3] The nature of the metal (or counterion) is known to play a crucial role. For example, X-ray structural studies show that lithium enolates exist as dimers or higher aggregates, depending upon the carbonyl precursor, solvent and additive.[3, 4] Of theoretical and practical interest is the propensity of certain lithium enolates to form hydrogen bonds with secondary amines R_2NH in which the enolate carbon atom rather than the oxygen atom is involved.[3b, 5] A rare case of an alcohol-solvated lithium enolate has recently been documented.[6] Accordingly, the lithium enolate derived from 1,3-cyclohexanedione undergoes hydrogen bonding to methanol, as shown by X-ray crystallography. Although several X-ray structural studies of chiral functionalized organolithium reagents have been reported,[7] the crystal structure of a chiral lithium enolate has not appeared in the literature thus far.

Ketone and ester enolates having tetraalkylammonium counterions as used in phase-transfer catalysis were long believed to be "naked" monomeric species.[8] However, we recently showed that the tetraalkylammonium salts of such CH-acidic compounds as malonic acid diesters[9] as well as phenylacetic and propionic acid esters[10] are in fact species in which anion and cation interact through hydrogen bonds,[11] often in the form of discrete supramolecular dimeric ion pairs in solution and in the solid state.[9] In all of these cases the α-methylene hydrogens of the tetraalkylammonium ion form hydrogen bonds with the basic oxygen atoms of the enolates.[9–12] In this context it is important to point out that MO calculations of $(CH_3)_4N^+$ show the positive charge to be delocalized on the carbon and hydrogen atoms,[13] that is, it is not localized on nitrogen as is often assumed. Indeed, the calculations show that nitrogen is neutral, which means that representation **A** describes the true state of affairs, whereas representation **B**, while easy to draw, is in fact incorrect.[13] It is therefore to be expected that in homologs such as $(n\mathrm{Bu})_4N^+$ the positive charge is delocalized on the α-methylene entities, which also means that these positions are somewhat acidified.



A

B

In this paper we describe the synthesis, X-ray structural analysis, aggregation state and stereoselective bromination of a chiral metal-free ketone enolate having $(n\mathrm{Bu})_4N^+$ as the counterion. It is stabilized by a novel intramolecular hydrogen bond and by hydrogen bonds between anion and cation.

Results and Discussion

Synthesis and Crystal Structure: Upon treating a toluene solution of acetophenone (**1**) with tetrabutylammonium hydroxide and removing the water azeotropically,[9, 10, 14] we failed to isolate any of the expected enolate **2** (Scheme 1). Rather, the sole product turned out to be the chiral enolate **4**, formed as a racemate by aldol addition of **2** to acetophenone and subsequent proton transfer reaction of the intermediate aldolate **3**.

The X-ray structural analysis of compound **4** reveals several remarkable features.[15] The anion exists in the form of a six-membered ring in which the hydroxyl group (O2) forms a hydrogen bond to the enolate oxygen atom (O1),[6, 16] the methyl and phenyl groups at the stereogenic center occupying the quasi-

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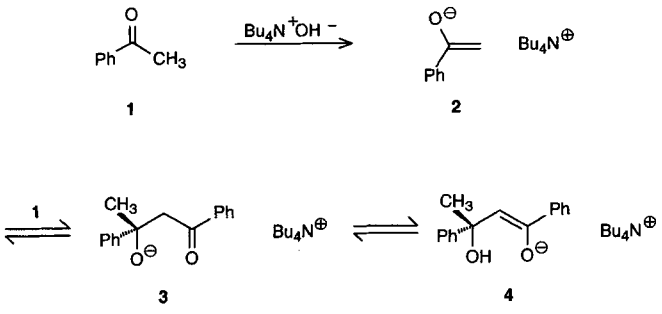


Scheme 1.

axial and equatorial positions, respectively (Fig. 1). Anions and cations alternate in an infinite one-dimensional array, forming hydrogen bonds to one another. Here again it is the α-methylene groups of the tetrabutylammonium ion which participate in the

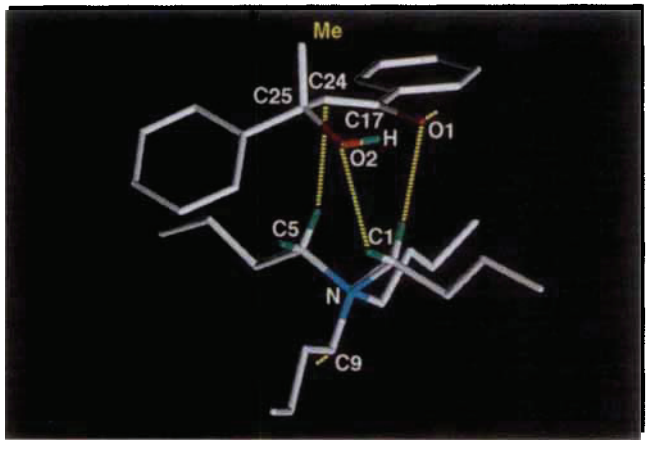
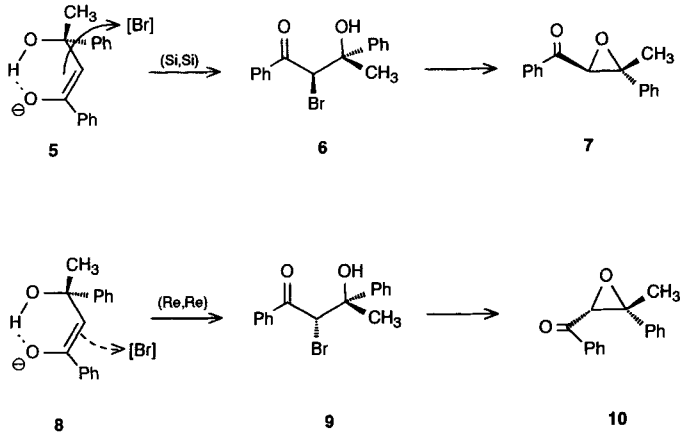


Fig. 1. Structure of **4** in the crystal, showing the three-point bonding on the *Re,Re* face of the enolate anion. H atoms, except those bonded to O2, C1 and C5 omitted for clarity. Selected interatomic distances (Å) and angles (°) (symmetry-related atoms denoted by *): O1–C17 1.317(2), C17–C24 1.358(2), C24–C25 1.520(2), C25–O2 1.428(2), O1···O2 2.554(1), O1···C9* 3.240(2), C1···O1 3.289(2), C1···O2 3.367(2), C5···C24 3.557(2); O2-C25-C24 110.7(1), C25-C24-C17 122.6(1), C24-C17-O1 123.8(1), C1-N-C5 106.1(1).

hydrogen bonds.[9–12] Importantly, the nature and extent of hydrogen bonding is rather different on the two diastereotopic sides of the enolate π system. The *Re,Re* side undergoes two hydrogen bonds involving two α-methylene units of the ammonium ion and the oxygen and carbon atoms of the enolate moiety.[17] Additionally, one of the α-methylene units forms a hydrogen bond to the oxygen atom of the hydroxyl group. In contrast, the *Si,Si* face of the enolate experiences only one contact to a tetrabutylammonium ion. The relevant C···O distance (O1···C9* 3.240(2) Å) is similar to the corresponding C···O distance (O1···C1 3.289(2) Å) on the opposite side. Therefore, three-point bonding on the *Re,Re* side characterizes the actual ion pairs, which in turn interact with one another in the crystal through weaker single contacts. Interestingly, each infinite one-dimensional array contains only one enantiomer; the other enantiomer occupies a similar but parallel chain running in the opposite direction.

Aggregation State in Solution: The aggregation state of compound **4** in THF was determined at −108 °C by a freezing-point depression study.[18] The average degree of association in three runs turned out to be 1.1, which means that **4** is monomeric. It is tempting to speculate that the structure of this monomer in solution is similar to the repeating ion pair units in the solid state (Fig. 1). Unfortunately, NMR studies in solution failed to provide conclusive evidence concerning this point.[19]

Stereoselective Bromination of the Enolate: We were interested in discovering whether electrophiles react stereoselectively with the chiral enolate **4**. However, we anticipated problems in the case of electrophiles of the type CH_3I, because the products of alkylations are sterically encumbered aldol adducts involving two ketones, intermediates which are likely to undergo stereochemically equilibrating retro-aldolization[19] under basic conditions. In contrast, bromination should lead to bromohydrins which are expected to form epoxides irreversibly under basic conditions without loss of stereochemical information. Indeed, upon treating the enolate **4** with *N*-bromosuccinimide (NBS) at −78 °C, rapid reaction took place. The products turned out to be the (*E*)- and (*Z*)-configurated epoxides **7** and **10**, formed in a ratio of 77:23, respectively (Scheme 2). Following chromatographic separation the compounds were isolated in 50% and 14% yield, respectively, and identified by comparison with authentic samples.[20]



Scheme 2.

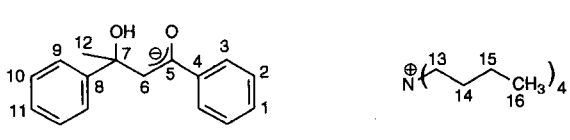
Epoxide formation must occur via the intermediate bromohydrins **6** and **9**, which undergo rapid base-induced (succinimide anion) intramolecular S_N2 reactions with inversion of configuration at the newly created stereogenic center. Assuming an enolate structure having the methyl group in the quasi-axial position as found in the solid state (Fig. 1) and neglecting the ammonium counterion, it would appear that NBS attacks preferentially the sterically *more* hindered *Si,Si* face of the enolate (cf. transition states **5** versus **8**).[21] Of course, in solution the most reactive conformer may be a different one. Alternatively, the monomeric enolate **4** in solution may, indeed, have the *Re,Re* side shielded by the hydrogen-bonded ammonium counterion within the context of three-point bonding, as in the crystal. In that case bromination would occur preferentially from the opposite *Si,Si* side, which is observed experimentally. A report by Dolling et al. is relevant; they postulated that *chiral* ammonium ions derived from alkaloids selectively shield one face of certain aromatic *achiral* ketone enolates in enantioselective phase-transfer catalyzed alkylations.[22] Specifically, multipoint bonding between the enolate and a benzylcinchoninium ion involving electrostatic attraction, π–π interactions, and hydrogen bonds between the enolate oxygen atom and the alcohol functional group of the catalyst was proposed.[22] Our work shows that this postulate is not pure speculation, and that additional bonding involving the basic positions of the enolates and the acidic CH moieties of the ammonium ions is likely.

Conclusion

In summary, we have shown by X-ray crystallography that the chiral metal-free enolate **4** is stabilized by a unique intramolecular hydrogen bond involving the enolate oxygen atom and the hydroxy group. Additionally, the α-methylene units of the tetrabutylammonium ions form hydrogen bonds with the enolate carbon and oxygen atoms and with the oxygen atom of the hydroxyl group. Such a novel type of three-point bonding occurs preferentially on one diastereotopic face of the enolate in the solid state. In solution it may well be the underlying factor in the selective shielding of one of the diastereotopic π faces of the monomeric enolate, this being the possible source of stereoselectivity in the NBS-induced bromination reaction. Indeed, the enolate **4** is monomeric in solution. Finally, the results described in this paper may be of help in the rational design of chiral phase-transfer catalysts.

Experimental Procedure

Preparation of Enolate 4: A 250 mL three-necked flask equipped with a 100 mL dropping funnel and a connection to a membrane pump was charged with dry toluene (50 mL) and a methanol solution of tetrabutylammonium hydroxide (20 mL of a 1 M solution, Aldrich). In order to remove the methanol, dry toluene (20 mL) was added and most of the solvents removed in vacuo at 15–19 Torr. In doing so, the total volume was not allowed to fall below 70 mL. The process was repeated 5 more times. Following the addition of toluene (50 mL), acetophenone (5.5 mL, 47 mmol) in toluene (60 mL) was slowly added, during which the reaction mixture was kept under vacuum in order to remove toluene and water azeotropically. The total volume of the yellow solution was not allowed to fall below 100 mL. The total time for addition of acetophenone was about 2.5 h. The total volume was then reduced to about 50 mL and the concentrated mixture was tranferred into a Schlenk tube under argon. High vacuum was then applied until the mixture had turned into a thick paste. (If this drying phase is too long, partial decomposition of the desired product sets in.) Under an atmosphere of dry argon a small amount of dry dimethylformamide (DMF) was added. The orange solution was then kept at −60 °C for two days, resulting in the formation of gold-yellow crystals of **4**. The solvent was removed under vacuum, and the crystals were washed with dry ether and dried in vacuo. The yield was 20% (in some runs higher). ^{13}C NMR (75 MHz, [D$_8$]THF): δ = 161.7 (s, C-5); 157.6 (s, C-8); 147.4 (s, C-4); 127.4 (d, C-2); 127.2 (d, C-10); 126.3 (d, C-3); 125.9 (d, C-9); 125.3 (d, C-11); 124.7 (d, C-1); 96.0 (d, C-6); 76.0 (s, C-7); 58.7 (t, C-13); 35.6 (q, C-12); 24.8 (t, C-14); 20.5 (t, C-15); 14.1 (q, C-16) (Scheme 3). The spectrum also shows weak signals corresponding to acetophenone (δ = 196, 169, 149, 129, 127), all appearing broad, indicating a retro-aldol/aldol process. The IR band (in THF) of the enolate functional group occurs at 1690 cm^{-1}, additional peaks appearing at 1585 and 1550 cm^{-1}. The O–H band is buried under the signals of THF (3050–2750, 2680 and 1980 cm^{-1}).



Scheme 3.

Reaction of Enolate 4 with NBS: The stirred solution of enolate **4** (362 mg, 0.75 mmol) in dry THF (6.6 mL) was treated with powdered *N*-bromosuccinimide (NBS) at −78 °C under an Ar atmosphere. After 3 h the reaction was quenched with water, and diethyl ether was added. The aqueous phase was extracted three times with diethyl ether, and the combined organic phases were washed with H_2O and dried over $MgSO_4$. Following removal of the solvent, the residue was examined by ^1H NMR spectroscopy, and showed a 72:28 ratio of the (*E*)- and (*Z*)-configurated epoxides **7** and **10**, respectively. Chromatography over silica gel (hexane/ethyl ester 97:3) afforded 90 mg (50%) of **7** and 39 mg of a mixture of **10** and 3-hydroxy-1,3-diphenyl-1-butanone in a ratio of about 1.7:1 (by ^1H NMR spectroscopy). Epoxide **10** was separated from this mixture by crystallization from ethanol, providing 14% of pure product. Epoxides **7** and **10** were identified by comparison with authentic samples [20].

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