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# Kinetics and Isotope Effects of the Aldol−Tishchenko Reaction between Lithium Enolates and Aldehydes

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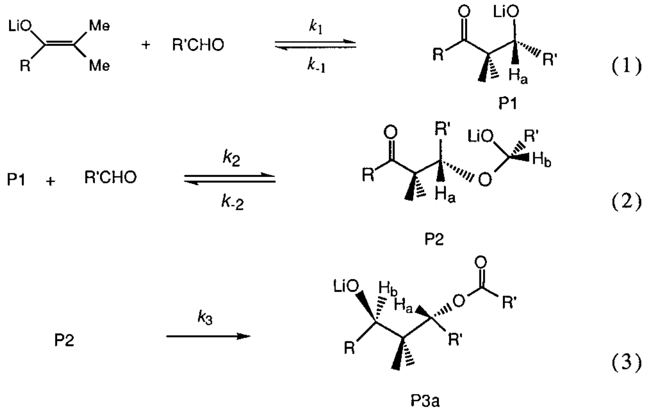
The lithium enolate of isobutyrophenone reacts with two molecules of benzaldehyde at room temperature in THF to yield after protonation a 1,3-diol monoester. The kinetics of this process was studied for the reaction of the lithium enolate of *p*-(phenylsulfonyl)isobutyrophenone (LiSIBP) and benzaldehyde in THF by monitoring the disappearance of LiSIBP. The observed rates obey the rate law $-d[\{LiSIBP\}]/dt = k_{ob}[\{LiSIBP\}]^{0.83}[benzaldehyde]^{2.0}$ (braces denote initial formal concentration of LiSIBP) and exhibit a kinetic isotope effect $k_H/k_D = 2.0$ (determined from independent experiments using benzaldehyde-*d*). These results and competitive isotope effect experiments are consistent with formation of an initial lithium aldolate (P1), followed by reaction with a second aldehyde to form a ketal (P2), and finally a rate-limiting intramolecular hydride transfer (Tishchenko reaction). These reactions are modeled with *ab initio* molecular orbital calculations. Corresponding theoretical kinetic and equilibrium isotope effects match the experimentally observed isotope effects and support the proposed reaction scheme.

The mixed Tishchenko reaction involves the reaction of the aldol product from one aldehyde with another aldehyde having no α-hydrogens to yield an ester.[1] The reaction has usually been run with aluminum alkoxides as catalyst, but other metal alkoxides have also been used.[2,3] Related reactions can be run in various ways. For example, Evans and Hoveyda have reported that reaction between *β*-hydroxy ketones and aldehydes with catalytic amounts of $SmI_2$ affords alcohol esters with high levels of stereochemical control.[4] Similar reaction products were observed by Burkhardt, Bergman, and Heathcock in the reactions of nickel and palladium enolates with aldehydes.[5] Aoki et al.[6] have found that anti diol−ester products are formed in good yields from addition of aldehydes to tertiary α-ketone iodides and *n*-BuLi at 0 °C in diethyl ether. Such products were proposed to be formed through an aldol step followed by addition of another aldehyde and an intramolecular hydride transfer (Scheme 1).

Several aspects of this mechanism remain to be clarified. As part of our continuing mechanistic studies of reactions of alkali enolates,[7−10] we found that the Aldol−Tishchenko reaction between several lithium enolates and benzaldehyde proceeds cleanly in THF at room temperature. The spectroscopic properties of the lithium enolate of *p*-(phenylsulfonyl)isobutyrophenone (LiSIBP) have allowed kinetic study of this reaction. This study together with a comparison of experimental and computed isotope effects are reported in this paper.

**Scheme 1. Reaction Sequence for Formation of a Diol−Monoester from the Reaction between a Lithium Enolate and Two Aldehyde Molecules**



## Kinetic Studies

Reaction of the lithium enolate of isobutyrophenone (LiIBP) with 1 equiv of benzaldehyde in THF at −65 °C afforded a convenient route to the normal aldol product (**1a**; P1 in Scheme 2 with R = R′ = Ph). At room temperature, however, the only product observed after protonation was the diol−monoester (**3a**, P3a in Scheme 2 with R = R′ = Ph), apparently produced from the corresponding lithium ester alcoholate P3a−Li.

In the presence of 2 equiv or more of benzaldehyde, the enolate was transformed quantitatively into P3a. Even when only 1 equiv of the aldehyde was used, P3a was the only product observed after quenching. As found in other systems,[4−6] only the anti diol monoester diastereomer is formed. In the reaction of LiIBP and tolualdehyde, the proton and carbon NMR spectra of the protonated product revealed the presence of equal amounts of two similar compounds, apparently two geometrical isomers differing in the location of the aromatic groups. Two such anti isomers are possible as derived from the lithium ester alcoholates P3a−Li and P3b−Li (R = Ph,

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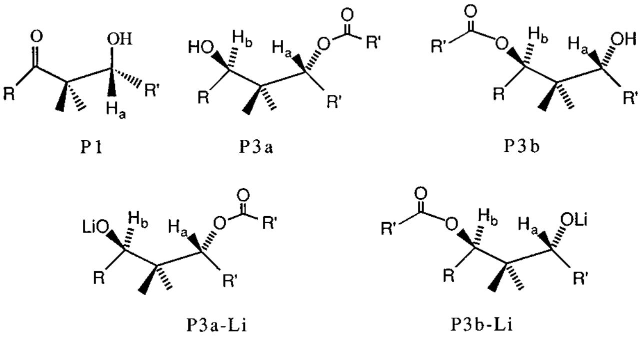
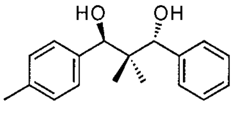
S0022-3263(97)02128-2 CCC: $15.00

**Scheme 2. Products of the Reaction between Lithium Enolates and Aldehydes**

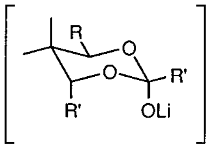


**1a** (P1, R = R' = Ph); **3a** (P3a, R = R' = Ph); **3b** (P3a, R = Ph, R' = Tolyl); **3c** (P3a, R = Phenyl-*p*-sulphonylphenyl, R' = Ph).

R′ = *p*-tolyl). Hydrolysis of the mixture gave only one diol product, **4**, containing one phenyl and one *p*-tolyl group. A likely route for the interconversion between P3a−Li and P3b−Li is via a six-membered intermediate P3i. Note that the intermediate P3i−Li retains the anti configuration of the diol−monoester. A similar phenomenon was observed in the nickel-mediated reaction.[5] When LiIBP and cyclohexanecarboxaldehyde were allowed to react at 25.0 °C, only the P3a isomer was observed.



**4**



P3i-Li

The diol **4** was crystalline and was submitted for X-ray crystal analysis.[11] The crystal showed significant disorder in the oxygen positions. Refinement of the occupancies between the two disordered sites on each carbon led to unequal populations. Without constraints applied between oxygens on different carbons excellent agreement was found between the occupancies of the anti-oxygens (occ = 0.57 each) as shown in Figure 1. The resulting anti-structure **4** is consistent with previous studies.

The lithium enolate (LiSIBP) from *p*-(phenylsulfonyl)-isobutyrophenone (SIBP) exists in THF primarily as a dimeric ion-pair aggregate, $Li_2En_2$, with a characteristic spectrum at $\lambda_{max}$ = 390 nm, in equilibrium with small amounts of the monomer, LiEn ($K_{d-LiEn} = 5.0 \times 10^4\ M^{-1}$).[9] Reaction between LiSIBP and benzaldehyde at 25.0 °C proceeds at rates amenable to kinetics study using the spectroscopic techniques and leads to the two geometrical isomers P3a and P3b in a 4:1 ratio. Any mechanism in which the reaction between the lithium enolate and the first molecule of the aldehyde is the rate-limiting step in the formation of P3 should exhibit a reaction rate law unimolecular in the aldehyde concentration.

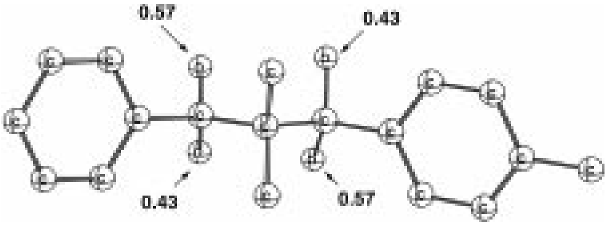


**Figure 1.** X-ray crystal structure of the diol obtained from the lithium enolate of isobutyrophenone and *p*-tolualdehyde. Occupancies of the oxygen positions in the disordered structure are indicated and show the trans orientation of the hydroxy groups. For clarity, hydrogens are not shown.

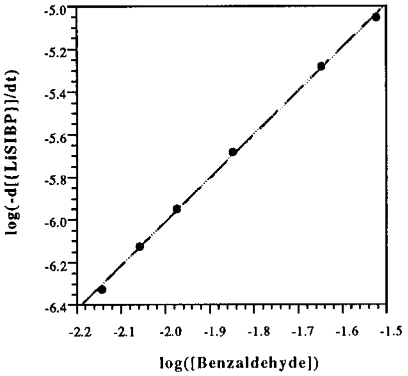


**Figure 2.** Determination of the aldehyde order in the observed rate law of the reaction between LiSIBP and benzaldehyde in THF. Reactions were carried out at 25.0 °C and a constant concentration of LiSIBP = 1.6 mM. The slope of the plot is 2.0 and corresponds to the order of aldehyde in the observed rate law.

The kinetics of the reaction between LiSIBP and benzaldehyde was studied at 25.0 °C at a constant concentration of LiSIBP (1.6 mM) and varying aldehyde concentrations (7−30 mM). Initial rates were determined by monitoring the disappearance of LiSIBP at its $\lambda_{max}$ for the first 10% reaction. The observed order in aldehyde is 2.0 (Figure 2) and implies that formation of the aldolate (eq 1) is not rate-limiting. Reaction rates measured at constant benzaldehyde concentration (15 mM) and varying concentrations of LiSIBP (0.3−3.4 mM) gives the order of the enolate as 0.83; thus, $-d[\{LiSIBP\}]/dt = k_{ob}[\{LiSIBP\}]^{0.83}[benzaldehyde]^{2.0}$ (braces denote initial formal concentration of LiSIBP) in which $k_{ob} = 2.68$.

Within the framework of the reactions in Scheme 1, the observed aldehyde order shows that either step 2 or 3 is rate-limiting. Consistent with a rapid equilibrium in eq 1, addition of LDA to a solution of the aldol from isobutyrophenone and benzaldehyde (P1, R = R' = Ph) results in fragmentation of the aldolate into the corresponding lithium enolate and P3. Since the enolate studied is mostly dimeric, if the first step were rate-determining, the order in enolate would have indicated whether reaction occurs via the monomer or dimer. With step 2 or 3 being rate-limiting, the observed order in enolate is more complex and not simply interpretable since P1 might also be aggregated and form mixed aggregates with the enolate. If step 3 is rate-limiting, any aggregation of P2 adds to this complexity.

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(11) We are indebted to Adam Matzger for assistence in this analysis.

## Isotope Effects

To examine whether step 2 or 3 is rate-limiting in Scheme 1, deuterium isotope labeling experiments were carried out, and results were compared with theoretical isotope effects obtained for the reactions in Scheme 1 using model ab initio calculations. If either the first (eq 1) or second (eq 2) step is rate-determining, reaction of the deuteriated aldehyde PhCDO should give only secondary kinetic isotope effects (KIE), which are expected to be small and inverse. The hydride-transfer step (eq 3), on the other hand, should be strongly sensitive to isotopic substitution and is anticipated to yield a normal primary KIE of substantial magnitude. Independent kinetic isotope effect experiments using PhCDO gave an observed $\mathrm{KIE_{ob}}$ of 2.1. This observed value is in a normal range for primary isotope effects and suggests that step 3 is rate-limiting in Scheme 1. In this case, $\mathrm{KIE_{ob}}$ reflects both the true KIE of eq 3 ($\mathrm{KIE_3} = k_{3(\mathrm{H})}/k_{3(\mathrm{D})}$) and the equilibrium isotope effects of eq 1 and 2; that is, from eqs 4 and 5, $\mathrm{EIE_1} = K_{1(\mathrm{H})}/K_{1(\mathrm{D})}$, $\mathrm{EIE_2} = K_{2(\mathrm{H})}/\mathrm{K}_{2(\mathrm{D})}$, and $\mathrm{KIE_{ob}} = \mathrm{KIE_3} \times \mathrm{EIE_1} \times \mathrm{EIE_2}$.

$$P_1 = (k_1/k_{-1})[\mathrm{LiSIBP}][\mathrm{PhCHO}] = K_1[\mathrm{LiSIBP}][\mathrm{PhCHO}] \quad (4)$$

$$P_2 = (k_2/k_{-2})P_1[\mathrm{PhCHO}] = K_2P_1[\mathrm{PhCHO}] = K_1K_2[\mathrm{LiSIBP}][\mathrm{PhCHO}]^2 \quad (5)$$

Any aggregation effects of $P_1$ and $P_2$ could make the actual equations more complex, but probably would not have large effects on the numerical values of the isotope effects.

Additional isotope labeling experiments were carried out using LiSIBP and a large excess of 1:1 PhCHO:PhCDO and allowing the reaction to proceed to completion. According to Scheme 1, the extent of deuteration of $\mathrm{H_a}$ in P3a reflects the equilibrium isotope effect in eq 1; $[\mathrm{H_a}]/[\mathrm{D_a}] = \mathrm{EIE_1} = K_{1(\mathrm{H})}/K_{1(\mathrm{D})}$. These experiments showed that $\mathrm{EIE_1} = 0.74$. This value agrees with other additions to benzaldehyde of $K_\mathrm{H}/K_\mathrm{D} = 0.74 - 0.78$.[12] Such a result is commonly attributed to an increase in the frequency of the C−H(D) bending vibration in changing from a tricoordinate sp$^2$ to tetracoordinate sp$^3$ bond.[13] As in the independent $\mathrm{KIE_{ob}}$, the extent of deuteration of $\mathrm{H_b}$ (the proton α to the hydroxyl group in P3a) reflects both $\mathrm{EIE_2}$ and $\mathrm{KIE_3}$ ($[\mathrm{H_b}]/[\mathrm{D_b}] = \mathrm{KIE_3} \times \mathrm{EIE_2}$). The observed $[\mathrm{H_b}]/[\mathrm{D_b}]$ ratio is 2.16. Approximating the equilibrium isotope effect for eq 2 ($\mathrm{EIE_2}$) to be the same as $\mathrm{EIE_1}$ (0.74) affords a value of 2.9 for $\mathrm{KIE_3}$. A comparable value of $\mathrm{KIE_3}$ (2.2 − 2.7) is obtained using $\mathrm{KIE_{ob}}$ from the independent KIE studies and the estimated value of 0.74 for $\mathrm{EIE_2}$. The magnitude of this primary isotope effect is less easy to interpret. Primary isotope effects for hydrgen-transfer transition structures are greatest when the transfer is linear[14] and frequently have $k_\mathrm{H}/k_\mathrm{D} > 6$ or so, but nonlinear transition structures have lower isotope effects[15] that can be as low as $2^{1/2}$.[16] Moreover, the hydrogen transfer in eq 3 is that formally of a hydride rather than a proton or hydrogen atom, and this difference could also affect experimental analogies. Because of these problems, our experimental isotope effects were compared to those calculated for a model system.

## Model Theoretical Study of Isotope Effects

The computations involved ab initio calculations[17] carried out on a model system using formaldehyde and the lithium enolate of acetaldehyde as the reacting species. Although the energetics obtained for this simplified unsolvated system may not be adequate for describing the energetics of the real reactions in solution, the computed isotope effects should still be useful, since they are often not very sensitive to solvent and substituent effects. Many examples are known in which theoretical isotope effects calculated for model systems successfully reproduce kinetic and equilibrium isotope effects measured in solution.[18−22] Calculations were carried out at the HF/6-31++g** level using the GAUSSIAN 94 series of programs.[23] The computed equilibrium and transition structures for the compounds in the sequence of reactions in Scheme 1 are given in Figure 3, and the computed reaction barriers and energies are given in Table 1 together with corresponding isotope effects calculated using the computed scaled harmonic vibrational frequencies. Selected calculations were also carried out on the reaction between lithium acetonate (LiAc) and acetaldehyde. Results of these calculations are also given in Table 1.

The lowest energy structure computed for LiEn has the cation lying above the plane of the enolate at a position that allows an $\eta^3$-bridging mode ($\eta^3$-LiEn).[23] Another structure in which the lithium is in the plane of the enolate anion and bound primarily to the oxygen ($\eta^1$-LiEn) exists at an energy level 2 kcal mol$^{-1}$ above $\eta^3$-LiEn. The two minima of LiEn are connected by a transition structure 1.7 kcal mol$^{-1}$ above $\eta^1$-LiEn. MP2 calculations at the HF geometries (MP2//HF) bring the energy difference between the two structures to 3.6 kcal mol$^{-1}$. Similarly, full geometry optimization at the MP2 level gives two distinct structures for LiEn, such that $\eta^3$-LiEn is 4.8 kcal mol$^{-1}$ above $\eta^1$-LiEn. The two distinct structures of LiEn are also retained in the presence of a water or $\mathrm{NH_3}$ molecule coordinated to the lithium atom (HF level). The energy difference between the two structures in the monocoordinated species is substantially reduced: 0.6 kcal mol$^{-1}$ for the water-coordinated

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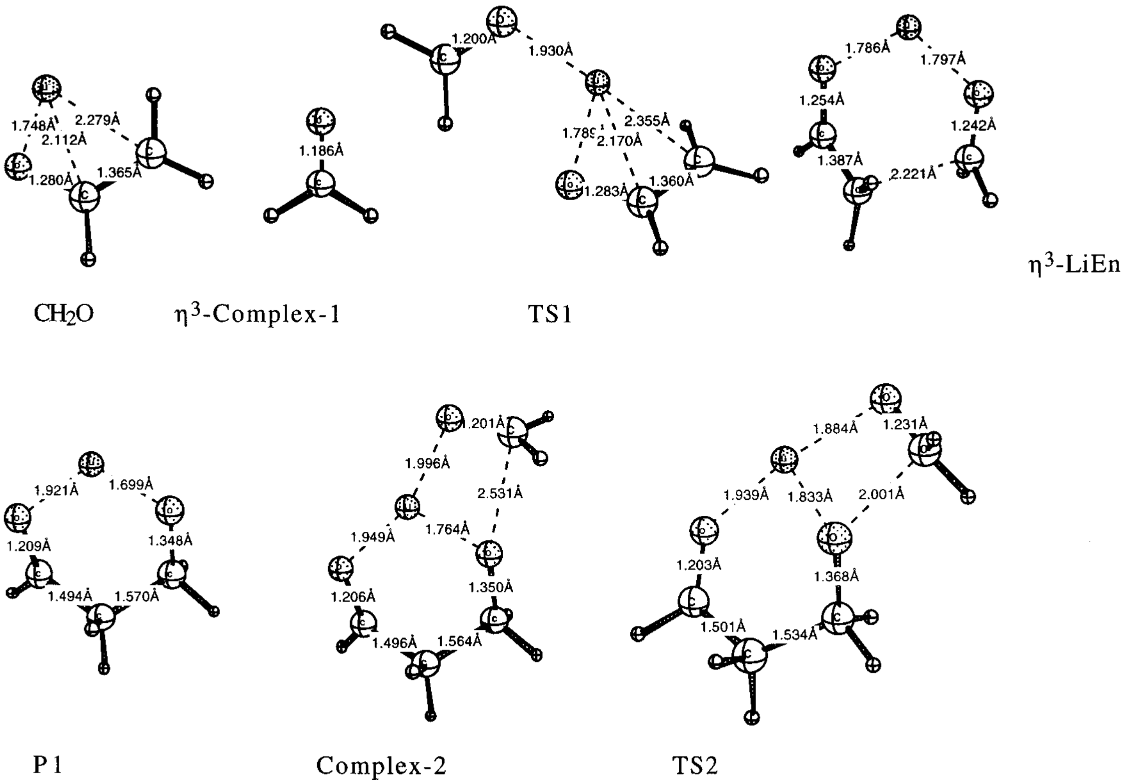

$CH_2O$ $\eta^3$-Complex-1 TS1 $\eta^3$-LiEn

P1 Complex-2 TS2

**Figure 3.** Optimized geometries for the reactants, transition structures, and products in the sequence of reactions between the lithium enolate derived from acetaldehyde and formaldehyde. The total reaction sequence is: LiEn + $CH_2O$ → complex-1 → TS1 → P1 → complex-2 → TS2 → P2 → TS3 → P3.

**Table 1. Computed Reaction and Activation Energies and Corresponding Isotope Effects for the Sequence of Reactions between Lithium Vinyloxide (LiEn) and Formaldehyde and between the Lithium Enolate of Acetone (LiAc) and Acetaldehyde**

| reaction | $\Delta E^a$ | $\Delta ZPE^b$ | $\Delta\Delta ZPE^c$ | $MMI^d$ | $EXC^d$ | $EXP^d$ | isotope effect$^{e,f}$ |
|---|---|---|---|---|---|---|---|
| LiEn + $CH_2O$ → complex-1 | −18.4 | 1.625 | 0.122 | 1.35 | 0.83 | 0.82 | $EIE_{com\text{-}1} = 0.92$ |
| LiEn + $CH_2O$ → TS1 | −12.2 | 2.379 | 0.225 | 1.35 | 0.91 | 0.68 | $KIE_1 = 0.84$ |
| LiEn + $CH_2O$ → P1 | −26.8 | 4.138 | 0.256 | 1.34 | 0.94 | 0.65 | $EIE_1 = 0.82$ |
| P1 + $CH_2O$ → complex-2 | −13.8 | 1.280 | 0.085 | 1.36 | 0.80 | 0.87 | $EIE_{com\text{-}2} = 0.95$ |
| P1 + $CH_2O$ → TS2 | −11.1 | 2.205 | 0.225 | 1.37 | 0.85 | 0.68 | $KIE_2 = 0.79$ |
| P1 + $CH_2O$ → P2 | −14.1 | 4.070 | 0.293 | 1.37 | 0.92 | 0.61 | $EIE_2 = 0.77$ |
| P2 → TS3 | 25.1 | −1.152 | −0.654 | 1.01 | 1.06 | 3.01 | $KIE_3 = 3.22$ |
| P2 → P3 | −3.0 | 0.315 | −0.033 | 0.99 | 1.00 | 1.06 | $EIE_3 = 1.05$ |
| LiAc + MeCHO → TS1-Me | −9.0 | 1.872 | 0.175 | 1.15 | 0.98 | 0.74 | $KIE_{1\text{-}Me} = 0.84$ |
| LiAc + MeCHO → P1-Me | −24.5 | 3.654 | 0.187 | 1.15 | 1.00 | 0.73 | $EIE_{1\text{-}Me} = 0.84$ |
| P1-Me + MeCHO → P2-Me | −10.2 | 3.348 | 0.240 | 1.16 | 1.00 | 0.67 | $EIE_{2\text{-}Me} = 0.78$ |
| P2-Me → TS3-Me | 27.9 | −1.584 | −0.702 | 1.00 | 1.02 | 3.27 | $KIE_{3\text{-}Me} = 3.33$ |

[a] Energies are given in kcal $mol^{-1}$ and corrected for ΔZPE (scaled by a factor of 0.9). [b] $\Delta ZPE = ZPE_{product} - \Sigma(ZPE)_{reactants}$; or $ZPE_{TS} - \Sigma(ZPE)_{reactants}$ (proteo species). [c] $\Delta\Delta ZPE = \Delta ZPE_H - \Delta ZPE_D$; $\Delta ZPE_D$ corresponds to the terms for the reactions of monodeuterated aldehydes. [d] Terms defined by eq 8. [e] Isotope effects were computed at 25 °C. The symmetry term due to $CH_2O$/CHDO has not been accounted for in the calculation, since this is unique to formaldehyde. [f] The two hydrogens of formaldehyde become inequivalent in the reaction products. Similar isotope effects are obtained when either of the two hydrogens is deuterated.

species and 0.2 for the $NH_3$-complexes. It is likely that additional solvation would reverse the relative energies of the two structures or might yield only one structure. Detailed elucidation of solvation effects on the properties of the given system is, however, beyond the scope of the present study.[24]

Previous theoretical work on aldol formation from lithium enolates (eq 1) has indicated that the reaction proceeds via a half-chair six-membered transition structure in which the lithium ion coordinates the two oxygen centers.[25−28] The energy barrier for the transformation from the separated reactants to this transition structure (TS-1, Figure 3) is computed in the present study to be substantially negative (−12.2 kcal $mol^{-1}$). This results from the additional ion-dipole interaction between lithium and the oxygen of formaldehyde in the transition structure. In ether solvents, however, the lithium ion is normally solvated, and higher activation energies are anticipated. The activation barrier computed for the

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transformation from a LiEn−aldehyde precomplex (complex-1) to TS-1 is computed to be only slightly positive (6.4 kcal mol$^{-1}$). Formation of the lithium aldolate, P1, is computed to be substantially exothermic, −26.8 kcal mol$^{-1}$, or −8.4 kcal mol$^{-1}$ for reactions starting with complex-1. The activation and reaction energies computed for the reaction between lithium acetonate (LiAc) and acetaldehyde (−9.0 and −25.4, respectively) are slightly less exothermic than the energetics of the LiEn−formaldehyde reaction.

As in the case of LiEn, the calculations locate a precomplex between $CH_2O$ and the lithium aldolate (complex-2, Figure 1) with an energy of complex formation of −13.8 kcal mol$^{-1}$. A transition structure (TS2) for formation of an O−C bond between P1 and $CH_2O$ yielding P2 is computed to be only 2.7 kcal mol$^{-1}$ above complex-2. This strongly suggests that addition of an aldehyde molecule to a lithium aldolate is a kinetically facile process. The C−O distance in TS2 is 2.00 Å, halfway between the corresponding distance in the precomplex-2 (C−O = 2.53 Å) and product (C−O = 1.50 Å). The overall reaction energy for addition of the aldehyde to P1 is −14.2 kcal mol$^{-1}$, substantially less exothermic than addition of an aldehyde to LiEn.

A closed-shell transition structure was located for the intramolecular hydride transfer between P2 and P3 (TS3). This transition structure has a six-membered chair conformation in which the transferring hydrogen ($H_t$) is almost equidistant from the two involved carbon centers. Only the conformation in which lithium is coordinated to two exo-oxygens was considered. The structural arrangement of the lithium and the two oxygens in TS3 is similar to those computed for TS1. In particular, the lithium ion is computed to be equidistant from the two oxygen atoms. At the HF level, the barrier for hydride transfer is computed to be relatively large (25.1 kcal mol$^{-1}$). A comparable value was computed for intramolecular hydride transfer in P2-Me. Inclusion of correlation effects at the MP2/6-31++g**//HF/6-31++g** level reduces the barrier substantially, down to 12 kcal mol$^{-1}$, suggesting that such a process should be feasible at ambient temperatures. Finally, the overall reaction energy for the formation of P3 is computed to be slightly exothermic (−3 kcal mol$^{-1}$).

The kinetic (KIE) or equilibrium (EIE) isotope effect of a transformation from A to B can be defined as the equilibrium constant of the isotopic exchange equilibrium:

$$\mathrm{A} + \mathrm{B}^* \overset{\mathrm{IE}}{\rightleftharpoons} \mathrm{A}^* + \mathrm{B} \tag{6}$$

where the asterisk denotes the heavier isotopic molecule.[29,30] This equilibrium can be expressed as a partition function ratio:

$$\mathrm{IE} = \left(\frac{Q_{\mathrm{tr}}^{\mathrm{A}^*} Q_{\mathrm{rot}}^{\mathrm{A}^*} Q_{\mathrm{vib}}^{\mathrm{A}^*}}{Q_{\mathrm{tr}}^{\mathrm{A}} Q_{\mathrm{rot}}^{\mathrm{A}} Q_{\mathrm{vib}}^{\mathrm{A}}}\right)\left(\frac{Q_{\mathrm{tr}}^{\mathrm{B}} Q_{\mathrm{rot}}^{\mathrm{B}} Q_{\mathrm{vib}}^{\mathrm{B}}}{Q_{\mathrm{tr}}^{\mathrm{B}^*} Q_{\mathrm{rot}}^{\mathrm{B}^*} Q_{\mathrm{vib}}^{\mathrm{B}^*}}\right) \mathrm{e}^{-(\Delta\Delta\mathrm{ZPE}/RT)} \tag{7}$$

where $Q_{\mathrm{tr}} = (2\pi mkT)^{3/2}/h^3$, $Q_{\mathrm{rot}} = 8\pi^2(8\pi^3 I_{\mathrm{A}} I_{\mathrm{B}} I_{\mathrm{C}})^{1/2}(kT)^{3/2}/\sigma h^3$, $Q_{\mathrm{vib}} = \Pi_i 1/1 - \mathrm{e}^{-(h\nu_{\mathrm{i}})/kT}$, and $\Delta\Delta\mathrm{ZPE} = \Delta\mathrm{ZPE}_{\mathrm{B}}^{\mathrm{B}^*} - \Delta\mathrm{ZPE}_{\mathrm{A}}^{\mathrm{A}^*}$ ($\Delta\mathrm{ZPE}_{\mathrm{A}}^{\mathrm{A}^*} = \mathrm{ZPE}^{\mathrm{A}} - \mathrm{ZPE}^{\mathrm{A}^*}$; ZPE = zero point energy). This is usually written as a product of three terms

$$\mathrm{IE} = \mathrm{MMI} \times \mathrm{EXC} \times \mathrm{EXP} \tag{8}$$

where MMI is the mass moment of inertia term representing the rotational and translational partition function ratios, EXC is the vibrational excitation term, and EXP is the exponential zero point energy term.

As in eq 1, both the kinetic and equilibrium isotope effects for eq 2 are computed to be inverse. The isotope effects are more pronounced for eq 2 ($\mathrm{KIE}_2 = 0.79$ and EIE2 = 0.77). Similarly, the equilibrium isotope effect for reaction of acetaldehyde ($\mathrm{EIE}_{2-\mathrm{Me}}$) is computed to be inverse and more pronounced than $\mathrm{EIE}_{1-\mathrm{Me}}$.

Both the kinetic and equilibrium isotope effects for the aldol reaction (eq 1; Scheme 1) are computed to be inverse (Table 1). Comparable isotope effects are calculated for reaction of formaldehyde and acetaldehyde. Table 1 shows that the isotope effects for the reactions of formaldehyde have a large MMI contribution (1.34 − 1.36; symmetry term not included), arising primarily from the rotational partition function ratio in eq 7. Since formaldehyde is a small molecule, monodeuteration has a substantial effect on its moments of inertia. Upon reaction of formaldehyde, the rotational and translation degrees of freedom are transformed into vibrational modes.[31,32] Since the rotational properties of formaldehyde are sensitive to isotope labeling, some of the newly formed vibrations in the products are also isotope sensitive. Due to lack of symmetry in TS1 and P1, and because of extensive coupling among various low lying modes, however, unambiguous assignment of these isotope sensitive modes has not been possible. The effects of such vibrations on isotope effects are inverse contributions to the EXC and EXP terms. To illustrate the importance of these effects, equilibrium isotope effects were calculated for complex formation between formaldehyde and LiEn ($\mathrm{EIE}_{\mathrm{comp}-1}$, Table 1). Complex formation is expected to cause minimal changes in the aldehydic C−H bond and in the absence of other factors should not be influenced by isotope labeling. Nevertheless, Table 1 shows that $\mathrm{EIE}_{\mathrm{comp}-1}$ has significantly inverse EXC and EXP terms (0.83 and 0.82, respectively), which can be attributed directly to additional low-lying isotope-sensitive frequencies in the complex. These effects are particular to formaldehyde. In the reaction of acetaldehyde, for example, the MMI term is close to unity. In this case, the calculated inverse isotope effect can be attributed to the EXP component, which suggests that the vibrations associated with the aldehydic C−H bond become stronger in the transition states and products of the aldol reactions.

The experimental system is so much larger than the model formaldehyde system that the MMI term can be safely ignored. The computed isotope effects derived only from the zero point energy effects (EXP) are in excellent agreement with experiment. In particular, the calculated equilibrium isotope effect $K_{\mathrm{H}}/K_{\mathrm{D}} = \mathrm{EIE}_1$ for addition to the carbonyl group of formaldehyde of 0.65 and for

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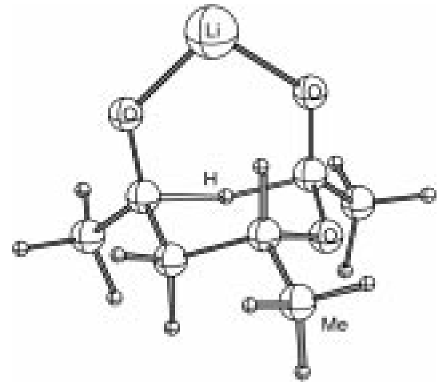
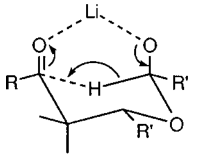


**Figure 4.** Computed transition structure (TS3-Me) for hydride transfer in the reaction of the lithium enolate of acetone with acetaldehyde. The methyl substituent (Me) is equatorial as shown in **5**.

acetaldehyde of 0.73 compare well with the experimental value of 0.74. As expected, the computed EXP isotope effect for formation of P2 is also inverse and of comparable magnitude (0.61).

The computed isotope effect for the rate-determining hydride transfer is normal and substantial. The calculated isotope effects of 3.22 for formaldhyde and 3.33 for acetaldehyde are in excellent agreement with the experimental value of 2.9. This agreement indicates that the model computation is reasonable, that the proposed reaction mechanism is substantially correct, and especially that the computed structure for TS3 is a suitable model for the experimental reaction. The computed transition state also rationalizes the observed stereochemistry; because both preceeding reactions are reversible, the stereochemistry is determined by the hydride-transfer transition state. Applied to the current reactions, this transition structure is represented as **5**. In this structure the three substituent groups, R and R′, are all equatorial and give rise to the anti-product. The corresponding syn product would require a highly strained structure in which one R′ group is axial.



**5**

This result is clearly shown in the computed transition structure for intramolecular hydride transfer in the reaction between the lithium enolate of acetone and acetaldehyde in Figure 4 (TS3-Me in Table 1). The other structures are similar to those in Figure 3 and are given in the Supporting Information.

## Experimental Section

**General Methods.** *p*-(Phenylsulfonyl)isobutyrophenone and *p*-phenylisobutyrophenone were available from previous studies.[7−9] Benzaldehyde-*d* was prepared by the method of Seebach et al.[33] $^{1}$H and $^{13}$C NMR spectra were recorded on 300 and 400 MHz Bruker instruments, respectively. Kinetic measurements were made in the glovebox-spectrometer facility described previously.[34]

**Reaction Products**. A solution of 30 mg (0.1 mmol) of isobutyrophenone in 5.2 f of THF was deprotonated with a slight excess of LDA. To this mixture was slowly added 4 equiv of benzaldehyde with the reaction monitored by UV. The mixture was quenched with ammonium chloride and the product, 3-hydroxy-2,2-dimethyl-1,3-diphenylpropyl benzoate, was isolated on a preparative GLC plate using chloroform−hexane. $^{1}$H-NMR $\delta$: 8.18−7.30 (15H), 6.380 (s, 1H), 4.711 (d, 1H, proton α to the hydroxyl group, becomes singlet upon deuteration of OH, $J_{1-3} = 3.57$ Hz), 2.832 (d, 1H, hydroxyl proton, exchanges with $D_2O$, $J_{1-3} = 3.57$ Hz), 0.887 (s, 3H), 0.824 (s, 3H). $^{13}$C-NMR gd: 166.12, 141.11, 137.94, 130.26, 133.27, 129.76, 128.60, 128.26, 128.18, 127.83, 127.81, 127.57, 127.39, 80.16, 77.01, 42.99, 19.30, 17.96. Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.56; H, 6.71.

The similar product from lithiated isobutyrophenone and *p*-tolualdehyde was a 1:1 mixture of two geometrical isomers. $^{1}$H-NMR $\delta$: 8.05−7.10 (13H), 6.352 and 6.325, (s, 1H), 4.754 and 4.736 (d, 1H, protons α to the hydroxyl groups, $J_{1-3} =$ 3.66 and 3.60 Hz, respectively, become singlets upon deuteration of OH), 3.978 and 2.938 (d, 1H, hydroxyl protons, $J_{1-3} =$ 3.66 and 3.60 Hz, respectively, exchange with $D_2O$), 2.450 and 2.450 (s, 3H), 2.346 and 2.334 (s, 3H), 0.877 and 0.825 (s, 6H). $^{13}$C-NMR $\delta$: 166.27 and 166.19, 144-135, 130-126, 80.05, 79.97, 77.48 and 77.16, 21.78, 21.21 and 21.15, 19.45, 19.32, 18.10 and 18.01. Anal. Calcd. for $C_{26}H_{28}O_3$: C, 80.40; H, 7.22. Found: C, 80.72; H, 7.44.

This mixture gave a single diol on hydrolysis. $^{1}$H-NMR $\delta$: 7.34-7.06 (9H); 4.617 (d, 1H, $J = 3.63$ Hz), 4.588 (d, 1H, $J = 3.42$ Hz), 4.029 (d, 1H, $J = 3.63$ Hz), 3.779 (d, 1H, $J = 3.44$ Hz), 2.355 (s, 3H), 0.816 (s, 3H), 0.802 (s, 3H). $^{13}$C-NMR $\delta$: 141.325, 138.197, 137.074, 128.399, 127.985, 127.839, 127.840, 127.387, 81.062, 80.945, 41.334, 21.395, 21.148. X-ray crystal structure analysis was consistent with the structure assigned as *anti*-1-phenyl-3-*p*-tolyl-1,3-propanediol, $C_{18}H_{22}O_2$.

LiSIBP was prepared by deprotonation with lithio-9-benzylfluorene. The alcohol−ester from reaction of LiSIBP and benzaldehyde gave a 4:1 mixture of two isomers. Major Isomer. $^{1}$H-NMR $\delta$: 7.32−8.13 (19H), 6.343 (s, 1H), 4.731 (d, 1H, proton α to OH, becomes singlet upon exchange of OH with $D_2O$, $J_{1-3} = 3.9$ Hz), 3.377 (d, 1H, hydroxyl proton, exchanges with $D_2O$, $J_{1-3} = 3.96$ Hz), 0.837 (s, 3H), 0.749 (singlets, 3H). $^{13}$C-NMR (CDCl3) $\delta$: 17.733, 19.098, 43.134, 76.269, 80.015, 126.881, 127.63, 127.927, 128.039, 128.220, 128.653, 129.103, 129.238, 129.780, 133.135, 133.510, 137.238, 140.413, 141.592, 144, 146.835, 166.417.

Minor Isomer. $^{1}$H-NMR: 7.32−8.13 (19H), 6.390 (s, 1H); 4.784 (d, 1H, proton α to OH, becomes singlet upon exchange of OH with $D_2O$; $J_{1-3} = 3.9$ Hz); 2.529 (d, 1H, hydroxyl proton, exchanges with $D_2O$; $J_{1-3} = 3.96$ Hz); 0.846 (s, 3H), 0.765 (s, 3H).

Major Isomer from Benzaldehyde-*d* ($H_a$ and $H_b$ in P3 Deuteriated). $^{1}$H NMR Δ: 7.32−8.13 (19H), 3.348 (s, 1H, OH; exchanges with $D_2O$), 0.749 (s, 3H), 0.836 (s, 3H).

Minor $H_a$, $H_b$ Dideuteriated Product. $^{1}$H NMR gD: 7.32−8.13 (19H), 2.496 (s, 1H, OH; exchanges with $D_2O$), 0.765 (s, 3H), 0.844 (s, 3H).

**Isotope Effects.** Independent isotope effect experiments were carried out by separate kinetic and competition experiments. The kinetic measurements used 2 mM of LiSIBP and 10 mM of aldehyde or aldehyde-*d*, and the reaction was monitored until 10% reaction, which afforded $KIE_{ob}$ 2.1. The competition experiments were carried out by adding 20 equiv of 1:1 benzaldehyde and benzaldehyde-*d* to solutions of 4 mM LiSIBP. For a given diastereomer, the sum of the protio and deutero hydrogens ($[H_{tot}]$) of either $H_a$ or $H_b$ was estimated as the total integrand of the hydroxyl hydrogens. Although this proton is susceptible to exchange, the proton spectrum of the completely protiated or completely deuteriated compounds showed that it integrates well with the rest of the protons.

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The secondary equilibrium isotope effect corresponding to the first addition of the aldehyde was calculated using the integrand of $H_a$ ($[H_{a\text{-}ob}]$), as $EIE_1 = [H_{a\text{-}ob}]/([H_{tot}] - [H_{a\text{-}ob}])$. Similarly, the ratio of $H_b/D_b$ was estimated as $H_b/D_b = [H_{b\text{-}ob}]/([H_{tot}] - [H_{b\text{-}ob}])$.

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**Supporting Information Available:** Energies and structures of all of the ab initio calculations and some experimental results from the kinetics experiments; X-ray crystal structure analysis of **4** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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