

112. Insight into the Behaviour of a Lithium Enolate in Solution

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(2*S*,4*S*)-2-(*tert*-Butyl)-5-oxo-1,3-dioxolan-4-acetic acid (**1**) was dilithiated to the enolate **2** in toluene and THF with lithium diisopropylamide (LiN(*i*-Pr)₂) under various conditions. Deuteration experiments with **2** showed that two different stable forms of the enolate could be produced, depending on whether the deprotonation of **1** had been carried out in toluene or THF. The generated (*i*-Pr)₂NH was coordinated to the enolate and, hence, served as a strong lipophilic solvating agent. LiN(*i*-Pr)₂ could substitute the amine ligands of the two species to a different extent. THF was partially able to displace (*i*-Pr)₂NH that solvated the species produced in toluene, but the coordination of the amine to the one produced in THF was quantitative. Correlations with given explanations are made.

Introduction. – *C*-Alkylations of enolates with alkyl halides often suffer from low conversion, if the corresponding ketones [1], carboxamides [2], or esters [3] are previously deprotonated with secondary lithium amides in THF containing some hexane. Sometimes, this difficulty can be overcome by adding a strong ligand as a co-solvent such as hexamethylphosphoric triamide (HMPT) or *N,N'*-dimethyl-(1,3-propanediyl)urea (DMPU) [1] [3]. Another possibility to enhance the yield of the alkylation is to use other bases, *e.g.* alkyllithium derivatives [4] or alkali alcoholates [1] [5]. Still another very simple and widely applied method to solve this problem consists of adding an excess of secondary amide to the substrate [6]. A plausible reason for adding an excess of base to acidic substrates may be to shift the reaction equilibrium to a more favourable position. However, in the case where the *pK* values of commonly used secondary Li-amides exceed those of the substrates by a factor 10⁴ to 10¹⁰ [7], a more subtle explanation for the better alkylation yields is required.

All the methods offer no general solution to the problem because of their individual disadvantages. The excess of a secondary Li-amide will deprotonate an acidic electrophile. For instance, a halide containing an H-atom in a chiral α -position to a carboxylate moiety cannot be used in this manner, even if it would not be deprotonated by the enolate. Often, an excess of alkyl halide is needed [6]. Only the less electrophilic tertiary carboxamides [4], or sterically hindered ketones [1] and esters [5] can be deprotonated by non-amide bases such as alkyllithium derivatives and Li-alcoholates, because of their strong nucleophilicity. On the other hand, the addition of a very tightly coordinating [8] HMPT molecule can induce the ester or ketone enolate – as an *ambident* anion – to react with the now more reactive O-atom to give *O*-alkylated products [9].

Recently, a new, elegant method to enhance the alkylation yields was published [2a] [10] explaining the low conversion of the above mentioned alkylations and why a large

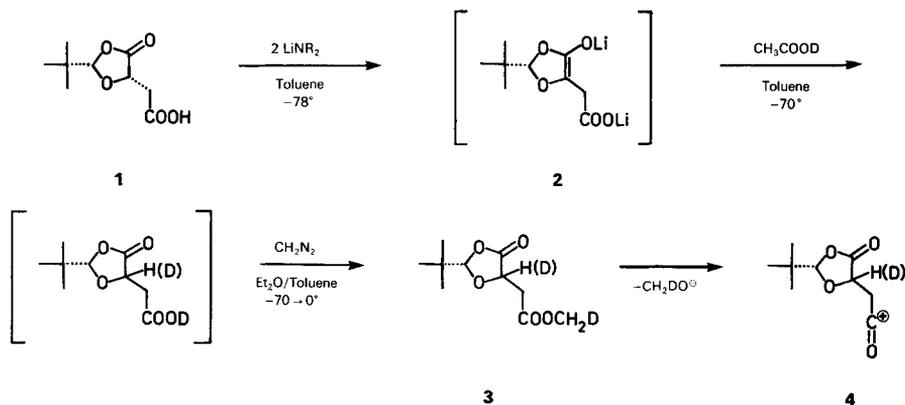
¹⁾ Part of the Dissertation by P. S.

quantity of reprotonated carboxamide, ester, or ketone is regenerated. X-Ray structure analysis, deuteration, and alkylation experiments on ester and amide enolates generated in THF with lithium diisopropylamide ($\text{LiN}(\text{i-Pr})_2$) demonstrated that the secondary amine was *partially* coordinated as a Li ligand to the tetrameric aggregate. This species reacted in a different way to that of an aggregate, where the Li cations were coordinated to one or more [9a] THF molecules. The Li cation of the ‘solvent-solvated’ enolate could coordinate for instance to the I-atom of the electrophile pushing out a THF molecule and allowing both C-atoms to react. The ‘amine-solvated’ enolate would not react the same way. This amine had partially the character of a Li-amide because of the proton-withdrawing effect of the neighbouring carbanion. The result was a nucleophilic attack of the amine on the electrophile and reprotonation of the enolate. If the proton was removed by adding BuLi to the reaction mixture after deprotonation with $\text{LiN}(\text{i-Pr})_2$, the alkylation (and deuteration) yields rose to a very high level. The reacting enolate could be some sort of a ‘Li-amide-solvated’ species. The drawback of this method is that on regenerating Li-amide a more nucleophilic species is produced which may react with alkyl halides first. An excess of the electrophile is required.

In consideration of the fact that the amines used are sterically strongly hindered, a third mode of action could be involved, in which an electrophile such as deuterium first reacted with the O-atom of the ‘amine-solvated’ enolate. In the subsequent reaction, the amine took over the deuterium, thus, reprotonating the enolate again. This assumption would explain the fact that in some cases *O*-alkylation occurred in THF without polar co-solvents. Direct deuteration of the carbanion in an ‘amine-solvated’ species seems to be unlikely because of the steric hindrance.

Deuterium Exchange Experiments. – In connection with studies on *C*-alkylations of the dilithiated enolate **2** generated by double deprotonation of **1** with $\text{LiN}(\text{i-Pr})_2$ or lithium hexamethyldisilazide (LHMDS) [11], we have investigated the reaction with CH_3COOD . It was carried out in toluene, a non-polar, non-dative solvent (*Scheme 1*). After lithiation of **1** under various conditions, an aliquot of the solution containing **2** was added to an excess of CH_3COOD in toluene (at $\leq -70^\circ$) and quenched afterwards with an Et_2O solution of CH_2N_2 until the colour of the mixture remained yellow. After

Scheme 1



purification of the diester **3** by GC, it was possible to determine the degree of deuteration by MS *via* the fragments **4** (m/z 185 (186)).

We planned to add 0.33 equiv. of an alkyl iodide in the forthcoming alkylation reactions in toluene. Therefore, 0.67 equiv. of THF in toluene were used in the first deuteration experiments in order to simulate the alkylation conditions. These were predicted to function only with 2 equiv. of THF per equiv. of alkyl iodide as described by Collum and Wanat [12]. They presumed that the alkylation of a lithiated hydrazone (generated with $\text{LiN}(i\text{-Pr})_2$) in benzene/hexane 7:3 with EtI only took place if THF had acted as a LiI-solvating agent. We doubt, whether this assumption was the real reason for this behaviour, because LiI could crystallize out. Also the following experiments which were carried out without an alkyl halide confirmed our doubts. When 2 equiv. of LHMDS in hexane were added to **1** in toluene containing little THF at -78° , to our astonishment, a deuteration degree of only *ca.* 6% was found. With 2 equiv. of lithium cyclohexyl(isopropyl)amide (LICA), the percentage did not rise. Under identical conditions with 2 equiv. of $\text{LiN}(i\text{-Pr})_2$, *ca.* 20% of D exchange had taken place. The lithiation of **1** was decided to be carried out with 1 to 8 equiv. of $\text{LiN}(i\text{-Pr})_2$ in pure toluene containing some hexane, but no THF. After the addition of each equiv., an aliquot was removed for deuteration as already described (Fig. 1, Curve A). With 2 equiv. of $\text{LiN}(i\text{-Pr})_2$, no significant deuteration ($0.3 \pm 0.06\%$ D, *cf.* the Table, *Exper. Part*) was observed, but after addition of more $\text{LiN}(i\text{-Pr})_2$ the deuteration degree increased progressively up to 5 or 6 equiv. These results indicated the presence of a 'Li-amide-solvated' enolate. Because the degree of the deuteration of *monomeric* enolates must have been proportional to the excess of $\text{LiN}(i\text{-Pr})_2$, this experiment showed that differently solvated *oligomeric* enolate aggregates existed in solution. The higher the excess of $\text{LiN}(i\text{-Pr})_2$, the greater was the concentration of higher ' $\text{LiN}(i\text{-Pr})_2$ -solvated' aggregates. An aggregate with two mole-

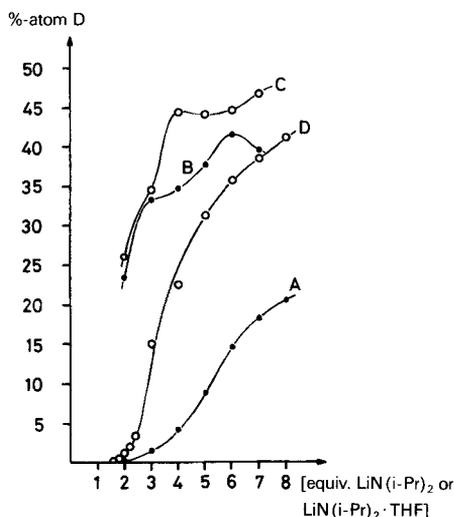
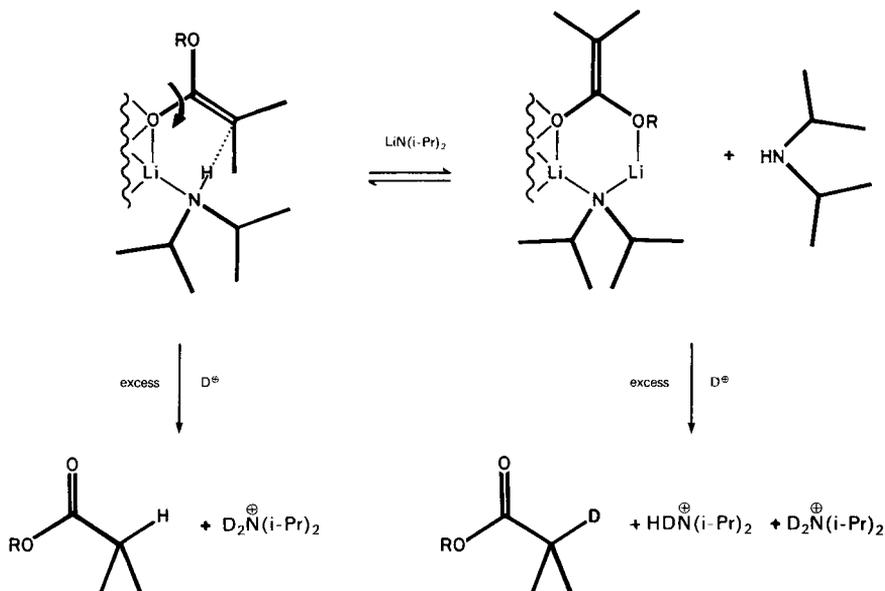


Fig. 1. Dependence of the degree of deuteration of the enolate **2** by CH_3COOD upon increasing amounts of $\text{LiN}(i\text{-Pr})_2$ in toluene (Curve A and C), toluene containing 3 equiv. of THF (Curve B), and THF (Curve D). ●: equiv. of $\text{LiN}(i\text{-Pr})_2$; ○: equiv. of $\text{LiN}(i\text{-Pr})_2 \cdot \text{THF}$.

Scheme 2



cules of $\text{LiN}(\text{i-Pr})_2$ as solvating ligands seemed to be more reactive towards direct deuteration by CH_3COOD than an aggregate with only one molecule of $\text{LiN}(\text{i-Pr})_2$. An ‘ $\text{LiN}(\text{i-Pr})_2$ -solvated’ enolate can be modelled from a ‘ $(\text{i-Pr})_2\text{NH}$ -solvated’ by changing from a proton to a Li cation which is coordinated to the other ester O-atom by rotation of the C–O bond for *ca.* 180° , thus, exposing the carbanion into the solution (Scheme 2). We suppose that the curve flattened with a further excess of $\text{LiN}(\text{i-Pr})_2$ because of a limit of a ‘ $\text{LiN}(\text{i-Pr})_2$ -loading’. The increased steric crowding due to the unusual conformation of ‘ $\text{LiN}(\text{i-Pr})_2$ -solvated’ enolates hindered additional $\text{LiN}(\text{i-Pr})_2$ molecules to increase amine substitution. The bulky Li-enolates of esters derived from carboxylic acids and sulfonamide-substituted bornanols are suspected to form dimeric aggregates in THF [13]. An explanation for better alkylation yields achieved by adding an excess of Li-amide to such esters might be the easier substitution of the amine by Li-amide. The latter might coordinate more tightly without greatly changing the conformation of the enolate because a sulfonic O-atom could coordinate to the additional Li cation.

This model differs from the hypothesis in which the Li-amide cleaved the aggregate and substituted an enolate by an amide moiety [14] [8c]. If indeed the Li-amide could have been nucleophilic enough (probably not even HMPT is able to effect this [15]) to replace the enolate and induce a rearrangement of aggregates, no dramatic enhancement of the degree of deuteration would be expected under the conditions used because the amines would remain in a position solvating Li cations. Deuteration would cause protonation of the adjacent ester enolate. The flattening of the curve might also be a sign for enolate substitution and aggregate rearrangement at very high excess of $\text{LiN}(\text{i-Pr})_2$, as described above.

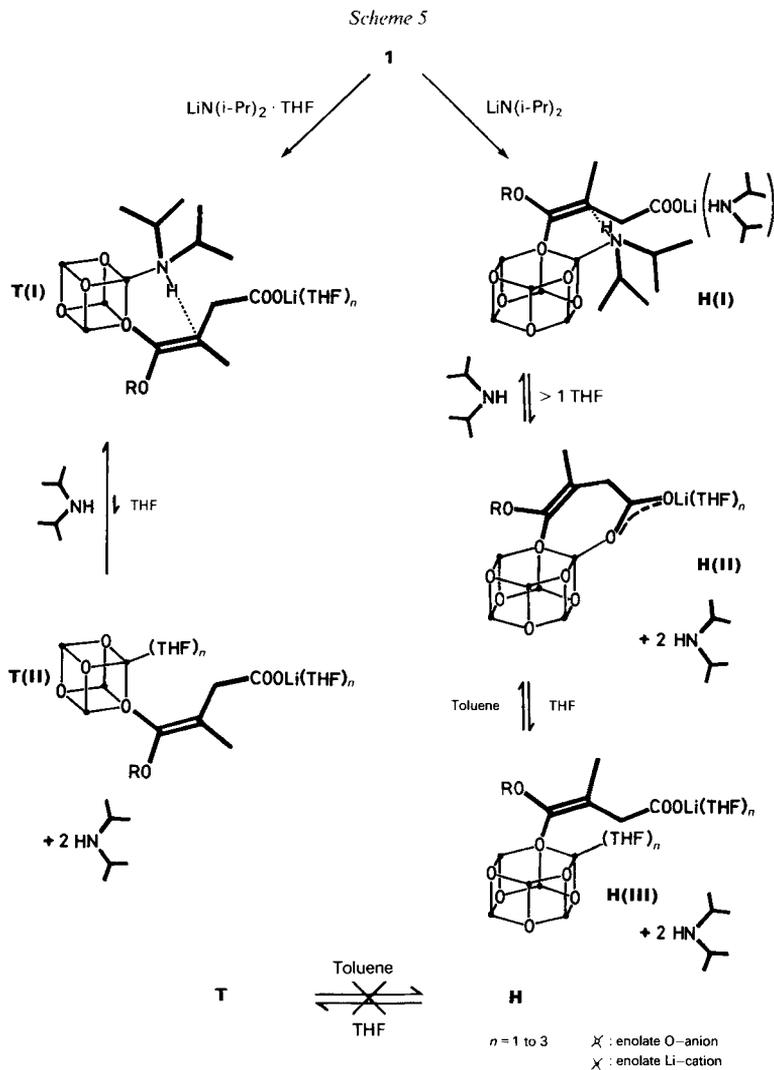
The effect of THF on the degree of deuteration of enolate **2** is demonstrated by the second experiment. Small portions of THF were added to **1** which has been treated with **2**

If one compares the D exchange in the experiments, in which 2 equiv. of THF were added after the enolate has been generated with 2 equiv. of $\text{LiN}(\text{i-Pr})_2$ in toluene (Fig. 2, 15% D), with the experiment in which the enolate has been generated with 2 equiv. of $\text{LiN}(\text{i-Pr})_2 \cdot \text{THF}$ (Fig. 1, Curve C, 26% D), one might conclude that the two enolates may differ from each other. Therefore, an experiment was performed in THF which showed the dependence of D exchange upon increasing amounts of $\text{LiN}(\text{i-Pr})_2$ added (Fig. 1, Curve D). The curve obtained was similar to Curve A. The region of a much more progressive rise of D exchange was smaller (up to ca. 2.5 equiv. of $\text{LiN}(\text{i-Pr})_2$) indicating a much easier substitution of the amine ligands by $\text{LiN}(\text{i-Pr})_2$. It also meant that the steric hindrance caused by ' $\text{LiN}(\text{i-Pr})_2$ -solvation' in the enolate formed in THF affected the degree of D exchange at an earlier stage than in the enolate formed in toluene. The most striking fact was the low degree of deuteration as compared to Curves B and C (2 equiv. of $\text{LiN}(\text{i-Pr})_2$).

The following experiments provided evidence for two types of enolates which are formed either in the presence or absence of THF during deprotonation with $\text{LiN}(\text{i-Pr})_2$. The deprotonation of **1** by 2 equiv. of LDA in pure toluene at -78° is completed after ca. 1 h. When during this period of time the concentration of THF was raised (0.5 to 50% (v/v)) and the deuteration performed after 1 h with an excess of CH_3COOD , the degree of D exchange varied to a great extent in solutions containing the same amount of THF with the time of deprotonation in pure toluene. If, however, the deprotonation with 2 equiv. of $\text{LiN}(\text{i-Pr})_2$ had enough time for completion (110 min at -78°), the degree rose to ca. 41% of deuteration with 0.5% of THF (ca. 5 equiv.). It remained between 40% and 50% of D, even when kept for 1 h in a solution containing 80% of THF at -78° . If the enolate **2** was generated with 2 equiv. of $\text{LiN}(\text{i-Pr})_2$ in THF at -78° , the samples containing increasing amounts of toluene (98.5% to 20% of THF) were deuterated after 80 min to an extent of not more than 1% of D, according to the type of enolate showed in Fig. 1, Curve D (2 equiv. of $\text{LiN}(\text{i-Pr})_2$).

These results indicate that the experiments corresponding to Curves B and C in Fig. 1 cannot be fully interpreted, because they show the mixed influences of both types of enolates.

Conclusion. - In general, the structure of ester enolates is analogous to the structure of ketone enolates [8c]. The crystal structures of the Li-enolates of pinacolone differ greatly if generated in the absence of THF (crystallized in heptane) or with $\text{LiN}(\text{i-Pr})_2 \cdot \text{THF}$ [16] [8a]. While the latter enolate is a THF-solvated tetrameric aggregate (Scheme 5, frame type **T(II)**), the structure of the enolate generated without THF is a hexameric prism of the frame type **H** (without solvating ligands). The results of our deuteration suggest analogous structures **T** and **H** for the Li-enolate **2**. It seems plausible that $(\text{i-Pr})_2\text{NH}$ in THF is mostly bound to the enolate **T**, since there is enough space between the enolate moieties, and $(\text{i-Pr})_2\text{NH}$ is a stronger Lewis base than THF. Nevertheless, additional $\text{LiN}(\text{i-Pr})_2$ may substitute the amine ligands to some extent quite easily. A different behaviour can be expected from enolate **H**. Although the bond lengths between Li- and O-atom are only 0.05 to 0.1 Å shorter in the hexameric form of Li-pinacolone (**H**) than in the tetrameric form (**T**) [16b], the steric crowding in a hexameric aggregate must be much greater than in a tetrameric one, as shown by the degree of substitution of $(\text{i-Pr})_2\text{NH}$ by $\text{LiN}(\text{i-Pr})_2$ in toluene (enolate **H**), which is smaller



than the degree in THF (enolate **T**). However, the substitution of $(i\text{-Pr})_2\text{NH}$ by THF which, according to our hypothesis, requires no significant conformational change, is much easier achieved in the 'amine-solvated' enolate **H** than in **T**. The easier substitution of a stronger ligand by a weaker one at the enolate **H** in toluene at minimal THF concentrations may be attributed to a general effect. The tendency of a two dentate ligand towards chelation to a *Lewis* acid decreases with the polarity of the solvent because of its competition as a ligand. Therefore, in enolate **T** mainly THF is expected to compete with $(i\text{-Pr})_2\text{NH}$, whereas in enolate **H** at very low THF concentrations, a chelated structure (**H(II)**) should be preferred. This isomeric THF-solvated enolate involves a coordinative bond between the Li cation of the enolate and the carbonyl O-atom of the carboxylate. Bonding between carbonyl O-atoms and Li- or Na-cations of ketone enolates have been

found recently [15] [16b]. Unfortunately, on deuterating the enolate **H**, the isomeric THF-solvated enolate aggregates **H(II)** and **H(III)** cannot be distinguished. Our mass measurements merely reveal that the conversion of **H** in presence of THF with CH_3COOD exceeds the one of **T** greatly.

The question of how the degree of deuteration of both types of enolates **2**, **T** and **H**, correlates with the degree of *C*-, *O*- and *N*-alkylation under various conditions can only be answered by further investigations. Our results demonstrate the presence of a mixture of differently solvated enolate aggregates in solution. While these aggregates interchange *via* thermodynamic equilibria with various solvating ligands, they are unable to rearrange from one frame type to another under usual alkylating conditions.

Enolates solvated by $(i\text{-Pr})_2\text{NH}$ (and probably also by Li-amides) seem not to be observable by X-ray structure analysis due to the high degree of disorder in the crystals. Therefore, the dynamic way of observing enolates during a reaction by deuteration of aliquots is an analytical tool for their individual determination.

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Experimental Part

General. Toluene and THF were distilled over Na/K. Ar was dried with conc. H_2SO_4 and blue silica gel, N_2 with blue silica gel. GC/MS: HP 5790 A (EI, 70 eV), cross-linked 5% phenyl-methyl-silicone capillary column of 0.2 mm inner diameter and 25 m length (film thickness: 0.11 μm). Reference MS: double focussing MS VG 70-250. LHMS and LICA were prepared by adding 1.0 equiv. of BuLi in hexane (*Aldrich Corp.*) to 1.0 equiv. of stirred, chilled (-70 to -50°), dry, pure amine (*Fluka*) under Ar. $\text{LiN}(i\text{-Pr})_2$ was prepared in the same way, but since the suspension in hexane was rather sensitive to air and difficult to handle, an equal amount of toluene was added after deprotonation with BuLi ($\text{p}K(\text{butane}) > 50$; $\text{p}K(\text{toluene}) = 41$ [17]). The base solns. were titrated and stored under Ar. The $\text{LiN}(i\text{-Pr})_2$ suspension was shaken before use, pipetted with a dry, Ar-flushed, calibrated pipette or syringed. Its concentration was well reproducible ($\pm 2\%$). The substrate **1** [11] was dried (P_2O_5) in the reaction vessel at 0.05 to 0.1 Torr for 30 min at 50° and 1.5–12 h at r.t. Et_2O solns. of CH_2N_2 were stored at 0° over aq. KOH soln. [18].

Lithiation and Deuteration. The lithiations were performed on a 2- to 3-mmol scale. In a 50-ml flask (inlet and outlet for Ar, thermometer) containing 559.7 mg (2.77 mmol) of **1**, 38.5 ml of toluene was added and cooled to -78° . Dropwise, 6.45 ml (2 equiv.) of a 0.86M $\text{LiN}(i\text{-Pr})_2$ suspension in hexane/toluene 53:47 were added to the soln. at a speed so that the temp. did not rise above -70° . After 1 h, first Ar, then ca. 1.0 ml of the cold soln. were sucked into a 1-ml calibrated pipette and quickly poured at -70° into a stirred suspension of 135 μl CH_3COOD (99.5%-atom D, *Ciba-Geigy*; at least 38 equiv.) in ca. 2 ml of toluene in a N_2 -flushed 10-ml flask. The soln. must be poured directly into the toluene/ CH_3COOD mixture and should not touch the glass wall. After 15 to 30 s, ca. 8 to 10 ml of the Et_2O soln. of CH_2N_2 were pipetted into the acidic soln., and after decanting off Li-acetate, toluene, $\text{CH}_3\text{COOCH}_2\text{D}$, and Et_2O were evaporated at r.t. *in vacuo*. After adding the next equiv. of $\text{LiN}(i\text{-Pr})_2$ suspension to the soln. (exactly 30 min of reaction and equilibration time were allowed for each step), the 10-ml flask equipped with a magnetic stirrer was washed twice with hot H_2O and twice with acetone, dried with a hot fan, and flushed with N_2 , before the addition of toluene, CH_3COOD , and cooling for the next use. The 1-ml calibrated pipette was washed in the same way, dried under reduced pressure with a hot fan and connected to the Ar outlet.

The experiments which contained THF were carried out the same way, except for the reaction time, which was 40 min for the first 2 equiv. of base (instead of 60 min) and 15 min between addition of the next equiv. of base or THF and deuteration (instead of 30 min). The aliquots of the exper. in THF (*Fig. 1, Curve D*) were poured into a mixture of 135 μl of CH_3COOD and ca. 2 ml of THF at -70° . In the exper. corresponding to *Figs. 1* and *2* the concentration of **2** with 2 equiv. of $\text{LiN}(i\text{-Pr})_2$ was 0.062M. In the deuteration experiments with varying concentrations of THF, the concentration of **2** during deprotonation with 2 equiv. of $\text{LiN}(i\text{-Pr})_2$ or $\text{LiN}(i\text{-Pr})_2 \cdot \text{THF}$ was also 0.062M. Then aliquots therefrom were diluted 5-fold and kept for 110 min or 80 min, resp. before deuteration.

Measurements. The probes were chromatographed at 270°/20 psi (He pressure) (interface temp. 300°). The retention time of **3** was *ca.* 1.9 min. In our case, the lower the column temp. (for retention times longer than 3 min), the lower was the degree of deuteration of the deuterated samples. This did not occur with the undeuterated samples. To ensure that in the process of chromatography at 270°, deuterated **3** were not subject to significant H/D exchange in the column, the following exper. was performed. Deuterated **1** was prepared on a prep. scale (*Sample 3*). Then, 10 to 20 reference CI-MS (NH₃) were performed on each of the undeuterated and three differently deuterated samples of the acid **1** (*Samples 1* and *2* were recrystallized; *m/z* 220 (100%, [M + NH₄]⁺), 221 [M(D) + NH₄]⁺). For comparison, aliquots of each sample were esterified with CH₂N₂. The samples of **3** were measured by GC/MS. These and all other GC/MS probes were measured 6 times each with the moment of detection triggered on *m/z* 185. The abundance of mass fragment **4** (*m/z* 185 in the undeuterated example) was *ca.* 10% of the base peak (*m/z* 103 without treatment with CH₃COOD, *m/z* 43 after treatment with CH₃COOD). Smaller ion fragments of the deuterated probes were all partially deuterated during ionization; so only **4** was measured. The mass range was kept small (*m/z* 184–189) to prolong the detection time per mass, thus, enlargening the sensitivity about 10-fold. In none of the probes was an *m/z* 184 found. The *Table* shows that the *absolute* degree

Table. Comparison of Deuterium-Exchange Values Measured as **1** and **3**

Sample	Molecule measured	$y \pm \Delta y$ %-atom D $\left(\frac{\Delta y}{y} \cdot 100\%\right)$	$100\% \cdot \frac{y(3) - y(1)}{y(1)}$
1	1	0.09 ± 0.02 (18.6)	} 211
	3	0.28 ± 0.08 (28.6)	
2	1	2.29 ± 0.02 (0.9)	} 23.6
	3	2.83 ± 0.06 (2.3)	
3	1	18.1 ● 0.4 (2.1)	} -0.55
	3	18.0 ± 0.4 (2.0)	

of deuteration measured by GC/MS was not accurate below 0.1% D (*Sample 1*). The degree measured by GC/MS in *Sample 2* still differed significantly from the degree measured of **1**. The degree of deuteration in *Sample 3* is in the middle of the range measured in the deuteration experiments (*Figs. 1* and *2*). Both degrees determined by two independent methods were the same within the limits of their standard deviations. However, the *relative* degrees of deuteration of the aliquots in the deuteration exper. are more important for the interpretation of the curves. As one can see in *Curve D* (*Fig. 1*), the value between 1.6 and 2.4 equiv. of LiN(i-Pr)₂ lie exactly on a continuous course below 0.5% D.

Deuteron Method. The reaction and equilibration times used in all exper. were determined by exper. in which the period of time between addition of base or THF and deuteration had been varied. To exclude changes during the transfer of the soln. from one vessel to another due to a rise of the temp. in the pipette, temp.-dependent exper. were carried out. They demonstrated that the degree of deuteration of **2** did not change significantly between -78 and -40°. Exper. demonstrated that no hydrolysis and, thus, partial protonation of **2** by moisture had occurred while transferring the cold soln. Shortly after deuteration a probe with CD₃COOD (99.9%-atom D, *Ciba-Geigy*) in the above described manner, the rest of the soln. was deuterated by quick quenching with an excess of CD₃COOD. The differently deuterated acid probes were treated with an Et₂O soln. of CH₂N₂. The degrees of deuteration were both the same within exper. error limits (*e.g.* 39.8 and 37.5% D). To reassure that no fast cross enolization of CH₃COOD with **2** took place during deuteration, probes were deuterated both with an excess of CH₃COOD and CD₃COOD and again had the same degree of deuteration.

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