Sodiated Oppolzer enolates: solution structures, mechanism of alkylation, and origin of stereoselectivity†

Nathan M. Lui and David B. Collum*  
NMR spectroscopic studies reveal camphorsultam-derived sodium enolates known as Oppolzer enolates reside as monomers in neat THF and THF/HMPA solutions and as dimers in toluene when solvated by \(N,N,N',N''\)-tetramethylethylenediamine (TMEDA) and \(N,N,N',N''\)-pentamethyldiethylenediamine (PMDTA). Density functional theory (DFT) computations attest to the solvation numbers. Rate studies show analogy with previously studied lithiated Oppolzer enolates in which alkylation occurs through non-chelated solvent-separated ion pairs. The origins of the selectivity trace to transition structures in which the alkylation agent is guided to the exo face of the camphor owing to stereoelectronic preferences imparted by the sultam sulfonyl moiety. Marked secondary-shell solvation effects are gleaned from the rate studies.

Introduction

Alkylations of camphorsultam-derived enolates referred to colloquially as Oppolzer enolates have occupied a central position in asymmetric synthesis (eqn (1)).1 In addition to the relatively low-cost auxiliary, there is an unmistakable appeal to the widely held logic that a chelate of type 1 imparts rigidity while the camphor methyl protruding above the enolate directs the electrophile to the endo face of the bicyclo[2.2.1]heptane ring system. The Oppolzer enolates merged our interest in understanding the structure–reactivity–selectivity relationships of alkali metal enolates2 with efforts to promote the long-overlooked potential of organosodium chemistry.3

In the first of a two-part study, we explored the structures of alkyl- and aryl-substituted lithiated Oppolzer enolates in a variety of solvents and their reactivities in THF/HMPA.4 Focusing on the aryl cases was justified by a notable lack of their development for generating medicinally important aryl propionate derivates,5 and they were more tractable in what proved to be a complex study under the best of circumstances. There are, of course, always surprises when one probes alkali metal chemistry, the most poignant in that study was that the alkylation proceeds via a mechanism based on a solvent-separated ion pair (2). The enolate showed a marked preference to rotate nearly 180 degrees relative to chelate 1 with the preferred facial attack coming from the exo face proximate to the protruding camphor methyl. Needless to say, the irrelevance of chelation, the counterion, and even van der Waals interactions with the camphor methyl moiety flew in the face of conventional wisdom. We attributed the high selectivity to a stereo-electronic preference of the electrophile to approach anti to the endo-oriented sulfonyl oxygen.

Our motivations to examine the sodium enolates focused on confirming or refuting the stereochemical model in which the alkali metal cation was simply a counterion of little structural importance. We immediately confronted the first challenge: unbeknownst to us and probably the practitioners who routinely use NaHMDS/THF to enolize the acylated Oppolzer sultam,6,7 the alkyl-substituted substrates (3a–f below) are only partially (\(K_{eq} \approx 1\)) metalated by NaHMDS (eqn (2)).8 Although the transiently formed sodium enolate appears to be adequate...
for the applications, the lack of full enolization makes enolate structure–reactivity relationships elusive.

We considered several approaches to overcoming this issue. First, rate studies with NaHMDS and alkyl-substituted sultams as the resting state would provide detailed insights into the mechanism of the enolate alkylation and were appealing given the detailed understanding of the aggregation and solvation of NaHMDS in solution.\[^3\] Second, we could retreat to the aryl-substituted cases that are quantitatively metalated, which also allows direct comparisons with the aryl-substituted lithium enolates. Third, a stronger base would readily generate the alkyl- and aryl-substituted enolates quantitatively. Although sodium diisopropylamide (NaDA) offers more than adequate basicity,\[^3\] the excellent stability and solubility profiles of sodium isopropyl(trimethylsilyl) amide (NaPTA) with an additional 4–5 $K_b$ units above NaHMDS make it a far superior choice (eqn (2)).\[^3\]

We describe herein studies showing a high penchant for sodiated Oppolzer enolates to reside as monomers in THF solution and dimers when solvated by N,N,N′,N′-tetramethyl-ethylenediamine (TMEDA) and N,N,N′,N″,N″-pentamethyl-ethylene triamine (PMDTA) in toluene. Rate studies show that the ion-pair-based model represented by 2 held firm. The results also shed light on the role of HMPA and how two research groups managed to omit the HMPA through careful control of reaction conditions.\[^7\]

**Results and discussion**

As foreshadowed in the introduction, the alkyl-substituted substrates 3a–f (Scheme 1) require the more basic NaPTA.\[^3c\] Substrates 3g–j bearing aryl substituents were enolized using solutions of NaHMDS or NaPTA in a variety of solvents including toluene, MTBE, and THF. Enolates solvated by di-NaPTA and trimine PMDTA were generated in toluene. Aging studies revealed no evidence of temperature-dependent aggregate changes and that decomposition commenced above 0 °C.

We routinely determine enolate aggregation states using the Method of Continuous Variations (MCV)\[^3\] in which binary mixtures of structurally similar enolates or even enolate enantiomers afford heteroaggregates whose number, symmetries, and mole-fraction dependencies monitored using $^{13}$C, $^1$H, or $^{19}$F NMR spectroscopies attest to the aggregation states of the homoaggregates. This study, however, is dominated by monomeric enolates in THF wherein binary mixtures of either aryl- or alkyl-substituted enolates afford no heteroaggregates. Density functional theory (DFT) computations provided best-guess solvation numbers of the monomers,\[^10–12\] which we use to interpret the rate data.

**THF**

Two enolates showing lack of heteroaggregation are illustrated in Fig. 1. The region of the $^{13}$C NMR spectrum shown affords the most well-resolved hetero- and homoaggregate resonances when heteroaggregates appear (vide infra). Analogous pairings showing no additional resonances expected for heteroaggregates are in the ESI.\[^†\] Both aryl- and alkyl-substituted enolates are monomeric in neat THF. The rate studies described are also consistent with the monomer assignment. DFT computations on enolate 4g suggest di-, tri-, and tetrasolvated exo-chelates 5–7 are nearly isoenergetic. A more definitive distinction would have been more satisfying.

At low THF concentrations or in weaker donor solvents such as MTBE or N,N-dimethylethylamine (DMEA) resonances of higher aggregates appear. Similarly, binary mixtures of eno-

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**Scheme 1.** The N-acyl camphorsultam derivatives and their enolates that are studied in this work.

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**Fig. 1.** Partial $^{13}$C NMR spectra of 0.20 M of 4i, a 1:1 mixture of enolates 4i and 4j, and 4j in THF at −20 °C. No new peaks appear indicating the absence of heteroaggregation consistent with a monomeric enolate.
lates in these weak donor ligands afford additional resonances attributed to heteroaggregates. However, the results from lithium Oppolzer enolates revealed extraordinary stereochemical complexity within tetramers examined in excruciating detail.\(^4\) Such potential complexity, lower data quality for the sodium enolates when compared to their lithium counterparts, and occasional solubility problems left us with no appetite for trying to repeat such a study.

**THF/HMPA**

The predominant protocol for alkylation of sodiated Oppolzer enolates uses THF/HMPA mixtures.\(^6\) MCV analysis using binary enolate mixtures confirm the absence of heteroaggregation. Probing serial solvation by \(^{31}\)P NMR spectroscopy under optimal conditions can provide explicit solvation numbers, but resolution was insufficient to distinguish differential solvation states in this case. DFT computations suggest disolvate \(^8\) and trisolvate \(^9\) to be viable with a 2.5 kcal mol\(^{-1}\) preference for \(^9\). This is not a definitive assignment but provides adequate context for the rate studies. The lithium enolates were shown spectroscopically and computationally to be disolvates analogous to \(^8\).

**TMEDA**

\(N,N',N'',N''\)-Tetramethylethlenediamine (TMEDA) has a long-standing reputation for promoting deaggregation despite mounting evidence over three decades of a more nuanced story.\(^13,14\) The impetus to examine TMEDA comes from previous studies of both simple and complex sodium enolates which suggest that TMEDA, while not necessarily as strongly binding or as prone toward deaggregating sodium salts, is often superior to THF for controlling structure.\(^14\) Binary mixtures of enolates \(^4g\) and \(^4i\) in TMEDA/toluene show resonance duplications consistent with a heterodimer (Fig. 2). DFT computations show exothermic serial solvation to form doubly chelated dimer. The dimer motif has three possible stereoisomers, \(^10\)–\(^12\), owing to chelation with the endo or exo sulfonyl oxygens (Scheme 2). DFT computations support doubly exochelated dimer \(^12\) as the preferred form by 10.6 kcal mol\(^{-1}\).

**PMDTA**

\(N,N',N'',N''\)-Pentamethyldiethylenetriamine (PMDTA) has a penchant for forming \(\kappa^3\)-solvated monomers,\(^16\) yet binary mixtures of \(^4g\) and \(^4h\) in 3.0 equiv. PMDTA/toluene show marginally resolved but unambiguous heterodimers akin to those observed with TMEDA solvates (ESI\(^+\)). Computational studies support \(\kappa^3,\kappa^3\)-solvated dimer \(^13\) akin to TMEDA solvate \(^12\). (Formally, there could be as many as 10 stereoisomers owing to the lower symmetry of the chelate and the exo and endo isomerism of the sultam sulfonyl moieties.)

**Kinetics of alkylation**

The mechanism of alkylation was studied using enolate \(^4g\) and allyl bromide (eqn (3)). The enolate was generated in situ using recrystallized NaHMDS.\(^3\) Rates were monitored by in situ IR spectroscopy\(^17\) following the loss of enolate \(^9\) (1616 cm\(^{-1}\)) and formation of product \(^14\) (1701 cm\(^{-1}\)). A typical decay is illustrated in Fig. 3. Alkylation under non-pseudo-first-order conditions (0.10 M enolate and 3.0 equiv. of allyl bromide) displayed no unusual curvatures emblematic of intervening autocatalysis or autoinhibition.\(^18\)

Following protocols developed to study the lithium enolates with enolate \(^4g\) as the limiting reagent, the enolate order, \(n\), is determined by best-fit to the non-linear van’t Hoff equation (eqn (4)).\(^19\) The curve in Fig. 3 stems from such a fit.
Considerable variation of $n$ from run to run is compensated by replication, affording $n = 1.04 \pm 0.25$ from the 48 independent decays used to obtain values for $k_{\text{obsd}}$. The first order in excess allyl bromide was confirmed by a three-point control experiment showing a direct relationship of $k_{\text{obsd}}$ to concentration. Curiously, comparing the relative rates for the lithium and sodium enolates under otherwise identical conditions afforded $k_{\text{Li/Na}} = 2.7$: the lithium enolate is almost threefold more reactive than the analogous sodium enolate.

As a preface to the rate studies described below it is constructive to consider the backdrop provided by the alkylations of the lithium enolates. In particular, first-order dependencies of the alkylation rates on alkyl halide and enolate monomer implicated a monomer-based alkylation. Second-order dependencies on both THF and HMPA suggested a hexasolvated ion pair. However, the THF dependence proved to be 100% secondary shell (medium) effect rather than primary solvation in which an inverse-first-order dependence on toluene owing to stabilization of the HMPA in the reactant and a first-order dependence on THF owing to stabilization of the transition structure combined to create an apparent second-order THF dependence. Using 2,5-dimethyltetrahydrofuran (2,5-Me$_2$THF) removed both the influence of toluene and the drifting dielectric constant of the medium, revealing a true zeroth-order dependence on primary-shell solvation by THF. We suspected this primary and secondary-shell solvation narrative would reappear with sodium.

In this event, the first-order dependencies on enolate and allyl bromide followed for the sodium enolates. A second-order HMPA dependence (Fig. 4) implicated a $^+\text{Na}(\text{HMPA})_3$ gegenion based on the computed trisolvated monomer 9. (If disolvate 8 is the dominant form, then we have a $^+\text{Na}(\text{HMPA})_4$ gegenion.) The second-order THF dependence in toluene (Fig. 5) and approximate zeroth-order THF dependence using 2,5-Me$_2$THF with a downward drift (see insert) mirrored the lithium enolates. Once again, the second order in THF is attributed to a first-order medium effect on THF and an inverse-first-order medium effect on toluene (Fig. 6), both of which were negated using 2,5-Me$_2$THF as cosolvent.

Omitting HMPA

Hoping to eliminate HMPA from the protocol we tried alkylations using TMEDA and PMDTA without much luck. In neat THF the alkylation (eqn (5)) is approximately 100-fold slower than in THF with 10 equiv. of HMPA. However, alkylation with...
the highly reactive methyl iodide is sufficiently fast to allow the methylation to occur at −40 °C over 2 hours, which is sufficiently below the −20 °C onset of decomposition.

The highly abbreviated mechanistic story is that alkylation follows the rate law in eqn (6) (see ESI†), which, given the assignment of enolate 4g as tetrasolvated monomer, is consistent with a hexa-solvated ion-pair-based mechanism. This is the mechanism found for the HMPA-solvated lithium and sodium enolates with the only difference being the \(^+\text{Na(THF)}_6\) counterion. Supporting data suggests to us that \(^+\text{Na(THF)}_6\) is the most probable.\(^{22}\) As a reminder, the assignment of enolate 4g in neat THF-solvated monomer as a tetrasolvent was not unassailable, though the \(^+\text{Na(THF)}_6\) is computationally quite credible.

\[
\frac{-d[\text{enolate}]}{dt} = k[\text{enolate}]^1[\text{THF}]^2[\text{MeI}]^1 \tag{6}
\]

Conclusions

The structural and rate studies of sodiated Oppolzer enolates in THF/HMPA solution are strongly aligned with the results from the lithium enolates in THF/HMPA, differing only in the solution number of the monomeric reactant and the counterion in the solvent-separated ion-pair.\(^{23}\) Consequently, the stereoechemical model involving an open transition structure crudely depicted as 2 in the introduction and as the ball-and-stick structure in Fig. 7 differs only in the remote \(^+\text{MS}_n\) counterion—\(^+\text{Li(HMPA)}_4\) or \(^+\text{Na(HMPA)}_5\). The secondary shell influences of toluene on the reactant HMPA and THF on the transition structure are some of the most dramatic we have seen from literally hundreds of rate studies. We will not reiterate the extensive computations pointing to the stereoelectronically preferential attack of the electrophile anti to the endo sulfonyl oxygen.\(^4\) Curiously, several recent reactions that do not involve potentially chelate-forming at all can be explained by the same stereoelectronic control.\(^{24}\) One might surmise that the only advantage of sodium over lithium is the much higher reactivity but that would be wrong. The lithium and sodium enolates studied show a three-fold greater reactivity of the lithium enolate.

We can take some solace in locating a narrow window of reactivity using the highly reactive methyl iodide in which the undesirable HMPA can be excluded as reported by two groups.\(^7\) The greater efficacy of NaPTA when compared with NaHMDS for generating recalcitrant sodium enolates is also notable.

Experimental

Reagents and solvents

NaHMDS and NaPTA were prepared as white crystalline solids.\(^{3a,c}\) Toluene, hexanes, THF, MTBE, and cyclopentane...
were distilled from blue or purple solutions containing sodium benzophenone ketyl. Methyl iodide and allyl bromide were distilled from 4 Å molecular sieves. Substrates 3a–j were prepared according to literature procedures.\(^1\),\(^4\)

**NMR spectroscopic analysis**

An NMR tube fitted with a double-septum under vacuum was flame-dried on a Schlenk line and allowed to cool to room temperature, backfilled with argon, and placed in a dry ice/acetone cooling bath. Individual stock solutions of the N-acyl sultams and NaHMDS were prepared at room temperature and 0 °C, respectively. The appropriate amounts of the N-acyl sultams, NaHMDS, solvent, and (when applicable) co-solvent were added sequentially via a gas-tight syringe. The tube was flame-sealed under a partial vacuum while cold to minimize evaporation. The tubes were mixed on a vortex mixer and stored at −80 °C.

Unless otherwise stated all tubes were sealed with a total enolate concentration of 0.10 M. Standard \(^1\)H, \(^19\)F, \(^13\)C, and \(^31\)P direct detection spectra were recorded on a 11.8 T spectrometer at 500.1, 470.6, 125.8, and 202.5 MHz, respectively. \(^1\)H, \(^13\)C, and \(^31\)P resonances are referenced to their respective standards (Me$_6$Si and H$_3$PO$_4$ at 0.0 ppm). \(^19\)F spectra are referenced to CF$_3$CO$_2$H (−113.15 ppm).

For quantitated \(^13\)C spectra, the spin–lattice relaxation (T1) was determined by standard inversion-recovery experiments on several samples. The relaxation delay (d1) was set to seven times the average relaxation lifetime. Integration of the NMR signals was determined using the line-fitting method included in MNova (Mestrelab research S.L.).

**Rate studies**

IR spectra were recorded with an \textit{in situ} IR spectrometer (ReactIR iC 10, Mettler Toledo AutoChem) fitted with a 30-bounce, silicon-tipped probe. The spectra were acquired at a gain of 1 and a resolution of 4 cm$^{-1}$. A pruned (99, 590) integration grid (equivalent to Gaussian’s “UltraFine” option) was used for all calculations. Where appropriate solvation effects were accounted for by the Self Consistent Reaction Field method using the SMD model of Truhlar and coworkers.\(^1\)\(^e\) Jensen’s polarization-consistent segment-contracted basis set, pceg-1, was used for geometry optimizations and the expanded pceg-2 basis set for single-point energy calculations.\(^1\)\(^f\) Basis set files were obtained from the Basis Set Exchange.\(^1\)\(^g\) Ball-and-stick models were rendered using CYLview 1.0b.\(^1\)\(^h\) A large number of DFT-computed energies are archived in the ESL.\(^1\)\(^i\) A frequency calculation was conducted at all stationary points to ensure the existence of real minima. All reported geometries have exactly zero imaginary (negative) vibrational frequencies.

**Author contributions**

N. M. Lui: conceptualization (equal), methodology, formal analysis, investigation, visualization, writing – review & editing. D. B. Collum: conceptualization (equal), supervision, funding acquisition, writing – original draft.

**Conflicts of interest**

The authors declare no competing financial interests.

**Acknowledgements**

We thank the National Institutes of Health (GM131713) for their support. This work made use of the Cornell University NMR Facility, which is supported, in part, by the National Science Foundation through MRI award CHE-1531632.

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