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Sodium Isopropyl(trimethylsilyl)amide: A Stable and Highly Soluble Lithium Diisopropylamide Mimic

Yun Ma, Nathan M. Lui, Ivan Keresztes, Ryan A. Woltornist, and David B. Collum*

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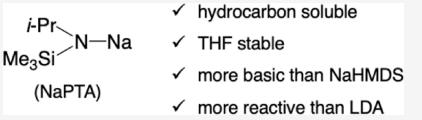
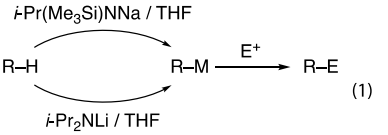
ABSTRACT: The preparation, structure, physical properties, and reactivities of sodium isopropyl(trimethylsilyl)amide (NaPTA) are described. The solubilities at room temperature range from *n*-heptane (0.55 M), *n*-hexane (0.60 M), toluene (0.65 M), MTBE (1.7 M), Et_3N (3.2 M), and THF (>6.0 M). The half-life to destruction in neat THF is >1 year at 25 °C and 7 days at 70 °C, which compares favorably to 2.5 months and 1.5 days, respectively, for LDA in neat THF. This study focuses on NaPTA in THF. ^{29}Si NMR spectroscopy shows exclusively a mixture of *cis* and *trans* stereoisomeric dimers in 0.10−12 M THF in hexane. Density functional theory (DFT) computations suggest that the pK_b is intermediate between dimeric sodium diisopropylamide (NaDA) and dimeric sodium hexamethyldisilazide (NaHMDS). Metalations of arenes, epoxides, ketones, hydrazones, alkenes, and alkyl halides show higher reactivities than LDA ($k_{NaPTA/LDA}$ = 1−30). While the rates of arene metalation are high, the lower pK_b of NaPTA limits the substrates. Metalation of pseudoephedrate-based carboxamides to form disodiated Myers enolates solves several challenging technical problems.



INTRODUCTION

Progress in organosodium chemistry has been muted by what appears to be a combination of minor technical problems and human bias in which it was pushed aside by successes in organolithium chemistry.[1,2] Sodium hexamethyldisilazide (NaHMDS) stands out as the premier sodium base with wide appeal and commercial availability.[3] In contrast to the omnipresent lithium diisopropylamide (LDA), lithium tetramethylpiperidide (LiTMP), and *n*-butyllithium (*n*-BuLi), however, minor inconveniences of the corresponding sodium diisopropylamide (NaDA), sodium tetramethylpiperidide (NaTMP), and n-butylsodium appeared to have disproportionately stifled their adoption.[4−10]

As part of a program to expand the applications of organosodium chemistry, we have emphasized a combination of strategies employing structural and mechanistic studies interfaced with synthetically emblematic transformations.[4,11] We surmised that alkyl trimethylsilyl amides[12,13] would be useful for both metalations requiring more driving force than NaHMDS—defined as more basic using the loosely defined pK_a or pK_b metrics[14−17]—and might find applications in C−N bond-forming reactions.[18] In this study, we describe the synthesis, physicochemical properties, and reactions of sodium isopropyl(trimethylsilyl)amide (NaPTA). NaPTA can be prepared without specialized glassware, and it is highly soluble even in saturated hydrocarbons, kinetically more reactive than LDA, and highly stable in THF solutions (eq 1). We see no impediment to commercial availability should demand appear and have no vested financial interests.



(1)

RESULTS

NaPTA was prepared using elemental sodium, isoprene, and readily available isopropyl(trimethylsilyl)amine[19] in standard hydrocarbon and ethereal solvents without specialized glassware.[20] The resulting amide solutions can be used directly and stored for months with no detectable decomposition. If desired, recrystallization from hexane at −78 °C ostensibly to remove low levels of impurities affords a white solid, but such purification has a negligible influence on reactivity. Most importantly, the solubilities of NaPTA determined by visual titration of solid NaPTA are as follows: *n*-heptane (0.55 M), *n*-hexane (0.60 M), toluene (0.65 M), MTBE (1.7 M), Et_3N (3.2 M), 2-methyltetrahydrofuran (MeTHF, 3.8 M), and THF (>6.0 M). A potential limitation is that the solubilities are decidedly temperature sensitive. For example, saturation in THF is 2.0 M at −20 °C and 0.30 M at −78 °C. MeTHF offers no improvement over THF at −78 °C.

In this study, we focus on NaPTA in THF. ^{29}Si NMR spectroscopy on [^{15}N]NaPTA shows two doublets ($^1J_{N-Si}$ =

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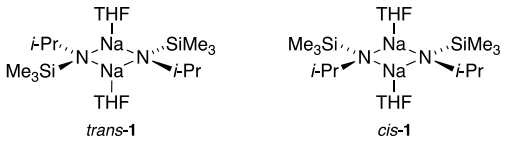
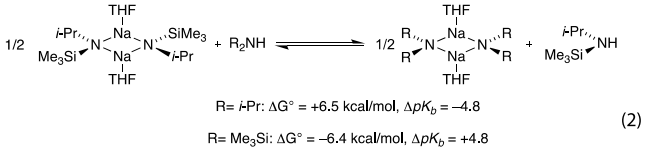
6.53 and 6.52 Hz) consistent with a 1:2 ratio of *cis*-**1** and *trans*-**1** from 0.12 M THF/toluene to neat THF.[21] Density functional theory (DFT) computations (Supporting Information) carried out at the M06-2X level of theory[22,23] do not readily distinguish di-, tri-, or tetrasolvates: serial solvation shows exothermicity to disolvation, a slight endothermicity to trisolvation, and steeply rising endothermicity to hexasolvation. Disolvation is assumed using analogy to NaDA[4a] and NaHMDS,[11b] at least until further notice. The disolvate shows a 1.0 kcal/mol preference for *trans*-**1** relative to *cis*-**1** well within the error bar of thermoneutral with a growing *trans* preference with the higher solvation numbers.



The thermodynamic basicity is best examined by direct computational comparison of NaPTA with NaHMDS and NaDA illustrated in eq 2 showing the free energies and ΔpK_b values.[14,15,17,18] Thus, the mixed alkyl-silyl amide lands squarely intermediate to the dialkyl and disilyl analogues.



(2)

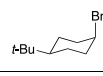
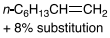
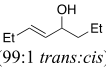
Metalations and substitutions of representative organic substrates are summarized in Table 1. The yields are of isolated, purified products or inferred using NMR spectroscopy (listed parenthetically) for not easily isolated salts. The relative reactivities of NaPTA and LDA under otherwise identical conditions, $k_{NaPTA/LDA}$, reveal a decidedly higher reactivity of NaPTA. The high temperatures required for epoxide eliminations (entries 3 and 4) are not as well tolerated by LDA. It is both fortuitous and ironic that the only reaction in which LDA shows a higher reactivity is THF decomposition ($k_{NaTPA/LDA}$ = 0.2 at 70 °C).[4,24]

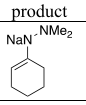
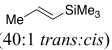
DISCUSSION

The solubility, cost, ease of preparation, and high basicity of NaPTA are compelling compared with other sodium bases. The 2:1 *E*-*Z* selectivity for the enolization of 2-methyl-3-pentanone (entry 9) pales in comparison with the 2000-fold range of solvent-dependent *E*-*Z* selectivities for NaHMDS.[11] The epoxide eliminations (entries 3−5) are similar to those observed for LDA and NaDA,[4a,25] although NaPTA is the only one of the three bases to give exclusively *cis*-cyclooct-2-en-1-ol (entry 3). The openings of terminal epoxides in entries 6 and 7 are precedented for sodium amides[26] while foreshadowing potential applications to C−N bond formation. Notably absent is the evidence of epoxide elimination to generate enolates.[27] The 1,4-addition in entry 10 is the most prevalent application of lithium alkyl(trimethylsilyl) amides.[18,28]

The highly selective isomerizations of allyl-[29] and allyloxysilanes[4a,30] (entries 12 and 13) have been reported previously. They can be carried out on preparative scales using neat

Table 1. Reactions of NaPTA in THF

	substrate	conditions	product	$k_{NaPTA/LDA}$	yield
1		25 °C, 1 hr		11	91%
2		25 °C, 3 hr	 + 8% substitution	4	81%
3		66 °C, 8 hr		4	88%
4		66 °C, 8 hr		1	80%
5		66 °C, 8 hr	 (99:1 *trans*:*cis*)	3	80%
6		66 °C, 8 hr	 (>30:1)	--	70%
7		66 °C, 8 hr	 (>30:1)	--	74%
8		–40 °C, 2 hr (w/ *n*-BuBr)		--	82%
9		–78 °C, 1 hr (w/ TMSCl)	 (*Z*:*E* = 2:1)	--	80%
10		–78 °C, 10 min		--	82%

	substrate	conditions	product	$k_{NaPTA/LDA}$	yield
11		–30 °C, 1 hr		8	(50%)[a]
12		25 °C, 2 hr	 (40:1 *trans*:*cis*)	12	95%
13		25 °C, 2 hr	 (>50:1 *cis*:*trans*)	30	86%
14		–40 °C, 1 hr		1	90%
15		–60 °C, 1 hr		2	(35%)[b]
16		–78 °C, 10 min		--	(92%)[b]
17		–78 °C, 30 min		--	(90%)[b]
18		–25 °C, 3 hr		--	82%
19		25 °C, 3 hr		--	70%
20		66 °C, 2 hr		--	78%

[a]Percent conversion shown by in situ IR spectroscopy. [b]Reflects percent conversion shown by deuteration.

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substrates and catalytic NaPTA. The thermochemical advantage of LDA is seen in hydrazone metalations, which are quantitative for LDA but not for NaPTA (entry 11). NaPTA proved effective for a Snieckus-Fries rearrangement[4a,31] (entry 14) as well as for relatively favorable orthometalations.[4a,32] It does not have the driving force for recalcitrant orthometalations that can be achieved with NaDA and LDA.[4a,32] The S_NAr reactions in entries 18−20[33] join the epoxide openings to foreshadow potential applications in C−N bond formation.

We are guilty of possibly burying the lede by putting the generation of Myers enolates as a mere table entry (entry 8) for several reasons. The renowned lithium variant is restricted to high dilution (0.10 M) owing to the requisite addition of 5.0 equiv of LiCl.[34] The disodium salt solved that problem, but it required the technically challenging preparation of NaDA in *neat* THF wherein THF decomposition precludes large-scale applications.[35] NaPTA, by contrast, readily afforded 0.50 M solutions of Myers enolates.

CONCLUSIONS

Organosodium chemistry seems to be picking up momentum again after a century of false starts.[1,2] NaPTA is superior to NaHMDS in many respects and is more convenient to work with than NaDA. It is, of course, not a replacement for LDA—nothing could be—but the higher reactivity than LDA and the facile access to sodium salts should find a niche. We have a few plans for probing other solvents, a few mechanisms, and other alkyl derivatives with an eye toward C−N bond formation. Other than that, future work will be left to the free market of ideas where need is the mother of invention.

EXPERIMENTAL SECTION

Reagents and Solvents. Toluene, hexane, *N,N*-dimethylethylamine (DMEA), MTBE, MeTHF, and THF were distilled from blue or purple solutions containing sodium benzophenone ketyl. Isoprene and isopropyl(trimethylsilyl)amine were distilled from 4 Å molecular sieves. All products in Table 1 have been prepared previously or are commercially available.[36]

Representative NaPTA Preparation: Method A. A 2.0−2.5 M solution of NaPTA in neat THF to be used without any purification was prepared as follows. Sodium slices (1.2 g) cut from sodium cubes were placed in a 50.0 mL pear-shaped flask. Dry THF (15.0 mL) and isopropyl(trimethylsilyl)amine (5.24 mL, 40.0 mmol) were added to the flask under positive argon pressure, and the mixture was maintained at 20 °C. Isoprene (1.85 mL, 20.0 mmol) was added at 0 °C all at once. Stirring for 2 min yielded a brown-yellow solution. Darkening of the sodium surface correlates with the completion of the reaction. The solution is readily decanted by canula, leaving the unreacted sodium slices. Titration[37] affords 80−90% of the anticipated normality (1.7−1.9 M). The spent sodium is quenched by adding hexane followed by isopropanol. ^{1}H NMR (10% THF/toluene-d_8, 500 MHz, −110 °C) δ 2.10 (m, 1H), 0.62 (br s, 6H), 0.02 (s, 9H). ^{13}C{^{1}H} NMR (10% THF/toluene-d_8, 125.79 MHz, −110 °C) δ 48.2, 47.9, 37.2, 5.0, 4.5. ^{29}Si NMR (10% THF/toluene-d_8, 99.36 MHz, −110 °C) δ −15.3, −15.6.

[^{15}N]Sodium isopropyl(trimethylsilyl)amide: Method B. Purified NaPTA can be prepared as a white crystalline solid as illustrated for [^{15}N]NaPTA. Sodium dispersion[38] in toluene (9.0 mL, 100 mmol) was added to a 100 mL Schlenk flask. The toluene was removed in vacuo, and *N,N*-dimethylethylamine (30.0 mL) and [^{15}N]isopropy(trimethylsilyl)amine (5.9 g, 45.0 mmol) were added to the flask. While stirring, isoprene (750 μL, 7.5 mmol) was added over 10 min. Stirring was halted after 30 min, and the mixture was filtered through a fine frit and evaporated to dryness to give a yellowish solid. Recrystallization from hexane gave [^{15}N]NaPTA as a white solid (5.5 g, 80% yield). ^{15}N{^{1}H} NMR (10% THF/toluene-d_8, 50.66 MHz, −110 °C) δ 66.1, 66.0. ^{29}Si NMR (10% THF/toluene-d_8, 99.36 MHz, −110 °C) δ −15.0 (d, $^1J_{Si-N}$ = 6.53 Hz), −15.3 (d, $^1J_{Si-N}$ = 6.5 Hz).

6-Fluoro-*N*-isopropylpyridin-2-amine (Entry 19). A representative reaction is as follows. 2,6-Difluoropyridine (46.0 mg, 0.40 mmol) was added to a 0.125 M solution of NaPTA (76.6 mg, 0.50 mmol) in THF (4.0 mL) with stirring at 25 °C for 3.0 h. Standard aqueous workup followed by purification via flash chromatography (30% ethyl acetate in hexanes) afforded 55.2 mg (70% yield) of product as a faint yellow liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (q, J_{H-F} = 8.1 Hz, 1H), 6.11 (dd, J = 8.1, J_{H-F} = 2.0 Hz, 1H), 6.03 (dd, J = 7.7, J_{H-F} = 2.0 Hz, 1H), 4.46 (d, J = 6.7 Hz, 1H), 3.82 (dhept, J = 6.7, 6.5 Hz, 1H), 1.16 (d, J = 6.5 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125.8 MHz): δ 163.3 (d, J_{C-F} = 235 Hz), 157.4 (d, J_{C-F} = 16.8 Hz), 141.5 (d, J_{C-F} = 8.7 Hz), 102.6 (d, J_{C-F} = 4.0 Hz), 95.0 (d, J_{C-F} = 36.8 Hz), 43.1, 22.7. HRMS (DART-Orbitrap) m/z [M + H]$^+$ calcd for $C_{11}H_{19}NF$ 198.1488, found 198.1568.

[^{15}N]Isobutyramide. Isobutyryl chloride (15.0 mL, 120.0 mmol) in Et_2O (50 mL) was layered onto a solution of [^{15}N]NH_4Cl (5.0 g, 91.5 mmol) in H_2O (20.0 mL) in a 250 mL flask. The flask was cooled to 0 °C, and NaOH (22.0 g, 550 mmol) in H_2O (30 mL) was slowly added by pipette to the aqueous layer with slow stirring to avoid mixing of layers. A white precipitate formed during the addition. The flask was warmed to room temperature with stirring for 15 min followed by vigorous stirring for an additional 10 min. The white solid was collected by filtration and washed with Et_2O. After drying under vacuum, the resulting white solid was purified by flash chromatography (15% EtOAc/hexane) to give [^{15}N]isobutyramide (9.5 g, 90% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.01 (dd, J_{H-N} = 88.3 Hz, J_{H-H} = 2.8 Hz, 1H), 5.56, (dd, J_{H-N} = 88.3 Hz, J_{H-H} = 2.8 Hz, 1H), 2.23 (hept, J_{H-H} = 6.9 Hz, 1H), 1.15 (d, J = 6.9 Hz, 6H). ^{13}C{^{1}H} ($CDCl_3$, 125.8 MHz) δ 184.5 (J_{C-N} = 5.0 Hz), 34.5 (J_{C-N} = 3.0 Hz), 18.6. HRMS (DART-Orbitrap) m/z[M + H]$^+$ calcd for $C_4H_{10}{}^{15}NO$ 89.07273, found 89.0726.

[^{15}N]Isopropyl Ammonium Tosylate. Following literature methods,[39] to a 250 mL flask containing [^{15}N]isobutyramide (8.8 g, 100.0 mmol) in CH_3CN (150 mL), hydroxy(tosyloxy)iodobenzene (HTIB) was added at room temperature. The solution was refluxed for 3.0 h and cooled to −20 °C overnight. The resulting white solid was collected by filtration and washed with cold acetonitrile to give [^{15}N]isopropyl ammonium tosylate (9.5 g, 90% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 (m, 2H), 7.63 (m, 1H), 3.25 (m, 1H), 2.34 (s, 3H), 1.16 (dd, J_{H-H} = 6.9 Hz, J_{H-N} = 2.1 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125.79 MHz) δ 141.4, 140.7, 129.1, 125.9, 44.3 (d, J_{C-N} = 4.4 Hz), 21.4, 20.6.

[^{15}N]Isopropylamine. [^{15}N]Isopropyl ammonium tosylate (11.6 g, 0.050 mol) and granular NaOH (6.0 g, 0.15 mol) were added to a 50 mL one-neck round-bottom flask equipped with an NaOH-filled drying tube used to transfer the amine gas to an 15 mL pear flask cooled to −78 °C. The mixture was heated with a heat gun for approximately 30 min. After the transfer of the amine was complete, it was distilled at atmospheric pressure using an oil bath (BP = 99 °C) to afford [^{15}N]isopropylamine (1.30 g, 48% yield) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.08 (hept, J = 6.0 Hz, 1H), 1.10 (s, 1H), 1.04 (dd, J_{H-H} = 6.2 Hz, J_{H-N} = 2.7 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125.8 MHz) δ 42.7 (d, J_{C-N} = 3.9 Hz), 26.09 (d, J_{C-N} = 2.4 Hz). ^{15}N{^{1}H} NMR ($CDCl_3$, 50.66 MHz): δ 45.3.

[^{15}N]Isopropyl(trimethylsilyl)amine. *n*-BuLi (2.50 M, 30.0 mmol) was added dropwise at room temperature to a stirred solution of [^{15}N]isopropylamine (1.8 g, 30.0 mmol) in THF (30 mL). After stirring for 6.0 h, Me_3SiCl (3.6 g, 33.0 mmol) in THF (40.0 mL) dropwise to the solution at −30 °C. The resulting colorless suspension was warmed to room temperature and stirred for 1.0 h. The solvent was removed in vacuo, and the colorless residue was extracted with hexane (30 mL) and filtered. Removal of the solvent in vacuo afforded [^{15}N]isopropyl(trimethylsilyl)amine as a colorless liquid (3.10 g, 84% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.08 (q, J = 6.0 Hz, 1H), 1.07 (dd, J_{H-H} = 6.3 Hz, J_{H-N} = 2.6 Hz, 6H), 0.06 (d, J_{H-N} = 1.0 Hz, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125.79 MHz) δ 43.1 (d, J_{C-N} = 7.1 Hz), 27.9 (d, J_{C-N} = 0.9 Hz), 0.5 (d, J_{C-N} = 2.7 Hz). ^{15}N{^{1}H} NMR ($CDCl_3$, 50.7 MHz) δ 47.9. ^{29}Si NMR ($CDCl_3$, 99.36

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MHz) δ 1.3 (d, J_{Si-N} = 16.9 Hz). HRMS (DART-Orbitrap) m/z[M + H]$^+$ calcd for $C_6H_{18}{}^{15}NSi$ 133.1173, found 133.1164.

IR Spectroscopic Analyses. IR spectra were recorded by using an in situ IR spectrometer fitted with a 30-bounce, silicon-tipped probe. The spectra were acquired in 16 scans at a gain of 1 and a resolution of 4 cm^{-1}. A representative reaction was carried out as follows: the IR probe was inserted through a nylon adapter and an O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and a T-joint. The T-joint was capped with a septum for injections and an argon line. After evacuation under full vacuum, heating, and flushing with argon, the flask was charged with NaPTA (76.6 mg, 0.50 mmol) in 5.0 mL of THF and cooled in a dry ice−acetone bath prepared with fresh acetone. After recording a background spectrum, the substrate stock (100 μL, 0.50 mmol) was added with stirring. For the most rapid reactions, the IR spectra were recorded every 6 s.

NMR Spectroscopic Analyses. NMR samples for monitoring reactions were prepared by using stock solutions and sealed with partial vacuum or under ambient argon pressure. Standard ^{1}H, ^{13}C, ^{15}N, and ^{29}Si NMR spectra were recorded at 500, 125.79, 50.66, and 99.36 MHz, respectively. The chemical shifts are referenced at −80 °C as follows: ^{1}H (Me_4Si, 0.0 ppm), ^{13}C (Me_4Si, 0.0 ppm), ^{15}N (neat Me_2NEt, 25.7 ppm), and ^{29}Si (Me_4Si, 0.0 ppm). ^{1}H NMR spectroscopic analysis can be used to follow the loss of NaPTA and formation of the amine in addition to characteristic resonances of the substrates and products.

Density Functional Theory Computations. All DFT calculations were performed using Gaussian 16.[22] Geometries were optimized at the M06-2X[23a] level of theory using Grimme's zero-dampened D3 dispersion correction[23b] (M06-2X-D3(0)) with the double-ζ polarization-consistent segment-contracted basis set pcseg-1 from Jensen and co-workers.[12c] For improved accuracy, single-point energies were calculated with the same dispersion corrected M06-2X-D3(0) functional[23a,b] using the slightly larger (triple-ζ) basis sets of the same family, pcseg-2.[23c] A pruned (99, 590) integration grid (equivalent to Gaussian's "UltraFine" option) was used for all calculations. Solvation effects were accounted for by the self-consistent reaction field method using the SMD model of Truhlar and coworkers (solvent = THF).[23d] Jensen's segment-contracted polarization-consistent basis sets were obtained from the Basis Set Exchange[23e] and included in Gaussian using the "gen" keyword. CYLview[23f] was used to render all ball-and-stick models. A vibrational frequency analysis was conducted at the same level of theory as the geometry optimizations (M06-2X-D3(0)/pcseg-1/SMD(THF)). The optimized geometries characterized as local minima on the potential energy surface have no imaginary frequencies.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01745.

Synthetic and experimental procedures, spectroscopic, and computational data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

David B. Collum − *Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301, United States;* orcid.org/0000-0001-6065-1655; Email: dbc6@cornell.edu

Authors

Yun Ma − *Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301, United States*

Nathan M. Lui − *Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301, United States;* orcid.org/0000-0003-4950-0914

Ivan Keresztes − *Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301, United States*

Ryan A. Woltornist − *Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.2c01745

Notes

The authors declare no competing financial interest.

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