Enantioselective Lithiation of *O*-Alkyl and *O*-Alk-2-enyl Carbamates in the Presence of (−)-Sparteine and (−)-α-Isosparteine. A Theoretical Study

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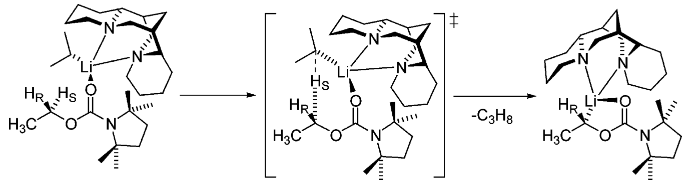

(*R*)-**13** TS (*R*)-*pro-S*-**13** (R_{Li},S)-**14**

Quantum chemical DFT calculations at the B3LYP/6-31G(d) level have been used to study the enantioselective lithiation/deprotonation of *O*-alkyl and *O*-alk-2-enyl carbamates in the presence of (−)-sparteine and (−)-α-isosparteine. Complete geometry optimization of the precomplexes consisting of the carbamate, the chiral ligand, and the base (*i*PrLi), for the transition states of the proton-transfer reaction, and for the resulting lithio carbamates have been performed in order to quantify activation barriers and reaction energies. For the lithiodeprotonation of ethyl carbamate **12** in the presence of (−)-sparteine (**5**) the preferred abstraction of the *pro-S* proton (by 2.75 kcal/mol) gives the (*S*)-lithio derivate (*S*)-**14**, which is in good agreement with experimental observations. (−)-α-Isosparteine (**6**) is predicted to be significantly less selective favoring the abstraction of the *pro-R* proton by 1.2 kcal/mol. The *O*-alkenyl carbamate **17** as an example of an allylic carbamate is more easily lithiated than **12**. As for **12** (−)-sparteine (**5**) favors the abstraction of the *pro-S* proton, although with smaller preference (0.7 kcal/mol). Structural parameters are discussed to rationalize the theoretical results.

As we reported first in 1990,[1] alkyl carbamates of type **1** are lithiated/deprotonated by *sec*-butyllithium /(−)-sparteine (**5**) with high stereoselectivity to form (*S*)-lithio derivatives **3** which were trapped by several electrophiles to yield the substitution products **4** with complete retention of the configuration. (Scheme 1).[2] Usually the enantiomeric ratios (e.r.) are above 97.5:2.5 (corresponding to >95%ee); e.r's up to 99:1 have been recorded for the ethyl carbamate **1** (R = CH_3).[3] The high stereoselectivity also holds for the corresponding *O*-alkyl *N,N*-diisopropylcarbamates.[4] Most likely, the formation of a precomplex **2**, consisting of the substrate **1**, (−)-sparteine (**5**), and *sec*-butyllithium, precedes the intramolecular deprotonation step.[5]

(*R,R*)-1,2-Bis(dimethylamino)cyclohexane (**7**) also supports the asymmetric lithiation of **1**, although with lower selectivity, whereas (−)-α-isosparteine (**6**) turned out to be completely inert for the deprotonation step.[6] By applying (+)-sparteine (*ent*-**5**)[7] or its truncated analogue **8**,[8] the opposite sense of chiral induction is observed. Since the 1-lithioalkyl carbamate complexes **3** are completely configurationally stable at the reaction conditions

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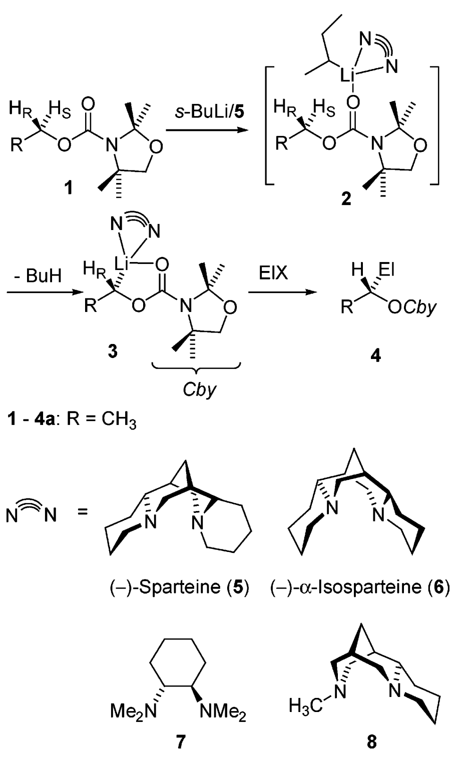
SCHEME 1



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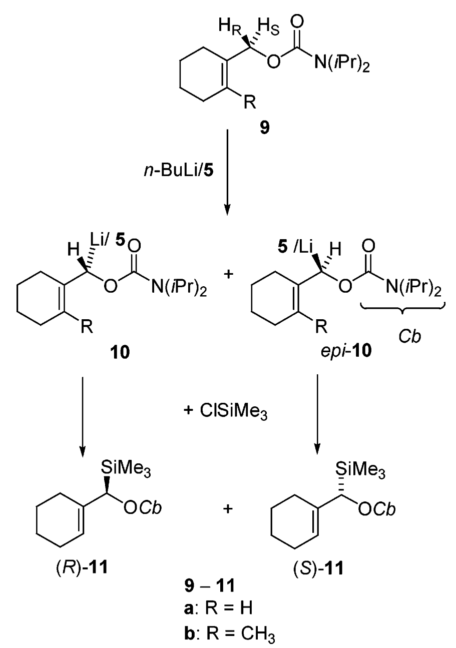

(−78 °C in pentane, toluene or diethyl ether) the ratio of intermediates **3** and *ep*i-**3**—and thus the ratio of trapping products **4** and *epi*-**4**—is kinetically controlled by the difference of the free energies of activation in the formation of the competing diastereomorphic transition states leading to **3** and *epi*-**3**. Our DFT calculations for the formation of slightly modified model systems in the presence of the simpler diamine **7** gave results which are in good accordance with the experimental values.[6] PM3 calculations on the deprotonation of alkyl carbamates without chiral ligands were published in 1996.[9]

Similar stereoselectivities on the (−)-sparteine-mediated deprotonation of *N*-Boc-pyrrolidine have been found by Beak et al.[10] and were successfully modeled with quantum-chemical methods, carried out by Wiberg and Bailey[11−17] and Kozlowski at al.[18]

Allylic *N*,*N*-diisopropylcarbamates have been lithiated enantioselectively by *n*-butyllithium (−)-sparteine (**5**);[2,19] however, the 1-lithio-2-alkenyl carbamate complexes usually epimerize rapidly under the reaction conditions to form a thermodynamically controlled diastereomeric mixture.[20,21] Fortunately, the lithium derivatives of (1-cycloalkenyl)methyl carbamates of type **10** show a considerable configurational stability (Scheme 2).[22] When generated at −78 °C in the presence of the trapping agent chlorotrimethylsilane, the er's of the α-silylation products (*R*)-**11** and (*S*)-**11**, formed with inversion of the configuration, closely reflect the kinetically controlled ratio of the lithium intermediates **10** and *epi*-**10** (**10a**, 76:24; **10b**, 96.5:3.5).

In this investigation, we study the reaction course of the (−)-sparteine- and (−)-α-isosparteine-assisted lithiodeprotonation reaction of *O*-alkyl and *O*-2-alkenyl carbamates by quantum chemical DFT methods. The aim of the work is the evaluation of the kinetic barriers of the rate-determining deprotonation step and of the reaction enthalpies for the formation of the diastereoisomeric lithium intermediates. This represents the first theoretical study of a (−)-sparteine-mediated lithiodeprotonation of conformationally unrestricted open-chain precursors and includes for comparison the corresponding reaction of an allylic carbamate.

Discussion

To investigate the mechanism and the stereochemical course of enantioselective (−)-sparteine- and (−)-α-isosparteine-assisted lithiodeprotonation reactions, exten-

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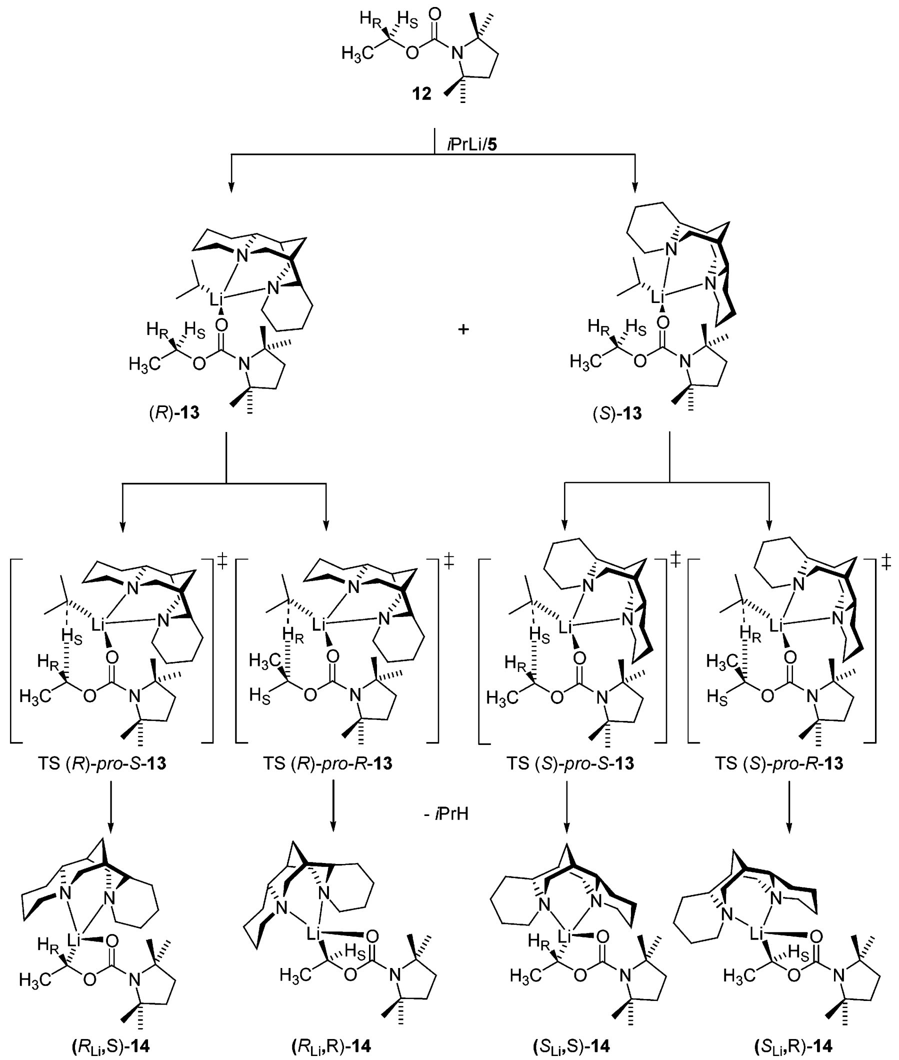
SCHEME 3



sive DFT calculations using the B3LYP hybrid functional with the basis 6-31G* were performed. As in our previous paper on the *trans*-1,2-bis(dimethylamino)cyclohexane-assisted deprotonation reaction, we have chosen ethyl 2,2,5,5-tetramethylpyrrolidino carboxylate as our model substrate (carbamate **12**), which has the advantage of a symmetrical amino subunit in contrast to the experimentally used oxazolidine derivative. It is expected that the steric influence of both amino substituents on the selectivity of these reaction is similar. In our thorough study, we have included the starting materials (−)-sparteine, its precomplex with isopropyllithium (as a symmetrical model for the experimentally used *sec*-butyllithium), the Lewis acid−base precomplex with carbamate **12** as a result of *O*-coordination at the carbamate carbonyl oxygen, the transition state for deprotonation, and the resulting lithium compound after loss of propane (Scheme 3). (−)-Sparteine (possessing C_1 symmetry) allows two diastereotopic modes of coordination, due to the stereogenic lithium cation produced. Furthermore, there are two different possibilities of interaction with respect to the abstraction of the *pro-(R)* and of the *pro-(S)* protons; consequently, four stereochemically different reaction channels result. In our opinion, the bulkiness of the three components does not allow for the participation of coordinating solvent molecules, which would make the modeling of the reaction sequence much more difficult.

Starting with PM3 reaction pathway calculations, which allow relatively easily the localization of the respective transition states, the computations were continued using the G98[23] packages of programs using the (deprecated, but rather useful) option “mndofc” (opt = (ts, noeigentest, mndofc)), at first using the RHF/3-21G method and finally B3LYP/6-31G*. Having obtained the transition-state geometries, the respective minima were localized by complete optimizations after appropriate shifting of the migrating hydrogen atom in the direction

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TABLE 1. **(−)-Sparteine-Induced Deprotonation: Precomplexes 13, Transition States TS-13, and Lithio Carbamates 14 (Including Zero-Point Energy (ZPE)) (Kcal/Mol)**[a]

complexes **13**			transition states TS-**13**				lithio carbamates **14**	
stereo notation	$E_{complex}$[b]	$E_{rel\ precomplex}$	stereo notation	E_{TS}[b]	$E_{rel\ TS}$	E_{act}[c]	stereo notation	$E_{product}$[b]
(R)-pro-S	**−40.52**	**0.00**	***(R)-pro-S***	**−26.17**	**0.00**	**14.35**	**(R_{Li},S)**	−59.96
(S)-pro-S	−38.84	1.69	*(S)-pro-S*	−22.65	3.52	17.87	*(S_{Li}-S)*	−60.08
(R)-pro-R	−38.16	2.36	*(R)-pro-R*	−22.11	4.06	18.41	*(R_{Li},R)*	**−60.39**
(S)-pro-R	**−39.32**	**1.20**	***(S)-pro-R***	**−23.42**	**2.75**	**17.10**	*(S_{Li},R)*	−59.80

[a] The best and the second best species are printed in boldface type. [b] Relative to the (−)-sparteine−*i*PrLi complex + ethyl carbamate **12**. [c] Relative to the best precomplex (*R*)-*pro-S*-**13**.

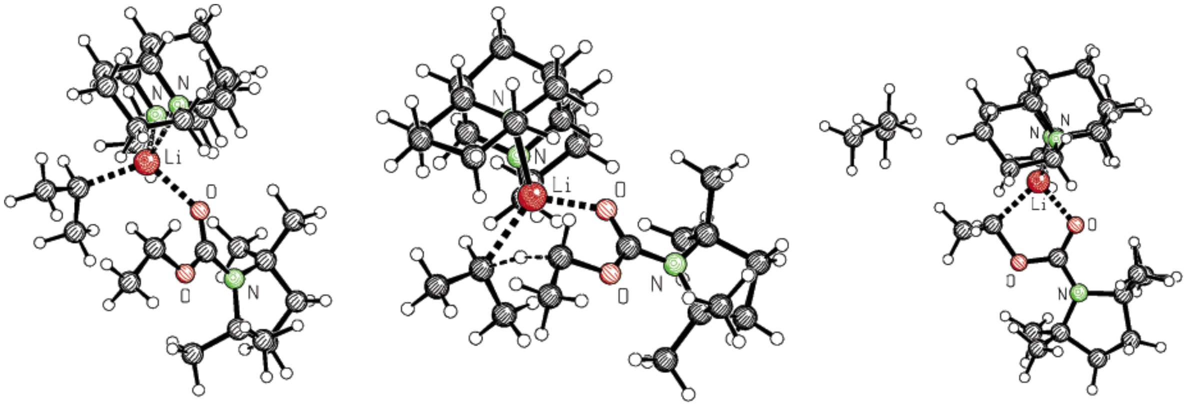

FIGURE 1. (−)-Sparteine/*i*-PrLi/ethyl carbamate precomplex (*R*)-**13** in the conformation, where the *pro-S* proton points to the lithium ion (left), the corresponding transition state TS-*(R)-pro-S*-**13** (middle), and the corresponding lithioethyl carbamate (R_{Li},*S*)-**14** (right) (B3LYP/6-31G*).

of the precomplex or of the lithium compound, respectively. From these calculations, the lithioalkyl carbamates were obtained as van der Waals complexes with propane.

For comparison, analogous calculations were performed for (−)-α-isosparteine **6**, which is experimentally by far not as successful compared to (−)-sparteine **5**. Since (−)-α-isosparteine **6** is C_2 symmetric, just one reaction channel for each *pro-(R)*- and *pro-(S)* proton abstraction is possible. Furthermore, the *O*-alk-2-enyl carbamate **17** has been included in order to study the deprotonation of an allylic system.

All stationary points were subjected to frequency analyses in order to verify their character. In the following text, we discuss *E* (0 K) energies, which contain zero point corrections. Calculated Gibbs free energies seem in such large systems to be less reliable due to very low frequencies, where the harmonic oscillator model produces significant deviations. Corrections for basis set superposition errors (BSSE) are not included.

As Table 1 indicates, the four precomplexes studied here, which were formed from (−)-sparteine (**5**), *i*PrLi[11] and the ethyl carbamate **12**, differ significantly with respect to their total and relative energy. The precomplex *(R)-pro-S*-**13** (with *R* configuration on lithium) in a conformation, where the *pro-S* proton points toward the lithium ion, is calculated to be lower in energy than all other precomplexes by at least 1.2 kcal/mol (Figures 1 and 2).

With regard to the four corresponding transition states TS-**13** it is noteworthy that again the structure TS-*(R)-pro-S*-**13**, where the *pro-S* proton is involved in the hydrogen transfer, is lower in energy than the three others by at least 2.75 kcal/mol. These data add to a calculated activation barrier of 14.35 kcal/mol. Activation barriers in this range are well compatible with the reaction conditions employed (several hours at −78 °C). The experimentally observed enantioselectivity (after trapping with an appropriate electrophile, which adds with complete retention of configuration) amounts to 99:1 in favor for the *pro-S* lithium compound; this corresponds to a difference in activation energy of ca. 1.8 kcal/mol at −78 °C.

As Table 1 clearly indicates, the lithium compound obtained from the kinetically controlled deprotonation process is not the thermodynamically best product; this is the species (R_{Li},*R*)-**14**. However, we assume configurational stability at this stage of the reaction, as indicated by the strong Li−methylene interaction (see below).

In summary, the reaction in question is a typically kinetically controlled process. Interestingly, as an inspection of the relevant dihedral angles of the carbamate moieties indicates (Table 2), the stereochemistry of the ethyl carbamate in the energy lowest transition state TS-(*R*)-*pro-S*-**13** is the same as the one of the energy lowest precomplex (*R*)-*pro-S*-**13**, consisting of the carbamate and the "chiral" base, constituted of (−)-sparteine (**5**) and isopropyllithium. The precomplex formed is conformationally flexible; hence, low barriers allow for quick population of the energy lowest conformation (Curtin−Hammett principle[24]). We derive from these data that the same stereochemical features, which determine the conformation in this precomplex, are also controlling the conformation in the transition state, as the energies of the precomplexes and the corresponding transition states parallel each other quite well. In contrast, the structures

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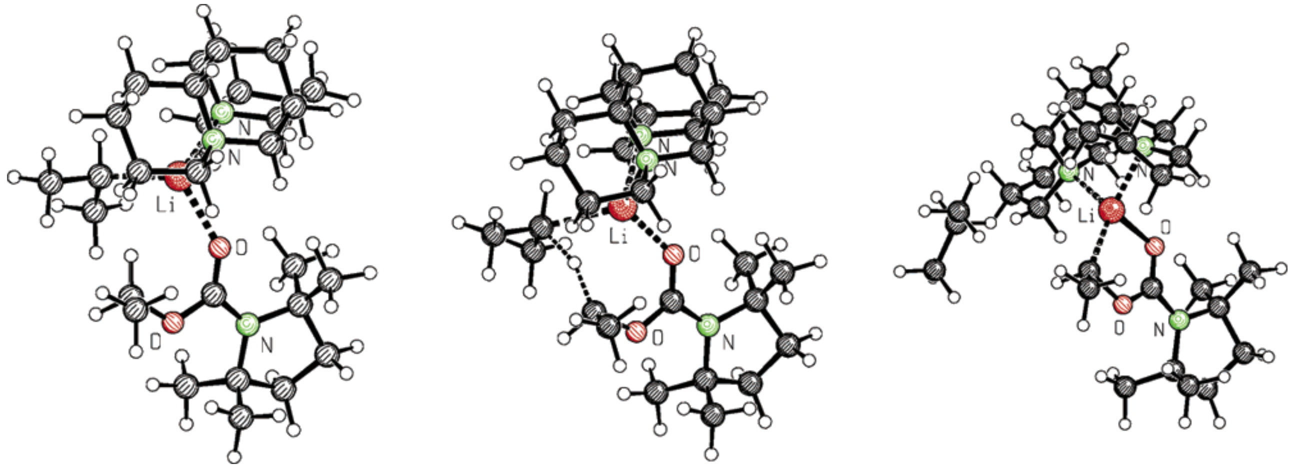

FIGURE 2. (−)-Sparteine/*i*-PrLi/ethyl carbamate precomplex (*S*)-**13** in the conformation, where the *pro-R* proton points to the lithium ion (left), the corresponding transition state TS-(*S*)-*pro-R*-**13** (middle), and the corresponding lithioethyl carbamate (S_{Li},*R*)-**14** (right) (B3LYP/6-31G*).

TABLE 2. Calculated Dihedral Angles (H_3C-CH_2-O−C) of the Carbamate Moieties for the (−)-Sparteine Precomplexes 13, the Transition States TS-13 and the Lithioalkyl Carbamates 14 [°](B3LYP/6-31G*)

Precomplexes **13**		Transition States **TS-13**		Lithioalkyl carbamates **14**	
(R)-pro-S	168.9	*(R)-pro-S*	178.0	(R_{Li},S)	129.0
(S)-pro-S	164.2	*(S)-pro-S*	175.1	$(S_{Li}\text{-}S)$	128.3
(R)-pro-R	−120.5	*(R)-pro-R*	−141.6	(R_{Li},R)	−140.5
(S)-pro-R	−104.6	*(S)-pro-R*	−98.8	(S_{Li},R)	−140.0

of the lithiated products of this deprotonation step, the lithio carbamates **14**, are obviously governed by other stereochemical influences. Wiberg and Bailey found for the enantioselective deprotonation of Boc-pyrrolidine also that the best precomplex (with the *pro-S* proton pointing to the base) leads to the energy lowest transition state of the deprotonation reaction.[14]

Besides the energies of the species studied here some structural features deserve interest. Detailed analysis has convinced us that it is not possible to reduce the observed stereochemical outcome to simple geometrical features of the precomplexes or the transition states. Therefore, we concentrate our discussion on the coordination sphere around the lithium ion and on the migrating proton (Table 4 of the Supporting Information). For the precomplexes **13**, we find very similar calculated distances between Li^+ and the basic center of the isopropyl group (2.151−2.157 Å), whereas the Li−O distances to the carbonyl group of the carbamate vary more (2.126−2.234 Å). Two different sets of Li−N distances are found ranging from 2.212 to 2.230 Å for the shorter contact to the nitrogen atom (N_{cis}) of the cis-annulated piperidine ring of (−)-sparteine to 2.262−2.281 Å for the longer contact to the nitrogen atom (N_{trans}) of the trans-annulated piperidine ring.

Similarly, in the calculated transition states TS-**13** the Li−O distances vary from 1.928 to 1.973 Å and the Li−N_{cis} contacts from 2.157 to 2.272 Å (short contact) and Li−N_{trans} 2.231−2.391 Å (long contact). The migrating proton is generally closer to the base (1.434−1.461 Å) compared to the distance to the carbamate (1.468−1.488 Å) reflecting a late transition state. Interestingly, the lithium ion is actively involved into the proton transfer, indicated by Li−H distances of 1.891−2.021 Å.

The products of the deprotonation reaction, the lithioalkyl carbamates **14** (still coordinated to (−) sparteine and weakly bound to propane), are characterized by less variable bond distances. Thus, we found very similar Li−C (2.102−2.113 Å) and Li−O (1.921−1.923 Å) distances. The Li−N contacts amount to 2.126−2.149 Å (Li−N_{cis}, short contact) and 2.137−2.157 Å) (Li−N_{trans}, longer contact). Interestingly the C−O bond in the carbamate is lengthened to 1.549−1.551 Å as a result of the unfavorable oxygen lone pair−carbanion interaction.[25]

In comparison to (−)-sparteine (**5**) as chiral chelating ligand, *trans*-1,2-bis(*N*,*N*-dimethylamino)cyclohexane (**7**), which we have studied previously,[6] is a significantly less potent inductor for chirality (see also ref 13). DFT-B3LYP/6-31G* calculations for the same ethyl carbamate as studied here with this ligand produce a difference in transition state energies of only 0.6 kcal/mol. Interestingly, here in both transition states the carbamate adopts the same conformation, but the base attacks from the two diastereotopic faces. This is quite in contrast to the deprotonation process involving (−)-sparteine (see above).

We have also included (−)-α-isosparteine (**6**) as chiral additive for the proton abstraction from **12** in this study (Scheme 4). A comparison of Table 2 ((−)-sparteine) with Table 3 with respect to the energies of the transition states TS-**13** and TS-**15** clearly indicates, that **6** is predicted to favor the *pro-R*-proton abstraction, in contrast to (−)-sparteine (**5**), which favors the *pro-S*-deprotonation. The stereoselection seems to be smaller than with (−)-sparteine as the difference of the activation energies for the two reaction channels amounts only to 1.20 kcal/mol (Figure 3). The formation of the precomplex **15** from (−)-α-isosparteine and *i*PrLi and the carbamate is by 4−6 kcal/mol less exothermic than that of the corresponding sparteine system **13**. However, the barriers for deprotonation are similar, as are the relative energies of the lithium compounds **16** after the abstraction. Here, we do not see a strong parallelism of the conformations

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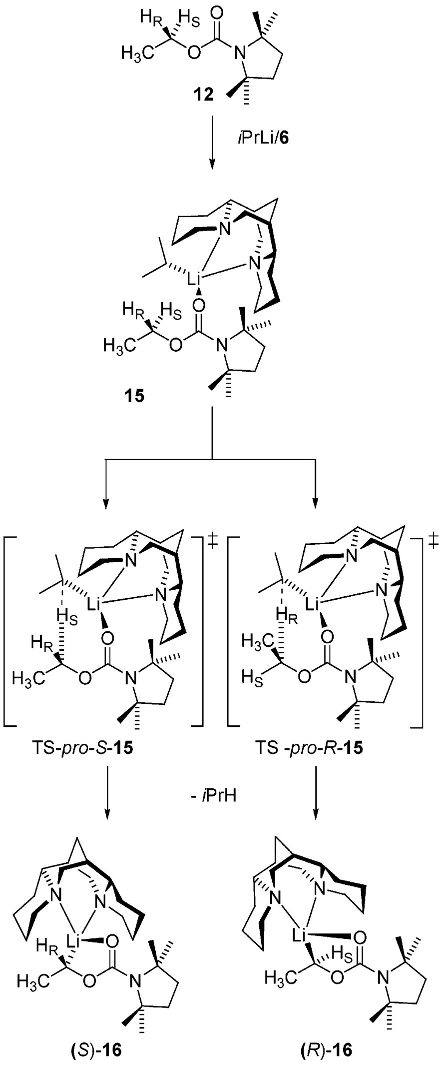
TABLE 3. Deprotonation of Ethyl Carbamate 12 Using (−)-α-Isosparteine (6) as Ligand (Including Zero Point Energy)[Kcal/Mol]: Precomplexes 15, Transition States TS-15 and Lithio Carbamates 16 (the Energy Lowest Species are Printed in Bold)

Precomplexes **15**			Transition States **TS-15**				Lithio carbamates **16**	
Stereonotation	$E_{Precomplex}$[a]	$E_{rel\ \mathrm{Precomplex}}$	Stereonotation	E_{TS}[a]	$E_{rel\ \mathrm{TS}}$	E_{act}[b]	Stereonotation	$E_{Product}$[a]
pro-R	**−34.90**	**0.00**	***pro-R***	**−19.36**	**0.00**	**15.54**	*(R)*	−59.39
pro-S	−34.27	0.62	*pro-S*	−18.16	1.20	16.74	*(S)*	**−59.49**

SCHEME 4



(for dihedral angles see Table 4) of the carbamate moiety in the precomplexes **15** and transition states TS-**15**.

The inspection of the bond distances reveals some distinct differences between both systems. (Table 5 of the Supporting Information) In the (−)-α-isosparteine precomplexes **15**, the distances of Li^+ to the basic center are significantly longer (2.183−2.193 Å), and the Li−N contacts are even longer (2.286−2.313 Å, short contact; 2.453−2.512 Å, long contact) compared to the corresponding distances in **13**. This might be the reason for the less exothermic coordination of (−)-α-isosparteine. The same is true for the transition states TS-**15**, where again the Li−N contacts are longer compared to the ones in the (−)-sparteine systems TS-**13**. The distances of the migrating proton to the carbon atoms, however, are similar in both systems. Different from the (−)-sparteine precomplexes **13**, the conformation of the carbamate moiety is significantly changed by going from the precomplexes **15** to the transition states TS-**15** (Table 4). In contrast, for the lithiated carbamates **16** the Li−N bonds are only slightly longer compared to those in **14**, the other corresponding bonds are similar in length. It is outside of the scope of this study whether other factors, like instability of the precomplex under the reaction conditions, may be responsible for the experimental failure of such reactions.

TABLE 4. Calculated Dihedral Angles of the Carbamate Moieties for the (−)-α-Isosparteine Precomplexes 15, the Transition States TS-15 and the Lithioalkyl Carbamates 16 [°](B3LYP/6-31G*)

Stereonotation	Precomplexes **15**	Transition states **TS-15**	Lithio carbamate **16**
pro-R	−155.6	179.2	−144.6
pro-S	148.4	163.6	127.8

Removal of an Allylic Proton: (1-Cyclohexenyl)-methyl Carbamate/(−)-Sparteine/*i*PrLi. As a second, more complex system we studied the deprotonation reaction of (1-cyclohexenyl)methyl carbamate **17** by computational methods. The corresponding compounds **9a** and the methyl-substituted derivative **9b** had been subject of a thorough experimental study.[22] The aim of this study was to elucidate any special properties of such allylic lithium compounds in comparison to the alkyl system (see above). Allyllithium compounds are known for their ability to form π-bonded complexes in addition to their possibility for σ-bonding as in alkyl systems.[26]

The computational treatment of these systems was performed in a similar manner as that of the simpler ethyl carbamates **12** described above, using the model system **17**. However, due to the conformational properties of the cyclohexenyl moiety, it was necessary to consider two conformations, resulting from rotation about the methylene-cyclohexenyl bond, which are denoted *endo* and *exo* with respect of orientation of the C=C double bond (allylic moiety) in the ring relative to the oxygen atom of the carbamate unit. On the other hand, for CPU time considerations, we included only the R_{Li} orientation of the carbamate to the (−)-sparteine ligand, which is lower in energy in the ethyl case (see above) (Scheme 5, Figures 4 and 5).

Not surprisingly, the calculated complexation energy for **17** to form the precomplexes **18** is similar to the ethyl system **12** (Table 5) with values ranging from −38.2 to −40.5 kcal/mol (relative energy with respect to the sum of the (−)-sparteine−*i*PrLi complex + the carbamate **17**). Again, the different conformers **18** are assumed to be in fast equilibrium, thus efficiently populating the energy

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[26] Schlosser, M.; Desponds, O.; Lehmann, R.; Moret, E.; Rauchschwalbe, G. *Tetrahedron* **1993**, *49*, 10175−10203.

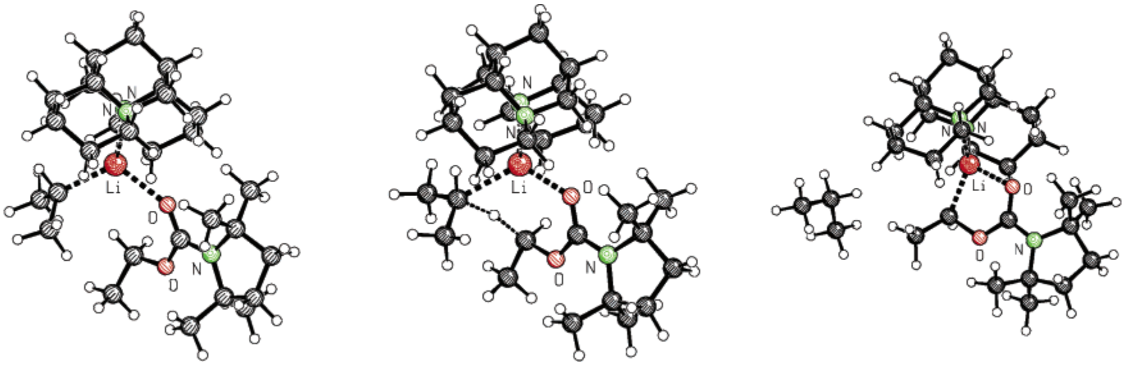


FIGURE 3. (−)-α-Isosparteine (**6**)/i-PrLi/ethyl carbamate precomplex lowest in energy **pro-R-15** (left), the corresponding transition state **TS-pro-R-15** (middle), and the corresponding lithioethyl carbamate (*R*)-**16** (right) (B3LYP/6-31G*).

TABLE 5. Relative Energies of (−)-Sparteine/*i*PrLi/Carbamate Precomplexes 18, of the Corresponding Transition States TS-18 and of the Resulting Lithio Carbamates 19 (v.d.Waals Complexes with Propane)

Precomplexes 18			Transition States TS-18				Lithio carbamates 19	
Stereonotation	$E_{Precomplex}$[a]	E_{rel} Precomplex	Stereonotation	E_{TS}[a]	$E_{rel\ TS}$	E_{act}[b]	Stereonotation	$E_{Product}$[a]
pro-S-endo	−38.80	1.65	***pro-S-endo***	−28.94	0.73	11.51	***(S)-endo***	**−68.06**
pro-S-exo	**−40.45**	**0.00**	**pro-S-exo**	**−29.67**	**0.00**	**10.78**	*(S)-exo*	−65.11
pro-R-endo	−38.36	2.10	*pro-R-endo*	−28.97	0.70	11.48	*(R)-endo*	−67.60
pro-R-exo	−39.51	0.94	*pro-R-exo*	−25.52	4.15	14.93	*(R)exo*	−64.84

The energy lowest systems are printed in bold. (incl. Zero Point Energy (ZPE)) [kcal/mol]. [a] Relative to the (−)-sparteine-*i*PrLi-complex + (cyclohexenyl)methyl carbamate **17**. [b] Relative to the best precomplex ***pro-S exo*-18**.

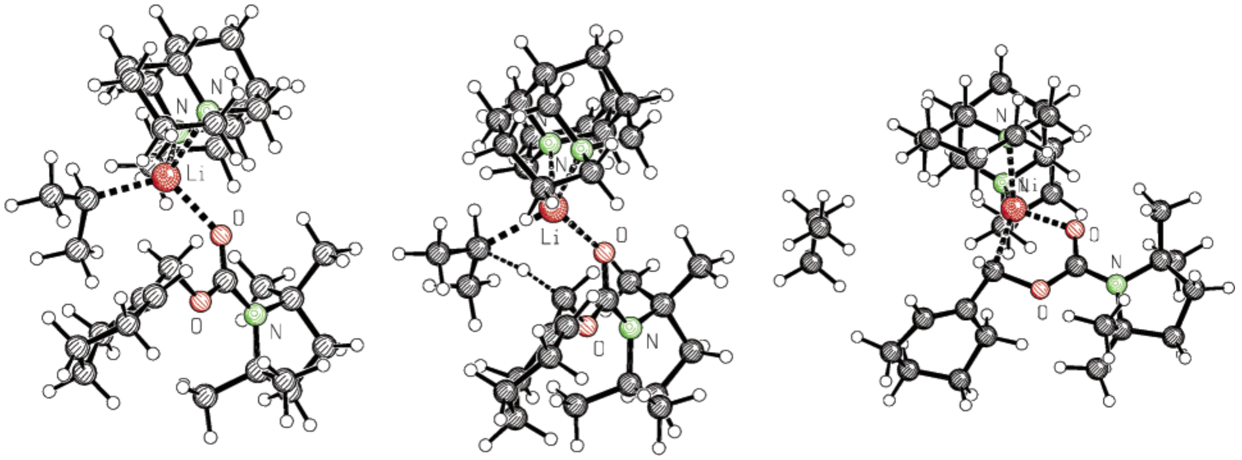


FIGURE 4. (−)-Sparteine/*i*-PrLi/cyclohexenylmethyl carbamate precomplex lowest in energy *pro-S-exo*-**18**, left), the corresponding transition state TS-*pro-S-exo*-**18** (middle), and the corresponding lithiocyclohexenylmethyl carbamate (*S*)-*exo*-**19** (right) (B3LYP/6-31G*).

lowest conformer *exo,pro-S*-**18** (−40.45 kcal/mol). The calculated transition states are significantly lower in energy than in the ethyl case by 2−3 kcal/mol, indicating a faster deprotonation reaction, as expected for allylic deprotonation due to the greater acidity of allylic protons in **17** compared to alkyl protons in **12** (see above). The topology of the energetically lowest transition state TS-*exo-pro-S*-**18** (−29.67 kcal/mol) is found to correspond to that of the energetically lowest precomplex *exo-pro-S*-**18**, i.e., to the removal of the *pro-S* proton (Table 6). However, the transition state of lowest energy for a *pro-R* deprotonation TS-*endo-pro-R*-**18** is only higher in energy by 0.7 kcal/mol. From these data, a less efficient stereodifferention between the two prochiral protons is derived, exactly as was found experimentally (76:24).[22]

Four different lithio carbamates **19** were found as products of the deprotonation reaction. The energy lowest diastereomer corresponds to a removal of the *pro-S* proton from the *endo*-orientation of the cyclohexenyl moiety, but not from the *exo* form, which was lowest in energy in the precomplex and in the transition state. Hence, here again the thermodynamics of the lithiated carbamates do not reflect the rates of the deprotonation reaction. We are dealing here again with a strongly kinetically controlled reaction pathway.

The structural parameters for the lithium environment in the four precomplexes **18** resemble very much those calculated for the ethyl species (**13**) (Table 6 of the Supporting Information). Thus, the Li−C_{base} bond shows a similar length, and the Li−O-bond is only slightly shorter than for the ethyl compound as is one of the two Li−N-distances.

This similarity does not apply to the transition states TS-**18** and to the lithio carbamate structures **19**. Al-

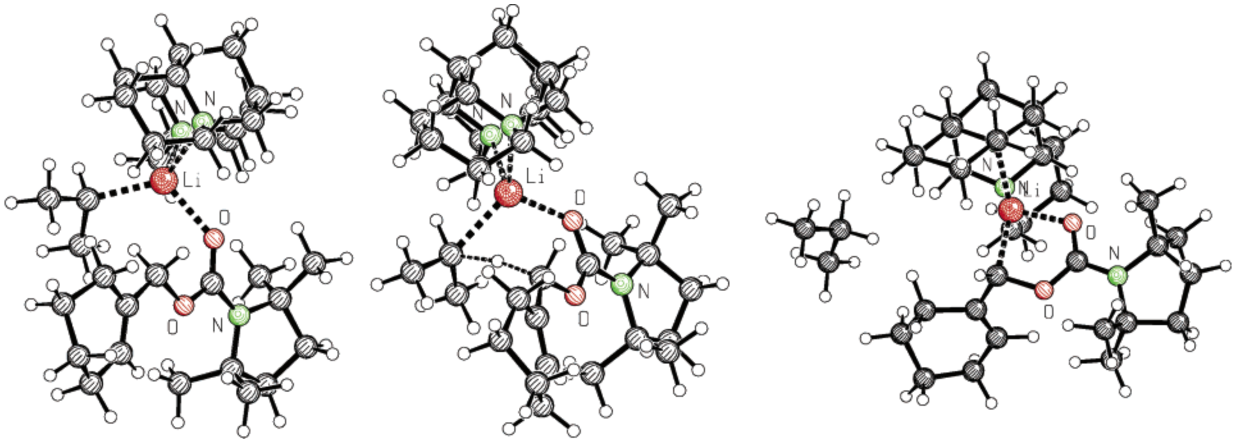
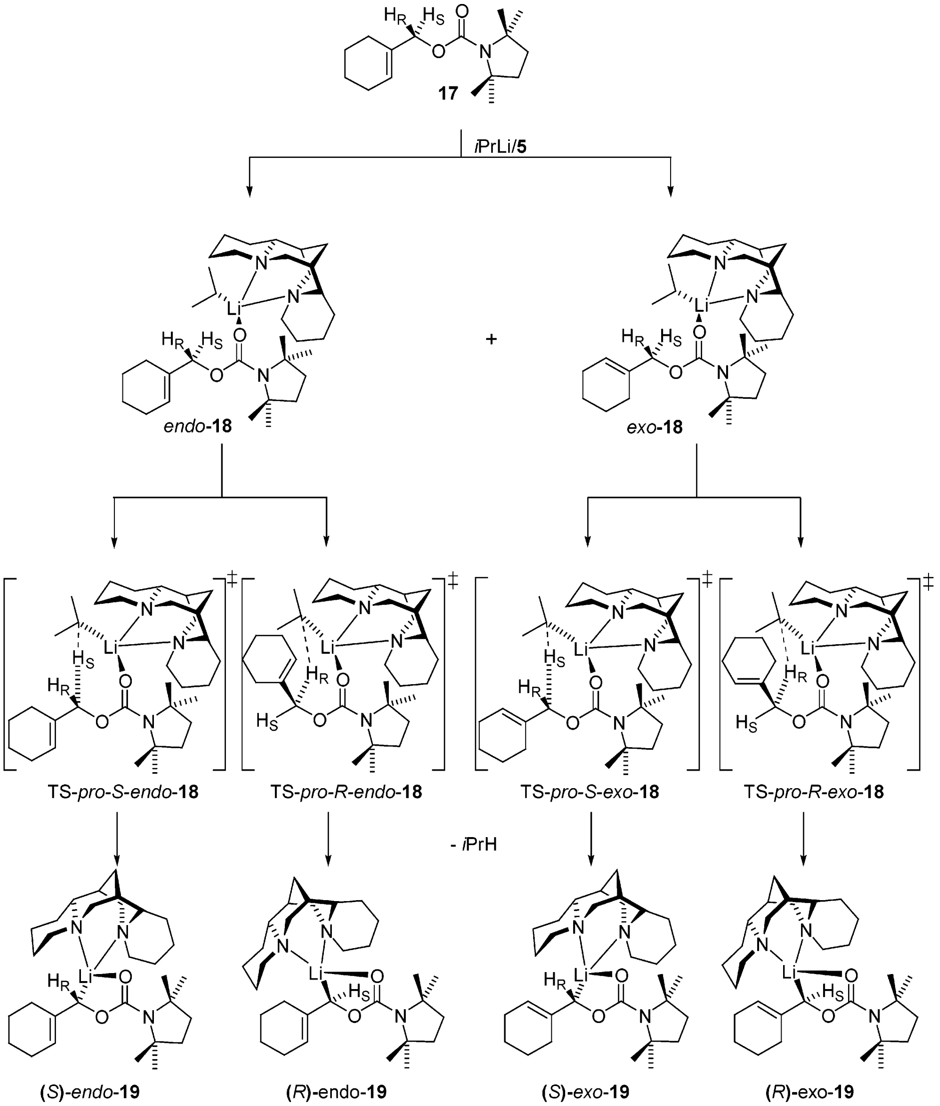


FIGURE 5. (−)-Sparteine/*i*-PrLi/cyclohexenylmethyl carbamate precomplex *pro-S-endo*-**18**, (left), the corresponding transition state TS-*pro-S-endo*-**18** (middle), and the corresponding lithiocyclohexenylmethyl carbamate *(S)-endo*-**19** (right) (B3LYP/6-31G*).

SCHEME 5

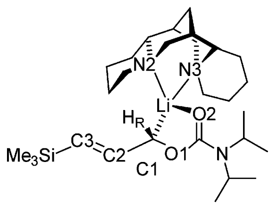


though at first view the lithium ion seems to be just monocoordinated to the C1-carbon atom of the (cyclohexenyl)methyl moiety as in **14** (vide supra), there are still various structural indications for an involvement of allylic interactions in the transition states and in the ground states of the lithio carbamates. The main difference in the transition states is seen in the C−H distances involving the migrating proton. Here, we find a short separation of this proton from the carbamate (1.423−1.433 Å) and a longer distance to the base (1.492−1.494

TABLE 6. Calculated Dihedral Angles I (−CH=C−CH$_2$-O-) and II -(C−CH$_2$-O−C-) of the Cyclohexenyl-methyl Carbamate Moieties for the (−)-Sparteine Precomplexes 18, the Transition States TS-18 and the Lithio Carbamates 19 [°](B3LYP/6-31G*)

	Precomplexes **18**		Transition States **TS-18**			Lithio carbamates **19**	
Stereonotation	I	II	I	II	Stereonotation	I	II
pro-S-endo	−9.4	179.9	−20.3	−174.1	*pro-S-endo*	−29.0	130.6
pro-S-exo	113.1	175.0	129.5	−171.2	*pro-S-exo*	130.0	134.1
pro-R-endo	20.1	−115.6	28.5	−102.8	*pro-R-endo*	24.9	−138.0
pro-R-exo	−111.1	170.2	−143.8	−103.3	*pro-R-exo*	−138.2	−132.5

SCHEME 6



20

TABLE 7. Comparison of Geometrical Parameters of 20 (X-ray) and *(S)-endo*-19 (Calculation) (Numbering According to Ref 27)

Parameter	**20** (X-ray)	***(S)-endo*-19** (DFT)
Li−C1	2.207(9)	2.148
Li−N2	2.075(8)	2.158
Li−N3	2.017(8)	2.121
Li−O2	1.899(8)	1.919
C1−C2	1.392(6)	1.468
C2−C3	1.362(6)	1.354
C1−O1	1.476(6)	1.508
C=O2	1.239(5)	1.253
Li1−C1−C2−C3	91.7(6)	85.3

Å), just opposite to the ethyl carbamate case. This is well described by an early transition state, where the maximum of energy is reached already at a relatively short elongation of the C−H bond. This is clearly an indication of a developing allylic interaction. The Li−O and Li−N bonds react less sensitive and show comparable parameters as found in the ethyl case. Finally, in the lithioalkenyl carbamates **19** relatively long C−Li bonds and (more or less) perpendicular positions of the lithium ion with respect to the plane of the allyl system are, together with a shortened C−O-bond, well compatible with an allylic subunit. As in the alkyl carbamates, the dihedral angles of the precomplexes **18** show much similarity to those of the transition states (Table 6), especially for the (*pro-S*)-species, whereas the products **19** display differing conformations.

It is of interest to compare the calculated structure of the lithio(cyclohexenyl)methyl carbamates **19** with the published X-ray diffraction study of a 1-lithio-3-trimethylsilylallyl carbamate **20** (Scheme 6, Table 7).[27] Although the allyl systems differ in substitution pattern, some common features between **20** and its closest analogue (*S*)-*endo*-**19** may be derived. In both cases, the lithium ion is located in an almost perpendicular position to the allyl plane. **20** displays more allylic character compared to (*S*)-*endo*-**19**, due to the anion stabilizing effect of the trimethylsilyl group, as seen in the less pronounced bond alternation. In general, the Li−N contacts are shorter in the crystal than calculated, whereas the Li−C1 bond is longer in the solid state.

Conclusion

The results presented here show clearly that modern quantum chemical methods have the potential to gain valuable insight even in such delicate chemical problems as enantioselective synthesis of relatively large systems (ca. 100 atoms), here the chiral ligand-assisted lithiodeprotonation reaction of carbamates. Important synthetic intermediates such as the organolithium compounds of this study may be reliably modeled, provided they are monomeric and solvent influences can be excluded. We have been able to study important steps within the reaction cascade, namely the diastereoselective formation of precomplexes and the hydrogen transfer reaction via a well localized transition state resulting finally in the formation of the lithiated carbamates. In cases where experimental data were available, good agreement with experiment was observed, suggesting the use of such methods also for predictive studies. Thus, the performance of (−)-sparteine in comparison to (−)-α-isosparteine may be understood on the basis of their different complexation behavior, and the electronic influences of an allylic system came out clearly in comparison to simple alkyl derivatives. For the future, we suggest further studies in this field paralleling the growing information becoming available from experimental studies. In this context, the next step, the electrophilic attack, which usually proceeds with retention of configuration, deserves also our computational interest.

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Supporting Information Available: Summaries of the quantum chemical calculations, i.e., total energies (E_{tot}), zero-point corrected energies (E (0 K)), relative energies (E_{rel}), reaction energies (E_{R}) and activation energies (E_{act}), selected geometrical information (6 tables) and GAUSSIAN ARCHIVE entries of the molecules studied. This material is available free of charge via the Internet at http://pubs.acs.org.

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