The Mechanism of the Stereospecific Intramolecular Arylation of Lithiated Ureas: The Role of Li⁺ Probed by Electronic Structure Calculations, and by NMR and IR Spectroscopy

Damian M. Grainger,^[a] Alison Campbell Smith,^[b] Mark A. Vincent,^[a] Ian H. Hillier,^{*[a]} Andrew E. H. Wheatley,^{*[b]} and Jonathan Clayden^{*[a]}

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In situ NMR and IR spectroscopy studies were carried out on the rearrangement of lithiated *N*-benzyl-*N'*-aryl ureas, which involves N-to-C aryl transfer with retention of configuration. The IR spectroscopy studies revealed that initial benzylic lithiation was followed by migration of the aryl ring to yield a lithiated urea product without a detectable dearomatised intermediate. Similar results were obtained by NMR spectroscopy, but when 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone (DMPU) was added to the solvent mixture, a transient dearomatised intermediate was detectable during migration of a 1-naphthyl ring. DFT calculations highlight the importance of coordinated lithium cations, and their migration from one site to another, in the rearrangement. Rearrangement is initiated by migration of a solvated lithium cation from the anionic centre of the starting organolithium

Introduction

The construction of quaternary centres^[1] adjacent to nitrogen^[2-4] or oxygen^[4,5] is a challenge that has been met in a number of ways, primarily by the addition of nucleophiles to one of the enantiotopic faces of a ketone or imine.^[3-6] Such an approach fails when the two substituents flanking the ketone or imine are sterically and electronically similar, and in these cases stereospecific construction of the quaternary centre from a pre-existing tertiary centre is an appealing alternative. Carbamate derivatives 1 of benzylic secondary amines^[7,8] or alcohols^[9,10] may be deprotonated to give configurationally stable lithio derivatives 2, which react with electrophiles either with retention or inversion,^[11] allowing the formation of quaternary centres in the products 3 (Scheme 1).^[12,13] Aggarwal et al. have extended the utility of the lithiated carbamates of secondary benzylic alcohols by showing that they may be transformed into tertiary alcohols and amines 4 through the addition and rearrangement chemistry of boron derivatives.^[14]

to a site close the adjacent phenyl ring, allowing retentive attack of the anionic centre on the more remote ring with movement of the solvated lithium cation to the remote ring stabilising the developing negative charge. A short-lived spirocyclic intermediate is predicted to undergo elimination by loss of the urea substituent, completing the migration. Coordination of the carbonyl group to a second solvated lithium cation appears to be essential for this step. Calculated shifts for this intermediate when a 1-naphthyl ring is migrating are consistent with the transient signals observed by NMR spectroscopy. Alternative pathways involving (1) invertive migration and (2) attack on the urea C=O group were also calculated and were found to require significantly higher energy transition states.

In complementary experimental work, we have shown that, when carbamates carry an N'-aryl substituent, the lithio derivatives (formed with either alkyllithiums or N-lithioamines) of benzylic ureas^[15,16] 5 and carbamates^[17,18] 6 undergo a remarkable $N \rightarrow C$ aryl migration (Scheme 2). Furthermore, related reactions occur with allylic ureas,^[19] cyclic ureas,^[20] lithiated ureas generated by carbolithiation,^[21] and benzylic thiocarbamates.^[22] Conversion of the rearranged ureas 7 or carbamates 8 into the amines 9 or alcohols 10 results in an overall stereospecific arylation of an α -methylbenzylamine or α -methylbenzyl alcohol derivative. However, the rearrangements of ureas and carbamates differ from one another in one very important respect: the aryl migration within the urea proceeds with retention of stereochemistry at the migration terminus,^[15] whereas the aryl migration within the carbamate proceeds with inversion of stereochemistry at the migration terminus.^[18] Chiral benzyllithium derivatives are known to react with electrophiles with erratic stereospecificity (retentive S_E 2ret or invertive S_E 2inv),^[10-12] and while the detailed stereochemical pathways by which such stereospecific electrophilic substitution reactions proceed are yet to be fully clarified, it is generally clear that Lewis base electrophiles capable of coordination to lithium favour retentive over invertive substitution.^[12]



 [[]a] School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK Fax: +44-161-275-4939
 E-mail: clayden@man.ac.uk
 [b] University Chemistry Laboratory

[[]b] University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK



Scheme 1. The synthesis of quaternary centres adjacent to N or O by lithiation of ureas and carbamates. For simplicity, external solvation of Li^+ is not detailed.



Scheme 2. The synthesis of quaternary centres adjacent to N or O by intramolecular aryl migration in lithiated ureas and carbamates. For simplicity, external solvation of Li^+ is not detailed.

Herein, we report electronic structure calculations and in situ IR and NMR spectroscopic studies aimed at the elucidation of the pathway by which the 1,4-aryl migrations of the lithiated ureas shown in Scheme 2 take place. In particular, the reason for the retention of stereochemistry during migration in ureas is addressed.

Results and Discussion

Experimental Evidence for the Mechanism of Aryl Migration

Previous work showed unequivocally that the rearrangement illustrated in Scheme 2 is an intramolecular process.^[15] Furthermore, evidence from the trapping of a dearomatised intermediate during migration of a naphthalene ring^[15] led us to propose that the rearrangement of lithiated ureas proceeds through the pathway illustrated in Scheme 3, in which nucleophilic attack of the organolithium centre in the reactive conformation **12Li** on the aryl ring generates the spirocyclic structure **13Li**. For simplicity, ligated solvent is not included in the structures. Subsequent elimination of the lithiated urea substituent restores aromaticity and provides a product **14Li**, which gives **9** upon protonation. The reactive conformation **12Li** cannot benefit from the intramolecular Li–O coordination typical of lithiated carbamates,^[23] and we assume that it is formed during the reaction pathway by C–N rotation from structure **5Li**, intramolecularly coordinated in the manner typically postulated for such structures.^[24]

The existence of the dearomatised spirocyclic intermediate **13cLi** was confirmed by air oxidation of the reaction mixture produced during migration of the 1-naphthyl ring of **5c**, from which the enone **16** was isolated.^[15] However, the general intermediacy of a dearomatised spirocycle **13Li** could not be proved, with attempts to trap similar structures during the migration of non-naphthyl rings being unsuccessful.^[25]

NMR Spectroscopic Studies

The lithiation and rearrangement of **5** to **9** occurs in THF, but is accelerated considerably by the addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU).^[15] By carrying out the rearrangement in an NMR tube in the presence or absence of DMPU, we were able to elucidate some details of the structures of intermediates in the conversion of **5** to **9**. These NMR spectroscopy



Scheme 3. Schematic pathway for aryl migration. For simplicity, external solvation of Li⁺ is not detailed.

studies were carried out by using 5b and 5d as substrates to allow the two aryl rings of the substrate to be readily distinguished.

Ureas 5b (Figure 1) and 5d (Figure 2) were each dissolved in THF in an NMR tube and cooled to -78 °C. sBuLi was added and the mixture was agitated and immedi-



Figure 1. ¹H NMR spectrum of **5b** (a) with sBuLi in THF, -40 °C, assigned to the structure **5bLi** and (b) with sBuLi and DMPU in THF, -40 °C. Signals marked with an asterisk are assigned to a THF decomposition product.



Figure 2. ¹H NMR spectrum of **5d** (a) with *s*BuLi in THF, DMPU, -40 °C, presumed to arise from the structure **14bLi**; (b) with *s*BuLi and DMPU in THF, -40 °C; and (c) with *s*BuLi and DMPU in THF after warming to room temperature. Signals marked with an asterisk are assigned to a THF decomposition product.

ately transferred to the NMR probe at -40 °C. Figure 1 (a) shows a portion of the spectrum obtained when using **5b**. Characteristic signals shifted upfield from the aromatic region indicate that complete lithiation of the substrate **5b** has given benzyllithium **5Li**.^[26] Delocalisation of charge into the ring accounts for the chemical shifts of the MeOC₆H₄ aryl protons in the region of $\delta = 6-7$ ppm and the partial double bond between the anionic centre and the ring results in doubling up of those signals. The signals between $\delta = 5.9$ and 4.8 ppm marked with asterisks appear to arise from the in situ elimination of lithiated THF to yield lithium but-3-ene 1-oxide, which is not the usual THF decomposition pathway,^[27] but one that has previously been observed in the presence of electron-rich ligands [hexameth-ylphosphoramide (HMPA) and DMPU].^[12,28]

Carrying out the same procedure with **5b** in an NMR tube, but now in the presence of DMPU (6 equiv.) gave a very different spectrum, as shown in Figure 1 (b). Immediately after transfer of the mixture to the NMR probe, broad signals were obtained, mainly in the aromatic region ($\delta = 6.5-7.5$ ppm). Clearly, no **5bLi** remains in the mixture, but there is also no evidence for dearomatised structure **13bLi**.

The spectra obtained from **5d** are more informative. Figure 2 (a) illustrates the result of lithiating **5d** in the absence of DMPU: as with **5b**, the upfield shift out of the aromatic region indicated complete benzylic lithiation. On lithiation in THF/DMPU – see part b of Figure 2 – a total of eleven new sharp signals immediately become evident between δ = 6.2 and 9.5 ppm, superimposed upon a much broader set

of signals at $\delta = 6.5$ –8.0 ppm. Slow warming of the reaction mixture in the NMR tube led to disappearance of the sharpened signals (Figure 2c), leaving only the broad signals at $\delta = 6.5$ –8.0 ppm similar to those seen when using **5b**. We assume that these broad signals arise from the lithiated products **14Li**, which are probably aggregated in solution. The sharp signals in part b of Figure 2, on the other hand, must arise from an intermediate en route to **14Li**, which we presume to be **13dLi**. Eleven signals in the region above δ = 6.0 ppm might be expected for this structure, although individual assignments, except for the remarkably deshielded multiplet at $\delta = 9.5$ ppm (see below), could not be made.

In-situ IR Spectroscopy

The rearrangements of **5a** and **5c** were followed by in situ IR spectroscopy in THF. A mixture of **5a** or **5c** and THF in a three-necked flask equipped with a ReactIR probe was cooled to -60 °C. Once the temperature had stabilized, spectroscopic analysis was commenced at a rate of one scan every 15 s. The initial spectrum was recorded, before *s*BuLi (1.43 mL, 1.4 M in cyclohexane, 2 mmol) was added. The reaction mixture was stirred at this temperature until the spectrum had stabilized and was then warmed in stages to -40, 0 and finally to 25 °C; at each stage the spectrum was allowed to stabilize if necessary before further warming. Once a stable spectrum was collected.



Figures 3, 4 (for the rearrangement of **5a**), 5 and 6 (for the rearrangement of **5c**) show the characteristic regions of the spectra where changes were observed. Both ureas show an initial strong signal at 1645 cm⁻¹ (blue lines in Figures 3 and 5) characteristic of a urea. In each case, the addition of *s*BuLi causes a shift of this carbonyl absorption to give a double peak (green line in Figures 3 and 5) centred approximately at 1605 cm⁻¹, which we consider arises from the initial lithiated species **5aLi** and **5cLi**, or **12aLi** and **12cLi**. Recently reported in situ IR studies of the lithiation of a carbamate directly observed the "pre-lithiation complex" between the substrate and lithiating agent,^[29] the existence of which had previously been deduced by kinetic studies on a related compound.^[30] However, with ureas **5a** and



Figure 3. Characteristic changes in the $1700-1500 \text{ cm}^{-1}$ region of the IR spectrum during rearrangement of **5a**. Four spectra taken at different stages in the experiment are overlaid, with the time elapsed at the point of observation of each spectrum given (h:min:s). Blue (00:00:53): urea prior to lithiation; green (00:07:28): after addition of *s*BuLi at -60 °C; red (01:44:14): after warming to 0 °C; pink (02:32:23): immediately after addition of MeOH at 25 °C.



Figure 4. Perspective view of the changes in the IR spectrum during the rearrangement of 5a.

5c we were unable to detect any transient intermediates between **5** and **5Li**.

Warming both samples led to a further significant change in the region illustrated in Figures 3 and 5, with a new strong signal forming close to 1575 cm^{-1} (red line), accompanied by a signal close to 1350 cm^{-1} (not illustrated). No further change was seen in either spectrum until

the reactions were quenched with MeOH, and we assume that the strong signals in the region of 1350 and 1575 cm⁻¹ arise from C–O and C–N stretches within the lithio urea function of rearranged compounds **14aLi** and **14cLi**. Despite the evidence described above and that reported previously^[15] for the intermediacy of a dearomatised intermediate **13Li** in the rearrangement of **5d**, no other intermedi-



Figure 5. Characteristic changes in the $1700-1500 \text{ cm}^{-1}$ region of the IR spectrum during rearrangement of 5c. Four spectra taken at different stages in the experiment are overlaid, with the time elapsed at the point of observation of each spectrum given (h:min:s). Blue (00:03:49): urea prior to lithiation; green (00:07:49): after addition of *s*BuLi at -60 °C; red (01:24:54): after warming to 0 °C; pink (02:31:54): immediately after addition of MeOH at 25 °C.



Figure 6. Perspective view of the changes in the IR spectrum during the rearrangement of 5c.

ate was detectable in the IR studies. This difference may be due to the use of DMPU to increase the rate of the reaction in the NMR spectroscopy studies – it is possible that intermediate **13Li** is an observable intermediate only in the presence of DMPU. Figures 4 and 6 illustrate the changes in the spectrum at each stage in the reaction.

Computational Studies

To illuminate further the pathway by which aryl migration occurs in these systems, and the reasons for its remarkable favourability, we have used electronic structure calculations to explore the mechanism outlined in Scheme 3, in which the lithiated carbanion **12Li** undergoes a 1,4-aryl shift to form **14Li** where the negative charge is located, at least formally, at oxygen. Such charge migration is expected to be facilitated by lithium cations, which are thus expected to undergo considerable movement during the course of the reaction. We also studied the corresponding 1,2-acyl shift reaction to give **15Li** with a view to understanding why this usually favourable reaction does not occur.

Computational Details

Our computational strategy was to explore the mechanism whereby the 1,4-aryl transfer occurs by employing DFT calculations of realistic clusters, involving the reactant 5 in the form of its benzylic anion interacting with species constructed from Li⁺, THF and a strong base to model the environment during rearrangement. We have employed several different models to try to understand the mechanism, given that there is considerable uncertainty in both the position and degree of coordination of the Li⁺ species. Structures were optimized at the B3LYP/6-31G and B3LYP/ 6-31++G** levels to obtain properly characterized minima and transition-state (TS) structures. To study the potential energy surfaces associated with these different models, our strategy was to locate the appropriate TS structures and then to follow each structure back and forward to obtain the corresponding reactant and product structures.

Harmonic frequencies were computed at the B3LYP/6-31G level and the resulting thermodynamic corrections (including zero-point effects) were combined with the electronic energies determined with the larger basis set to yield free energies. We have also examined the effect of using one of the newer functionals designed by Truhlar and Zhao.^[31] Thus, we used the B3LYP/6-31++G** optimal structures to determine single-point energies at the M06-2X /6-31++G** level and corrected these to give free energies as before. As far as bulk solvation is concerned, we decided, following the work of Streitwieser and co-workers,^[32] to ignore bulk solvation effects. They found that the integral equation polarisable continuum model (IEPCM) was poor at predicting the solvation energies of a range of organic species in THF, whilst with no bulk solvation the pK(Li) values of a range of lithium compounds can be well predicted.



As an aid to the assignment of the in situ ¹H NMR spectra reported above, ¹H chemical shifts were determined by the gauge-independent atomic orbital (GIAO) approach,^[33] using the 6-31++G(d,p) basis. All calculations were carried out by using the Gaussian 03 program.^[34]

Computational Results

To gain some initial insights into various aspects of the mechanism, we employed a small model (M1) with methyllithium as the base, solvated by two THF molecules, to give a tetrahedral Li⁺ ion when coordinated to the carbonyl oxygen. The Li⁺ ion coordinated to the anionic centre is solvated by a single THF molecule. The lowest energy initial reactant structure located (R1; Figure 7, a) had this Li⁺ close to the carbanion centre (2.09 Å, Table 1). To study the 1,4-aryl shift, we determined the TS structure (TS1) using this model. The reaction involves the migration of the negative charge from the anion centre in the intermediate **12Li** to the oxygen (O⁻) centre of the product **14Li** and, as expected, the solvated Li⁺ cation facilitates this charge trans-



Figure 7. Stationary structures from model M1: (a) lowest energy reactant (R1); (b) TS structure for retention of configuration (TS1); (c) intermediate (I1); and (d) higher energy reactant (R2), leading to retention of configuration.

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Model	Stereochemistry	Structure	C ⁻ ···C _{phen}	Li+…C-	Li+Phen	N····C _{phen}
M1	retention	R1	3.21	2.09	3.46	1.39
		R2	3.18	3.56	2.30	1.40
		TS1	2.17	3.33	2.72 (L), 2.80 (A)	1.46
		I1	1.58	3.53	2.32	1.52
		TS2	1.53	3.43	2.34	2.35
M2	retention	R2	2.92	4.09	2.55	1.43
		TS1	2.12	3.87	3.09 (L), 3.45 (A)	1.47
		I1	1.62	3.81	2.51	1.53
		TS2	1.57	3.81	2.50	2.11
M3	retention	R2	2.97	5.48	3.31	1.43
		TS1	2.02	5.26	3.50 (L), 4.98 (A)	1.48
		I1	1.61	4.46	3.57	1.55
M2	inversion	R1	3.04	2.27	3.13	1.44
		TS1	1.88	2.80	3.42	1.52
		Р	_	_	_	_
M3	inversion	R1	2.90	4.00	3.05	1.44
		TS1	1.62	4.97	3.45	1.77
		Р	1.56	4.32	Li ⁺ Bonded to N ⁻	3.27

Table 1. Interatomic distances [Å] in stationary structures.^[a]

[a] C_{phen} is the carbon atom that is attacked by C⁻ of the carbanion centre, N is the nitrogen atom not bound to C⁻, and Li⁺ is the labile lithium ion. Phen indicates one or other of the phenyl rings. Li⁺···Phen are average distances of the lithium ion to the carbon atoms of the phenyl ring. In some TS structures the lithium cation is passed from one phenyl ring to the other; L and A label the ring the cation leaves and the one it arrives at, respectively.

fer, as shown by its considerable movement during the course of the reaction. TS1, which leads to the experimentally observed retention of configuration at the asymmetric centre, is shown in part b of Figure 7. In this structure, monosolvated Li⁺ has moved away from the carbanion centre, by 1.24 Å relative to its position in R1, and now resides between the two aromatic rings, at a distance of 2.7-2.8 Å from them (Figure 7, b, and Table 1), thus stabilizing the developing negative charge on the organic moiety of 13Li. TS1 now leads to a five-membered-ring intermediate (I1, Figure 7, c), corresponding to 13Li, which undergoes ring opening to complete the 1,4-aryl shift. In preliminary calculations involving a migrating naphthyl ring, we find a similar cyclic intermediate such as that found experimentally. Methyllithium now stabilizes the negative charge that develops on the carbonyl oxygen atom during the ring opening of the cyclic intermediate I1, and it was found to be essential to bring about completion of the reaction. Indeed, no TS could be located for ring opening without coordination of MeLi to the carbonyl group. Consistent with this observation are experimental observations that suggest yields from the reaction are highest when two equivalents of base are used. Nonetheless, this second equivalent of base is not consumed during the reaction and the IR experiments clearly show that only one equivalent of base is needed for complete consumption of starting material.

When TS1 was followed back to the reactant stage, the lowest energy structure (R1) was not obtained. Instead structure R2 (Figure 7d) was achieved, which was higher in energy than R1 by 14.6 kJ mol⁻¹ (Table 2). In structure R2, the Li⁺ cation is located further from the carbanion centre than in R1 and is now located close to the adjacent phenyl ring (2.3 Å) (Figure 7, d, and Table 1). We note that the movement of Li⁺ away from the stereogenic centre in R2 could potentially give rise to a stereochemically random or

invertive pathway. However, stereochemical integrity at the carbanion centre is retained because conjugation with the adjacent phenyl group gives rise to a partial double bond, which prevents loss of stereospecificity by rotation or inversion.

Table 2. Free energies $[kJ mol^{-1}]$, relative to the lowest energy structure (R1), of stationary structures on the potential energy surface for retention and inversion of configuration.

icture Free energy ^[4]
0.0
14.6
44.8
-30.5
23.5
18.0 (24.8)
51.9 (52.0)
-3.1 (-29.0)
30.9 (30.7)
18.8 (51.8)
61.2 (82.9)
48.8 (31.3)
0.0 (0.0)
84.5 (70.3)
0.0 (0.0)
79.4 (92.1)
-61.4 (-66.3)

[a] The values are for the B3LYP functional; those for M06-2X are given in parentheses.

The major conclusions from model M1 concerning the 1,4-aryl shift relate to the movement of solvated Li^+ during the course of the reaction. We have found that (1) the reactive structure (R2) of **12Li** has the solvated Li^+ positioned over the phenyl ring adjacent to the carbanion centre rather than over the carbanion centre itself where it is in the lower



energy reactant structure (R1); (2) TS1, which leads to the five-membered cyclic intermediate 13Li has the solvated Li⁺ located between the two aromatic rings; and (3) coordination of lithium to the carbonyl oxygen atom is essential for ring opening of 13Li to give the final product 14Li.

Having studied simple model M1, we next explored the use of larger models (M2, M3), which involve the base lithium diisopropylamide (LDA) in place of MeLi and more realistic solvation of Li⁺. LDA has been used experimentally as an alternative to alkyllithiums in rearrangements of more sensitive ureas,^[16,19] and is essential for stereospecific rearrangements of the corresponding 1,4-aryl shift in carbamates.^[17,18] We note that a crystal structure of an LDA-THF complex^[35] shows a dimer with each Li⁺ ion coordinated to a single THF molecule and sharing two amide ligands with the second lithium ion. In the system studied herein, the carbonyl oxygen replaces one of the THF molecules of this dimer. Our models involve one explicit LDA dimer coordinated to the carbonyl oxygen, with the assumption that a further molecule of base leads to deprotonation of the urea.

Despite the presence of LDA dimer coordinated to the carbonyl oxygen, the lithium cation associated with the carbanion centre is still expected to interact with the carbonyl oxygen. Thus, in models M2 and M3 the LDA dimer is coordinated through one of its lithium cations to the carbonyl oxygen and the third Li⁺ is coordinated to the carbanion centre and to other electron-rich moieties of the urea.

 Li^+ coordinated to the carbanion centre was solvated by two and three THF molecules in models M2 and M3, respectively.

We now describe the use of models M2 and M3 to probe both the observed reaction, leading to retention of stereochemistry, and also an alternative mechanism, leading to stereochemical inversion. We should comment here that, in all of the models proposed, we have taken the reactive structure to be **12Li**, in which Li⁺ coordinates only to the carbanion centre, rather than structure **5Li**, in which it is additionally coordinated to the carbonyl oxygen. We find that, for model M2, structure **12Li** is indeed of lower energy (by 18 kJ mol^{-1}) than **5Li**, whereas if the LDA base is omitted from the model, then **5Li** is preferred. This observation may underlie the fact that excess base facilitates the reaction.

We consider first the stereochemically retentive mechanism we studied using small model (M1) calculations. For the larger systems, the overall picture leading to the formation of the five-membered intermediate **13Li** is nevertheless similar to that found for M1. Thus, for both M2 (with two solvating THF molecules) and M3 (with three solvating THF molecules) a reactant structure (e.g., R2, Figure 8a) is determined. This structure is higher in energy by $18-19 \text{ kJ} \text{ mol}^{-1}$ (Table 2) than the lowest energy structure [e.g., R1; Figure 8 (b)], with the solvated Li⁺ cation having moved from being close to the carbanion centre (2.27 Å in R1) to a position near the adjacent phenyl ring (4.09 Å from the carbanion centre in R2). In the case of the smaller



Figure 8. Stationary structures from model M2: (a) reactant (R2), leading to retention of configuration; (b) lower energy reactant (R1), leading to inversion of configuration; and (c) TS structure (TS1), leading to retention of configuration. For clarity, the LDA dimer is omitted.

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model (M1), the solvated Li⁺ in R1 is situated between the phenyl rings [Figure 7 (d)]. However, the size of the solvated cation in both M2 and M3 prevents a similar ring-stacked structure; the rings are displaced with respect to each other [e.g., Figure 8 (b)]. Thus, there needs to be considerably more motion of the solvated Li⁺ to achieve the reactive structure (R2) than was necessary for model M1. The major differences in the TS structures, leading to the formation of the five-membered intermediate (I1), seen by comparing TS1 for model M1 [Figure 7 (b)] with that for models M2 and M3 [Table 1 and, e.g., Figure 8 (c)], arise from the increase in the number of THF molecules that solvate the moving Li⁺ cation. Thus, in all of the TS structures [TS1; Figures 7 (b) and 8 (c)], the solvated Li⁺ cation is located between the two phenyl rings, but increased solvation in models M2 and M3 resulted in an increase in the distances of the Li⁺ ion from the phenyl rings (Table 1). This gives rise to an increase in the height of the barrier, which leads to I1, from 34 to 42 kJ mol⁻¹ for M2 and M3, respectively (Table 2), as the distance of the Li⁺ ion from the phenyl rings increases, and the associated charge stabilization decreases. Steric factors, which are included in our models, are also expected to play a role. We also note that there is a corresponding destabilization of the intermediate I1, as the degree of solvation of the Li⁺ ion increases.

We turn now to an alternative mechanism, leading to inversion of stereochemistry, which we have studied for models M2 and M3. The TS structure for this pathway is shown in Figure 9. This TS structure is connected to the lowest energy minimum (R1), so that for both M2 and M3 this structure gives rise to an invertive rearrangement. In these reactant structures both $\text{Li}^+(\text{THF})_2$ and $\text{Li}^+(\text{THF})_3$ ions are in a relatively uncrowded region of space compared with those leading to the retentive pathway. They thus lead to TS structures in which these $\text{Li}^+(\text{THF})_n$ ions occupy the face of the adjacent benzyl ring *anti* to the migrating ring (Figure 9). In contrast to the stereochemically retentive

Figure 9. TS structure for inversion (model M2). For clarity the

t structures both L1 (THF)₂ and L1 (THF)₃ lons are latively uncrowded region of space compared with eading to the retentive pathway. They thus lead to actures in which these Li⁺(THF)_n ions occupy the the adjacent benzyl ring *anti* to the migrating ring 9). In contrast to the stereochemically retentive

pathway, the charge developing on the migrating ring cannot therefore be stabilized by solvated Li⁺. We may thus attribute our finding that retention of stereochemistry is preferred to these different degrees of TS stabilization. Thus, we find that, for both M2 and M3, the absolute energy of the TS for inversion is greater than that for retention of configuration by 33 and 18 kJ mol⁻¹, respectively. We also noted that, for the reaction leading to inversion, we were unable to locate an anionic five-membered-ring intermediate, probably again due to the lack of stabilization by a nearby lithium species. We previously reported preliminary calculations of the corresponding reaction of a carbamate 6 (Scheme 2) by employing a small model similar to M1.^[17] We found that in this case inversion is favoured; a feature we attribute to the preferred binding of Li⁺ to the carbamate's benzylic oxygen atom rather than to the phenyl ring, as found herein for the urea.

We have also investigated the corresponding 1,2-acyl shift reaction to give **15**, in which the anionic centre attacks the carbonyl group. Reactions analogous to this are well known for related carbamates, amides, and allylic ureas.^[8,19,36] We employed model M2 and found that the TS (Figure 10) connected to a reactant structure higher in energy (by 43.3 kJ mol⁻¹) than R1. This TS is higher in energy than R1 by 102.6 kJ mol⁻¹, and is thus unfavourable compared with both 1,4-aryl shift reactions. We may attribute this to the considerable strain in the TS, which leads to a three-membered-ring intermediate.



Figure 10. TS structure for attack at the carbonyl group and a 1,2 acyl shift (model M2). For clarity, the LDA dimer is omitted.

We see that the major features of the potential energy surface for both retention and inversion of stereochemistry are unchanged when the M06–2X functional is employed (Table 2), although the actual magnitudes of the barriers have altered somewhat. Thus, retention of stereochemistry is again favoured over inversion and the calculated barriers are larger for the more highly solvated cation.

LDA dimer is omitted.

Calculation of NMR Shifts

For comparison with the spectrum of the transient species observed by NMR spectroscopy during the rearrangement of 5d [Figure 2 (b), assigned to structure 13dLi], we used model M1 to calculate the ¹H shifts for the cyclic intermediate 13cLi, which differed from 13dLi by the lack of a methoxy group. The computed chemical shifts shown in Figure 11 contains 12 resonances in the aromatic region, which yields 10 signals due to the averaging of the chemically equivalent pairs of hydrogen atoms at the ortho and *meta* positions of the benzylic phenyl ring. We see that all of the predicted resonances, except two, lie in the region δ = 5.4-8.5 ppm, and thus, can be correlated with the group of signals observed experimentally at $\delta = 5.0-7.8$ ppm. Experimentally a doublet is observed at remarkably low field, δ = 9.4 ppm. We assign this signal to the deshielded proton at the peri position of the naphthyl ring, for which we also predict a shift of $\delta = 9.37$ ppm. Thus, since the experimental spectrum is probably due to a mixture of species, agreement between theory and experiment is satisfactory.



Figure 11. Calculated proton chemical shifts [ppm] of intermediate **13cLi**.

Calculation of IR Spectra of Structures Along the Reaction Pathway

We attempted to correlate the changes in the IR spectra illustrated in Figures 3, 4, 5 and 6 with the minimum energy structures computed for the intermediates in model M3. Figures 3 and 5 show considerable changes in the experimental spectra when sBuLi is added to solutions of ureas 5a and 5c in THF, respectively. In the dissolved urea 5a, an intense band is observed at 1650 cm^{-1} , which we associate with the C=O stretch calculated to occur at 1632 cm^{-1} (Table 3); the weaker peaks seen at $1590-1600 \text{ cm}^{-1}$ are assigned to aromatic ring motions calculated at 1642-1664 cm⁻¹. On lithiation, the C=O peak at 1650 cm⁻¹ disappears and a fairly intense broad band comprised of at least two peaks appears at 1590–1610 cm^{-1} (Figure 5). This could be due to either structures 5Li or 12Li (R1, R2). Our calculations show a progressive decrease in the C=O frequency from 5a to 5Li and 12Li (Table 3). Although inaccuracies in the calculated frequencies and the use of LDA in the calculations (as opposed to sBuLi in the IR spectroscopic work) make a definitive assignment of the initial lithiated species problematic, the calculated shifts in the C=O frequency upon lithiation are probably a better guide. If we take the more intense peak to be due to the C=O stretch,



then the experimental shift of 50 cm^{-1} fits best with the lithiated species being R1 (12Li), which has a predicted shift of 52 cm⁻¹, rather than 5Li or R2 (12Li), which show calculated shifts of 15 and 27 cm⁻¹ respectively. We also note that, as far as using a comparison between experiment and theory to identify whether R1 or R2 is observed experimentally, although the evidence is not strong, the computed relative intensities of the two bands calculated at 1580- 1650 cm^{-1} for which that due to R2 is considerably more intense than that due to R1, may suggest that reactant R1 is observed, in line with our conclusions from the calculated C=O shifts. The spectrum measured for a reaction time of about 2 h shows a broad band centred at 1575 cm⁻¹, with only an extremely weak feature at 1650 cm⁻¹. This spectrum correlates very well with our predicted spectrum of the product anion (14Li) in which phenyl ring transfer has occurred. Here the broad band is mainly due to the conjugated N=C-O- group, but also involves a number of C-H modes that result in the observed broad band. Finally, the very weak band observed at about 1650 cm⁻¹ is calculated to arise from stretching modes of the aromatic rings. We have calculated the IR spectrum of the I1 in our predicted reaction scheme; this structure shows an intense C=O stretch at 1668 cm⁻¹, which is completely absent in the measured spectrum. Thus, we conclude that this cyclised intermediate has an extremely short lifetime.

Table 3. Predicted peaks in IR spectra for Model M3.

Species	Mode	Frequency [cm ⁻¹]	Intensity
Urea (5)	C=O stretch	1632	230
	ring modes	1642-1664	3–94
Li-Urea (5Li)	C=O stretch	1617	380
	ring modes	1637-1663	23-185
R1 (12Li)	C=O stretch	1580	452
	ring modes	1637-1657	11-319
R2 (12Li)	C=O stretch	1605	945
	ring modes	1635-1660	273–28
I1 (13Li)	C=O stretch	1668	814
Product (14Li)	N=C(-O)-N modes	1575, 1448, 1368	233, 168, 171
	phenyl ring stretches	1636–1659	1–10

We note that our experimental IR spectra for the corresponding naphthyl urea (5c) (Figure 5) are very similar to those for 5a (Figure 3).

Conclusions

In this work we have sought reasons for why an organolithium reagent might attack a phenyl ring intramolecularly rather than undergo more conventional nucleophilic addition to a carbonyl group. We found that the degree of coordination and movement of Li^+ associated with the carbanionic centre was critical to understanding the mechanism of the 1,4-aryl shift. The major difference between the structures, which led to retention or inversion of stereochemistry, lay in the position of this solvated Li^+ ion. We found that the TS arising from R2 and leading to retention of configuration had the solvated cation located between

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the phenyl rings, whereas in the TS leading to inversion, which arose from R1, the cation was located on the benzylic aryl ring and anti to the other phenyl ring. Thus, considerable movement of the Li⁺ was required to attain the reactive structure for retention of configuration. However, the TS structure for stereochemically retentive reaction from R2 was of lower energy than that from R1, which we attributed to stabilization of the developing negative charge on the phenyl ring subject to nucleophilic attack. This TS structure, which led to retention of stereochemistry, was also lower in energy than that leading to the alternative 1,2-acyl shift reaction. Thus, we found that the surprising nucleophilic attack at the aromatic ring was more favourable than the commonly observed attack at a carbonyl group. It would appear that the loss of aromaticity accompanying the 1,4-aryl shift incurred a lower energetic penalty than the reaction that led to the 1,2-acyl shift via a strained TS state. Nucleophilic attack on aryl rings is not uncommon when the rings carry anion-stabilizing groups,^[37] but is rarely observed on rings as electron rich as those undergoing migration in the present rearrangements of lithiated ureas. These may carry up to three electron-donating groups.^[15]

The "size" of the solvated Li⁺ complex, which had two or three THF molecules associated with it, had important implications for the structures of the reactants and TS structure (TS1), leading to the formation of the five-membered ring of 13Li. Thus, in the reactants (R1, R2), the more highly solvated cation lay further from the anionic centre, whilst in the TS structure (TS1), it was further from either of the two phenyl rings. In particular, in both R1 and R2, there was increased steric crowding around the anionic centre when the number of coordinated THF molecules increased from two to three, due to interaction of Li⁺(THF)₃ and the benzylic and N-methyl substituents. Thus, in structure R1, the more highly solvated lithium cation resided over the adjacent phenyl ring, with its distance from the anion centre increasing from 2.27 to 4.00 Å, in models M2 and M3, respectively, making the anion more available for subsequent reaction. However, the corresponding barrier for the reaction via TS1 was greater for model M3 than that for M2, since the ability of the more highly solvated Li⁺ to stabilize the developing negative charge on the migrating phenyl was reduced. We previously found that, when Li⁺ was highly coordinated, there was a reduced tendency for it to bind to an anion centre.^[38] We found a similar effect as far as the relative stability of the intermediate (I1) was concerned. Thus, with increasing Li⁺ coordination the effective charge on the Li⁺ decreased, leading to reduced stabilization of the pentadienyl anion of I1.

A comparison of the changes in IR spectra measured during the course of reaction with the computed IR spectra for the various minimum energy species, suggested that one reactant structure (R1) was dominant and that the five-membered intermediate had a short lifetime. Our calculations suggested that I1 (13Li) would probably not be observed, with the barrier leading to ring opening to give 14Li being only 34 kJmol^{-1} (model M2; Table 2). The trapping of the analogous structure in a naphthyl migration sug-

gested that, as expected, restoration of aromaticity in a naphthalene system was less favourable than in a simple phenyl ring.

By means of NMR spectroscopy, we were able to follow the conversion of initial lithiated derivatives of benzylic ureas **5b** and **5d** into species that could not be characterized, but the broad peaks of which were consistent with aggregated structures derived from **14Li**. In the case of the naphthyl migration in **5d**, transient peaks formed that we assigned to the dearomatized structure **13dLi**. However, in the case of phenyl migration in **5b** no such intermediate was observed.

Finally, we note that, although we have located two alternative pathways leading to a 1,4-aryl shift in the ureas studied herein, we believe that we cannot infer from these results the reasons for the stereochemical outcomes observed in the carbamates^[17,18] or thiocarbamates;^[22] each system requires individual investigation.

Experimental Section

General: Starting materials were synthesised by the methods described in ref.^[15] In situ IR spectroscopy was used to follow the rearrangements of **5a** and **5c**. A ReactIR 45m instrument was used with an Evacuated Conduit arm equipped with a DiComp (Diamond) probe tip. The technique involves placing a probe into the reaction mixture so that scans to establish IR absorbance can be taken throughout the course of an experiment. Data was subsequently analyzed by using iC-IR 4.0 software. For these reactions the change in absorbance of the characteristic carbonyl peak from the urea group was followed because changes in this frequency allowed remote monitoring of other changes within the molecule.

A three-necked flask was dried and subjected to a threefold evacuation-nitrogen purge cycle to exclude oxygen and moisture. The ReactIR probe was then inserted into the central neck, a temperature probe into one of the side necks and the final neck used for addition of reagents and solvents. The urea reagent (5a: 0.537 g, 2 mmol or 5c: 0.637 g, 2 mmol) was added to the flask, dissolved in THF (3 mL) and the reaction mixture was cooled to -60 °C. Once this temperature had been achieved, IR scans were commenced at a rate of one scan every 15 s. The initial spectrum was recorded and then sBuLi (1.43 mL, 1.4 M in cyclohexane, 2 mmol) was added. The reaction mixture was stirred at this temperature until the IR spectrum had stabilized and was then warmed in stages to -40, 0 and finally 25 °C. At each stage the IR spectrum was allowed to stabilize if necessary before further warming. Once a stable spectrum was observed at 25 °C, MeOH (0.08 mL, 2 mmol) was added and the spectrum was allowed to stabilize before termination of the experiment.

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