Radical Anions from Urea-type Carbonyls: Radical Cyclizations and Cyclization Cascades

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Radical Anions from Urea-type Carbonyls: Radical Cyclizations and Cyclization Cascades

Huan-Ming Huang^[a], Joseph J. W. McDouall^[a], and David J. Procter^{*[a]}

Abstract: Radical anions generated from urea carbonyls by reductive electron transfer are exploited in carbon-carbon bond formation. New radical cyclizations of urea radical anions deliver complex nitrogen heterocycles and, depending upon the proton source used in the reactions, a chemoselective switch between reaction pathways can deliver two heterobicyclic scaffolds. A computational study has been used to investigate the selectivity of the urea radical processes. Furthermore, radical cyclization cascades involving urea radical anions deliver unusual spirocyclic aminal architectures.

Carbon-carbon bond formation is integral to almost any synthetic endeavor and provides a focal point for contemporary synthetic method development.^[1] Radical reactions constitute one of the most important and attractive tools to achieve carbon-carbon bond formation.^[2] In particular, radical cyclizations and cyclization cascades are prized for their ability to construct carbonyl and heterocyclic motifs, including those found in complex natural products, biologically-active molecules and materials.^[3]

Within radical chemistry, ketyl radicals, typically derived by single electron transfer (SET) reduction of aldehydes and ketones, hold high status as one of the most important and versatile classes of open shell intermediates for use in synthesis.^[4] Cyclization reactions involving ketyl radicals inherently give oxygenated cyclic products, often possessing valuable three-dimensional shape, and have been achieved by deploying reagents based on Sm(II),^[5] Ti(III),^[6a-e] Ru(II),^[6f-i] Ir(III),^[6j] and electrochemistry,^[6k] amongst others.^[4] In particular, samarium(II) iodide (SmI₂) is the reagent most frequently used to generate ketyl radicals and the reactive intermediates formed in this way have found widespread application in myriad cyclization and cyclization cascade strategies^[5] thus establishing both reagent and reaction as standard tools for synthesis.^[7] Unfortunately, the formation of ketyl-type radicals is typically limited to aldehyde or ketone substrates, regardless of the reagent used for radical generation. Recently, we and others have begun to extend the rich chemistry of ketyl-type radicals to the reductive cyclizations of carboxylic acid derivatives,^[8a] including cyclic esters^[8b-d] and cyclic amide derivatives,^[8e-i] possessing more electron-rich carbonyls. However, engaging carbonyl-containing substrates in which the carbonyl is flanked by two heteroatom substituents in ketyl-type radical chemistry, until now, has not proved possible, despite the promise of new reaction space for exploration.

From the birth of organic synthesis in 1828,^[9] ureas, possessing carbonyls flanked by two nitrogen atoms, have remained an important compound class with members widely used as

catalysts, ligands, drugs, and materials, and exhibiting roles in nature.^[10] From a synthetic perspective, the electron rich character of the urea carbonyl typically exempts them from the signature reactions of the carbonyl group. Furthermore, their resistance to SET reduction^[10d] ensures that there are no examples of ketyl-type radical generation from urea carbonyls and therefore no examples of carbon-carbon bond formation using the hypothetical radical anions (Scheme 1A).^[11] Herein, we report the first examples of reductive cyclizations and cyclization cascades involving ketyl-type radicals derived from the carbonyl groups of urea derivatives by reductive SET (Scheme 1B). SmI₂ activated by a protic additive (e.g. H₂O) and LiBr is used to mediate SET and the choice of protic additive can be used to switch cleanly between two reaction pathways that deliver bicyclic scaffolds resembling those found in numerous natural products.^[12] Furthermore, radical cyclization cascades are described in which both radical anion intermediates formed during the sequential SET reduction of ureas are harnessed for multiple carbon-carbon bond formation.

Scheme 1. (A) Radical cyclizations involving ketyl-type radicals. (B) New radical cyclizations and cyclization cascades involving ketyl-type radicals from ureas: this work.

During our studies on reductive SET to important heterocyclic substrates, we prepared barbiturates **1a,b** in three steps from the corresponding substituted malonate esters. Treatment of **1a** (R = CH₃) with SmI₂ in the presence of H₂O and LiBr gave bicyclic enamine **2a**.^[8f,g] The process involves cyclization of a radical anion from the amide-type carbonyl followed by dehydration (Scheme 2). Surprisingly, when the starting material **1b** (R = Et) was treated under identical conditions, novel bicyclic

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aminal **3b** was obtained in 64% yield and with complete diastereocontrol. Surprisingly, **3b** results from cyclization involving a radical anion derived from the urea carbonyl (Scheme 2).

Scheme 2. Switching between the radical cyclization of an amide-type carbonyl and a urea-type carbonyl.

Optimization studies^[13] using substrate **1c** revealed that LiBr and H₂O were essential for the cyclization to form bicyclic aminals and **3c** was obtained in 75% yield and as a single diastereoisomer (Conditions A): no urea cyclization was seen in the absence of the additives. The use of LiI and LiCl in the place of LiBr resulted in lower conversions. Interestingly, the use of *t*BuOH as a proton source in place of H₂O gave **3c'** in 60% yield, the enediamine product of urea radical cyclization followed by dehydration (Conditions B). Thus, the urea radical cyclization could be switched between products of differing oxidation state by a simple change in protic cosolvent (Scheme 3).

Scheme 3. Optimized reaction conditions allow switching between cyclization outcomes upon a change of protic cosolvent.

It is known that the use of H₂O as a protic additive with Sml₂ gives rise to a more reducing reagent system.^[14] Thus, Conditions A deliver more-reduced products than Conditions B. The role of LiBr is also crucial. Flowers has demonstrated that adding LiBr to Sml₂ (−0.9 V vs SCE) generates more reducing SmBr₂ (−1.55 V vs SCE) in situ.^[15] In the presence of H₂O (Conditions A), SmBr₂ is even more reducing and has recently shown unique properties in radical cyclization and cyclization cascades.^[16,8f,g]

With optimized conditions established, the synthesis of a range of bicyclic aminals **3** was achieved using Sml₂–H₂O–LiBr (Scheme 4). In all cases, urea radical cyclizations proceeded efficiently and with complete diastereocontrol (>95:5 dr). Furthermore, changing to the Sml₂–*t*BuOH–LiBr reagent system switched the chemoselectivity of the radical process to give bicyclic enediamines **3'** in good to excellent yield (Scheme 5).

Scheme 4. Scope of urea radical cyclizations to form bicyclic aminal products **3**. Reaction conditions: To a solution of **1** (0.1 mmol), in THF (2 mL) under N₂, was added H₂O (100 equiv), followed by a mixture of Sml₂ (5 equiv) and LiBr (20 equiv with respect to Sml₂), the reaction was quenched after 8 h. Dr was determined from ¹H NMR of crude product mixtures.

Scheme 5. Scope of urea radical cyclizations to form bicyclic enediamines **3'**. Reaction conditions: To a solution of **1** (0.1 mmol), in THF (2 mL) under N₂, was added *t*BuOH (10 equiv), followed by a mixture of Sml₂ (3 equiv) and LiBr (20 equiv with respect to Sml₂), the reaction was quenched after 8 h. The corresponding aminals **3c**, **3e-v** were obtained in less than 5% yield. ^a Prepared by 5-exo-dig cyclization of alkynyl silane **1w** (R = TMS) using Sml₂–H₂O–LiBr.

The reductive processes are compatible with various alkyl substituents (**3b-d**) and a wide range of functional groups including fluoro (**3e** and **3e'**), bromo (**3g**, **3j** and **3g'**, **3j'**), chloro (**3i** and **3i'**), methoxy (**3h**, **3k** and **3h'**, **3k'**), trifluoromethyl (**3l** and **3l'**) and acetal (**3o** and **3o'**). The reductive radical cyclizations were also compatible with important heteroaromatic rings including indole (**3q** and **3q'**), benzothienyl (**3r**, **3s** and **3r'**, **3s'**), thienyl (**3t**, **3u** and **3t'**, **3u'**) and furanyl (**3v** and **3v'**). X-ray crystallographic analysis of **3h**, **3j**, **3q** and **3m'** confirmed the structures and, where relevant, the relative stereochemistry of the radical cyclization products.^[17] Interestingly, bicyclic enediamine **3w'** was obtained by 5-*exo-dig* cyclization of an alkynylsilane **1w** in moderate isolated yield. An attempted 6-*exo-trig* cyclization was unsuccessful.^[13]

We next investigated radical cyclization cascades in which both radical intermediates (**I** and **II**, Scheme 1) formed during reduction of the urea carbonyl were trapped. Substrates **4** bearing alkene radical traps on both nitrogen atoms were prepared in three steps from commercially available diethyl 2,2-diphenethylmalonate. Upon exposure to $\text{SmI}_2\text{-H}_2\text{O-LiBr}$, spirocyclic amination cyclization cascade products **5** were obtained in moderate isolated yield as a mixture of diastereoisomers. The structure of the major diastereoisomer of **5a** was confirmed by X-ray crystallographic analysis.^[17] The urea radical cyclization cascade was found to be compatible with chloro (**5b**), naphthyl (**5d**), and benzothienyl (**5e**) motifs (Scheme 6).

Scheme 6. Scope of urea radical cyclization cascades. Reaction conditions: to a solution of **4** (0.1 mmol), in THF (2 mL) under N_2 , was added H_2O (100 equiv), followed by a mixture of SmI_2 (5 equiv) and LiBr (20 equiv with respect to SmI_2), the reaction was quenched after 8 h. Dr was determined from ^1H NMR of crude product mixtures.

Larger scale transformations of **1c** (2 mmol, 0.96 g) gave bicyclic products **3c** (70%, 0.66 g) and **3c'** (51%, 0.47 g), respectively (Scheme 7A). Experimental and computational studies have been used to explore the mechanism of the urea radical cyclizations (Scheme 7B,C). A labeling study confirms that anions are generated and protonated during the formation of amination **3c** from **1c** using $\text{SmI}_2\text{-H}_2\text{O-LiBr}$: Use of D_2O with SmI_2 and LiBr converted **1c** to deuterated bicyclic amination **3c-D₂** in 69% yield. The labeling pattern in **3c-D₂** suggests that the final

stage of amination proceeds by reduction of an iminium ion intermediate rather than by formation and reduction of enediamine **3c'**.

Scheme 7. Preliminary mechanistic studies.

The nature of the radical anion formed upon SET to the barbituric acid system has been explored computationally. Calculations suggest that the spin density is delocalized^[18] although the highest spin density can be found on the amide-type carbonyl (0.19 total spin density on $\text{C}=\text{O}_{\text{amide}}$ and 0.14 on the urea carbonyl in the radical anion derived from **1a**; 0.18 total spin density on $\text{C}=\text{O}_{\text{amide}}$ and 0.15 on the urea carbonyl in the radical anion derived from **1b**). Thus, the switch from amide radical cyclization (observed for **1a**) to urea radical cyclization (observed for **1b**) is likely the result of selective trapping of a delocalized radical at two different sites. Calculated relative transition state energies support the experimental observations (Scheme 7C): the transition state energy for the amide cyclization of the radical anion derived from **1a** ($\text{R} = \text{Me}$) (amide **TS-1a**) is calculated to be 3.6 kJ mol^{-1} lower in energy than that of the analogous urea cyclization. Conversely, the transition state energy for the urea cyclization of the radical anion derived from **1b** ($\text{R} = \text{Et}$) (urea **TS-1b**) is calculated to be 16.3 kJ mol^{-1} lower in energy than that of the analogous amide cyclization. The switch likely arises from an increased barrier to amide cyclization in the radical anion derived from **1b** relative to the

urea radical cyclization due to the greater steric demands of the proximal ethyl groups.^[19] As expected, anti-transition states were found to be the lowest in energy in all cases.^[5]

A proposed mechanism for the urea radical cyclization is shown in Scheme 8. SET to substrates **1** and **4** gives delocalized radical anion **6**. When R' is larger than Me, carbon-carbon bond formation takes place at what was the carbon of the urea carbonyl and 5-exo-trig cyclization gives the corresponding bicyclic Sm(III) alkoxide intermediates **7** (Scheme 8).

Scheme 8. Proposed mechanism for the urea radical cyclizations.

When *t*BuOH is used as the proton source, bicyclic enediamines **3'** are obtained upon elimination. In contrast, when H₂O is used, the more reducing reagent system forms aminal radicals **8** and further reduction and protonation delivers bicyclic aminals **3**. When the R group in **8** contains a radical trap, the aminal radicals undergo cyclization to give cascade products **5**, after further reduction and protonation.

In summary, ketyl-type radical anions derived from the urea carbonyl by reductive SET undergo, intramolecular carbon-carbon bond formation. Depending upon the proton source used in the radical reactions, a chemoselective switch between reaction pathways delivers two important heterobicyclic scaffolds. Computational studies have been employed to explore the nature of the radical anion intermediates and their selective radical cyclization. Furthermore, radical cyclization cascades involving radicals derived from ureas by SET deliver unusual spirocyclic aminal architectures.

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Keywords: urea • radical • cyclization • samarium • nitrogen heterocycles

- [1] a) L. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133–173; b) N. Rodríguez, L. J. Goossen, *Chem. Soc. Rev.* **2011**, *40*, 5030–5048; c) M. Fagnoni, D. Dondi, D. Ravelli, A. Albini, *Chem. Rev.* **2007**, *107*, 2725–2756; d) J. Choi, G. C. Fu, *Science* **2017**, *356*, eaaf7230.
- [2] a) J. Iqbal, B. Bhatia, N. K. Nayyar, *Chem. Rev.* **1994**, *94*, 519–564; b) G. Bar, A. F. Parsons, *Chem. Soc. Rev.* **2003**, *32*, 251; c) M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 12692–12714; d) A. Studer, D. P. Curran, *Nat. Chem.* **2014**, *6*, 765–773; e) A. Studer, D. P. Curran, *Angew. Chem., Int. Ed.* **2016**, *55*, 58–102; *Angew. Chem.* **2016**, *128*, 58–106.
- [3] a) M. P. Plesniak, H.-M. Huang, D. J. Procter, *Nat. Rev. Chem.* **2017**, *1*, 0077; b) E. A. Anderson, *Org. Biomol. Chem.* **2011**, *9*, 3997; c) K. C. Nicolaou, J. S. Chen, *Chem. Soc. Rev.* **2009**, *38*, 2993; d) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186; e) K. K. Wang, *Chem. Rev.* **1996**, *96*, 207–222; f) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136.
- [4] a) K. N. Lee, M.-Y. Ngai, *Chem. Commun.* **2017**, *53*, 13093–13112; b) J. Cossy, D. Belotti, *Tetrahedron* **2006**, *62*, 6459–6470; c) A. Gansäuer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771–2788.
- [5] a) M. Szostak, N. J. Fazakerley, D. Parmar, D. J. Procter, *Chem. Rev.* **2014**, *114*, 5959–6039; b) C. Beemelmans, H.-U. Reissig, *Chem. Soc. Rev.* **2011**, *40*, 2199–2210; c) C. Beemelmans, H.-U. Reissig, *Pure Appl. Chem.* **2011**, *83*, 507–518; d) K. C. Nicolaou, S. P. Ellery, J. S. Chen, *Angew. Chem., Int. Ed.* **2009**, *48*, 7140–7165; e) R. Flowers, II, *Synlett* **2008**, *2008*, 1427–1439; f) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, *104*, 3371–3403; g) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307–338.
- [6] a) Y.-Q. Zhang, E. Vogelsang, Z.-W. Qu, S. Grimme, A. Gansäuer, *Angew. Chem., Int. Ed.* **2017**, *56*, 12654–12657; b) W. Hao, X. Wu, J. Z. Sun, J. C. Siu, S. N. MacMillan, S. Lin, *J. Am. Chem. Soc.* **2017**, *139*, 12141–12144; c) J. Streuff, *Chem. Rec.* **2014**, *14*, 1100–1113; d) J. Streuff, M. Feurer, P. Bichovski, G. Frey, U. Gellrich, *Angew. Chem., Int. Ed.* **2012**, *51*, 8661–8664; e) A. Fürstner, B. Bogdanović, *Angew. Chem., Int. Ed.* **1996**, *35*, 2442–2469; f) E. C. Gentry, R. R. Knowles, *Acc. Chem. Res.* **2016**, *49*, 1546–1556; g) A. G. Amador, E. M. Sherbrook, T. P. Yoon, *J. Am. Chem. Soc.* **2016**, *138*, 4722–4725; h) H. Yayla, R. Knowles, *Synlett* **2014**, *25*, 2819–2826; i) J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon, *Science* **2014**, *344*, 392–396; j) L. J. Rono, H. G. Yayla, D. Y. Wang, M. F. Armstrong, R. R. Knowles, *J. Am. Chem. Soc.* **2013**, *135*, 17735–17738; k) T. Shono, N. Kise, T. Fujimoto, N. Tominaga, H. Morita, *J. Org. Chem.* **1992**, *57*, 7175–7187.
- [7] Selected recent examples: a) N. J. Fazakerley, M. D. Helm, D. J. Procter, *Chem. -Eur. J.* **2013**, *19*, 6718–6723; b) M. D. Helm, M. Daâ Silva, D. Sucunza, T. J. â. K. Findley, D. J. Procter, *Angew. Chem., Int. Ed.* **2009**, *48*, 9315–9317; c) S. E. Reisman, J. M. Ready, M. M. Weiss, A. Hasuoka, M. Hirata, K. Tamaki, T. V. Ovaska, C. J. Smith, J. L. Wood, *J. Am. Chem. Soc.* **2008**, *130*, 2087–2100; d) J. Y. Cha, J. T. S. Yeoman, S. E. Reisman, *J. Am. Chem. Soc.* **2011**, *133*, 14964–14967; e) J. T. S. Yeoman, V. W. Mak, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 11764–11767; f) K. C. Nicolaou, A. Li, D. J. Edmonds, G. S. Tria, S. P. Ellery, *J. Am. Chem. Soc.* **2009**, *131*, 16905–16918; g) T. Xu, C. C. Li, Z. Yang, *Org. Lett.* **2011**, *13*, 2630–2633; h) G. K. Murphy, T. Shirahata, N. Hama, A. Bedermann, P. Dong, T. C. McMahon, B. M. Twenter, D. A. Spiegel, I. M. McDonald, N. Taniguchi, et al., *J. Org. Chem.* **2013**, *78*, 477–489; i) C. Beemelmans, H.-U. Reissig, *Angew. Chem., Int. Ed.* **2010**, *49*, 8021–8025; j) Z. Li, M. Nakashige, W. J. Chain, *J. Am. Chem. Soc.* **2011**, *133*, 6553–6556.
- [8] a) X. Just-Baringo, D. J. Procter, *Acc. Chem. Res.* **2015**, *48*, 1263–1275. Selected examples: b) K. D. Collins, J. M. Oliveira, G. Guazzelli, B. Sautier, S. De Grazia, H. Matsubara, M. Helliwell, D. J. Procter, *Chem. -Eur. J.* **2010**, *16*, 10240–10249; c) B. Sautier, S. E. Lyons, M. R. Webb, D. J. Procter, *Org. Lett.* **2012**, *14*, 146–149; d) D. Parmar, H.

- Matsubara, K. Price, M. Spain, D. J. Procter, *J. Am. Chem. Soc.* **2012**, *134*, 12751–12757; e) M. Szostak, B. Sautier, M. Spain, M. Behlendorf, D. J. Procter, *Angew. Chem., Int. Ed.* **2013**, *52*, 12559–12563; f) H.-M. Huang, D. J. Procter, *J. Am. Chem. Soc.* **2016**, *138*, 7770–7775; g) H.-M. Huang, D. J. Procter, *J. Am. Chem. Soc.* **2017**, *139*, 1661–1667; h) S. Shi, M. Szostak, *Org. Lett.* **2015**, *17*, 5144–5147; i) S. Shi, R. Lalancette, R. Szostak, M. Szostak, *Chem. -Eur. J.* **2016**, *22*, 11949–11953; j) S. Shi, R. Lalancette, M. Szostak, *Synthesis* **2016**, *48*, 1825–1854.
- [9] F. Wöhler, *Ann. Phys. Chem.* **1828**, *88*, 253–256.
- [10] a) R. Chingle, C. Proulx, W. D. Lubell, *Acc. Chem. Res.* **2017**, *50*, 1541–1556; b) P. Dydio, D. Lichosyt, J. Jurczak, *Chem. Soc. Rev.* **2011**, *40*, 2971; c) H.-Q. Li, P.-C. Lv, T. Yan, H.-L. Zhu, *Anticancer. Agents Med. Chem.* **2009**, *9*, 471–480; d) N. Volz, J. Clayden, *Angew. Chem., Int. Ed.* **2011**, *50*, 12148–12155.
- [11] For the reduction of cyclic ureas to the corresponding amins using LiAlH₄ and LiBH₄, see: a) H. A. Bates, N. Condulis, N. L. Stein, *J. Org. Chem.* **1986**, *51*, 2228–2229; b) D. J. Conn, J. J. Kaminski, D. M. Solomon, A. T. McPhail, *J. Org. Chem.* **1988**, *53*, 3265–3271.
- [12] For recent reports of natural products possessing related structures, see: a) S. D. Vaidya, N. P. Argade, *Org. Lett.* **2015**, *17*, 6218–6221; b) I. Bosque, J. C. Gonzalez-Gomez, M. I. Loza, J. Brea, *J. Org. Chem.* **2014**, *79*, 3982–3991; c) C. Zhang, C. K. De, R. Mal, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 416–417; d) J.-F. Liu, P. Ye, K. Sprague, K. Sargent, D. Yohannes, C. M. Baldino, C. J. Wilson, S.-C. Ng, *Org. Lett.* **2005**, *7*, 3363–3366.
- [13] See supporting information.
- [14] a) P. R. Chopade, E. Prasad, R. A. Flowers, II, *J. Am. Chem. Soc.* **2004**, *126*, 44–45; b) E. Prasad, R. A. Flowers, II, *J. Am. Chem. Soc.* **2005**, *127*, 18093–18099.
- [15] a) J. R. Fuchs, M. L. Mitchell, M. Shabangi, R. A. Flowers, II, *Tetrahedron Lett.* **1997**, *38*, 8157–8158; b) R. S. Miller, J. M. Sealy, M. Shabangi, M. L. Kuhlman, J. R. Fuchs, R. A. Flowers, II, *J. Am. Chem. Soc.* **2000**, *122*, 7718–7722; c) B. W. Knettle, R. A. Flowers, II, *Org. Lett.* **2001**, *3*, 2321–2324.
- [16] a) C. N. Rao, D. Lentz, H.-U. Reissig, *Angew. Chem., Int. Ed.* **2015**, *54*, 2750–2753; b) C. N. Rao, C. Bentz, H.-U. Reissig, *Chem. -Eur. J.* **2015**, *21*, 15951–15954.
- [17] See the Supporting Information for X-ray structures. CCDC 1586111 (**3h**), CCDC 1586112 (**3j**), CCDC 1586113 (**3q**), CCDC 1586114 (**3m'**), CCDC 1586115 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- [18] For an early EPR and computational study, see: H. C. Box, E. E. Budzinski, *J. Chem. Phys.* **1973**, *59*, 1588–1591.
- [19] Although our calculations do not involve samarium, two Sm(III) ions could be incorporated in the resonance forms set out in Scheme 7; one associated with the ketyl radical anion and one with the other carbonyl.

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COMMUNICATION

Huan-Ming Huang, Joseph J. W. McDouall, and David J. Procter*

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