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Rate constants for 1,*n*-hydrogen transfer reactions in some amino acid derived radicals

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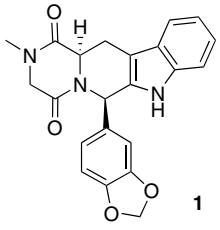
Abstract—Absolute rate constants for 1,*n*-hydrogen atom transfers in some substituted amino acid derived radicals have been determined in benzene through the use of competitive kinetic experiments. Radicals derived from methyl *N*-(2-iodobenzoyl)-*N*-(*tert*-butyloxycarbonyl)glycinate, -alaninate, -leucinate, -*tert*-leucinate and -phenylglycinate undergo intramolecular 1,5-hydrogen atom transfer to afford the corresponding α-amino acid ester radicals with rate constants in the range: $1.0–4.3 \times 10^7\ s^{-1}$ at 80 °C. Where abstractable hydrogen atoms exist in the amino acid side-chain, 1,6- and 1,7-translocations are competitive processes.

There are arguably 21 essential amino acids of relevance to man.[1] In their natural 'L' form, these molecules are mostly (*S*)-configured at the stereogenic centre, with cysteine and selenocysteine being obvious exceptions, but only because of a change in substituent priorities. Unnatural 'D' amino acids, while rare in nature, play a significant role as key intermediates in the synthesis of many pharmaceutical products.[2] High-value drugs such as: Cialis **1** (sexual dysfunction),[3] Zoloft **2** (depression),[4] Ceclor **3** (antibiotic)[5] and Lumota **4** (prostate cancer),[6] just to name a few, are prepared using one or more D-configured amino acids as building blocks. It is interesting to note that annual sales of Zoloft **2** exceeded US $370 million in 1996.[7]

The development of methods for the preparation of unnatural amino acids is an important objective and there are numerous research groups around the world working in this area. While separation techniques have been important in the past,[8] there are also many examples that utilize chiral templates, chiral auxiliaries and catalytic hydrogenation methods for the preparation of these important compounds.[8] Recent literature suggests that most efforts are currently directed toward enzymatic methods for direct enantiomeric synthesis or for the resolution of racemates.[9]

Recently, we reported the preparation of chiral, non-racemic stannanes for use in enantioselective free-radical reduction chemistry[10–12] and demonstrated that in conjunction with Lewis acids, these stannanes are capable of providing single enantiomer outcomes for a variety of transformations of synthetic and commercial significance.[13,14]

Given these outcomes, it seemed reasonable to apply this chemistry to the preparation of enantiomerically-pure unnatural amino acids. While we reported some



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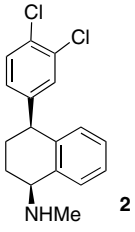

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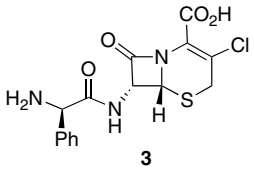

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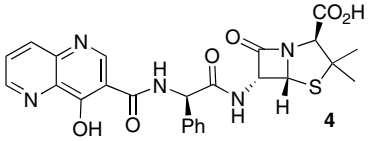

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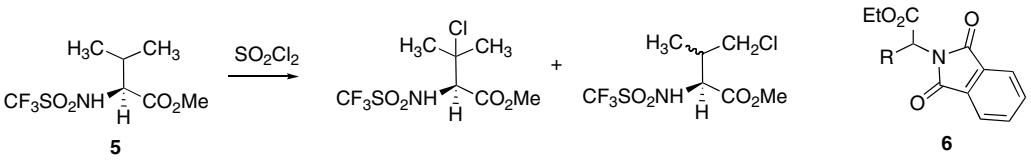


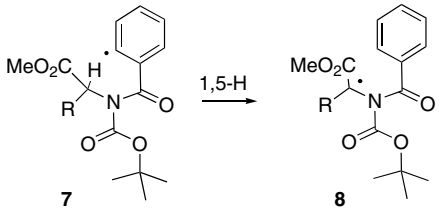
Scheme 1.

initial success utilizing α-bromoamino acids,[14] this chemistry suffered from serious drawbacks that included the instability of the radical precursors, as well as difficulties in their synthesis. Indeed, Easton reported that some substituted amino acids (e.g., **5**) undergo preferential free-radical halogenation in the alkyl side-chain rather than at the α-position (Scheme 1).[15] This has been attributed to both steric repulsion between the amide carbonyl and the side-chain in structures such as Naphthaloyl substituted (and other) amides **6**, themselves mimics of peptide residues, as well as the lower π-donating ability of amides and triflamides.[15,16]

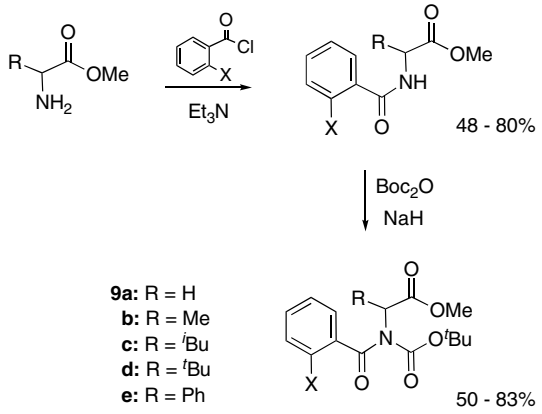
1,5-Hydrogen transfer chemistry has been used on a number of occasions to translocate a radical centre to a desired, but inaccessible location, so that further chemistry can be carried out. When used to generate α-amidyl radicals, Curran and Snieckus demonstrated the importance of influencing amide rotamer populations through the judicious choice a of nitrogen substitutent,[17] since 1,5-hydrogen transfers are faster than the rotation about the amide C–N bonds.[18]

With this in mind, together with an understanding that a knowledge of rate constant data is crucial to the design of free-radical reactions of synthetic significance, we set about determining kinetic data for 1,5-hydrogen transfer from the α-carbon in substituted Boc-protected amino acid radicals **7** to afford the α-centred radicals **8**. We reasoned that the bulky protecting group would ensure that the correct rotamer of **7** was available for reaction, and that, unlike the intermolecular radical chemistry described by Easton,[15] entropy would work in our favour (Scheme 2). During this work we discovered that while radicals **8** were able to be generated for these amino acids, competition with 1,6- and 1,7-abstractions by the radical centre in **7** are significant competing processes.

Aryl iodides **9** were prepared as precursors for **7** using standard synthetic methodology (Scheme 3). Accordingly, the required amino acid (glycine, alanine, leucine, *tert*-leucine, phenylglycine) methyl ester was treated



Scheme 2.



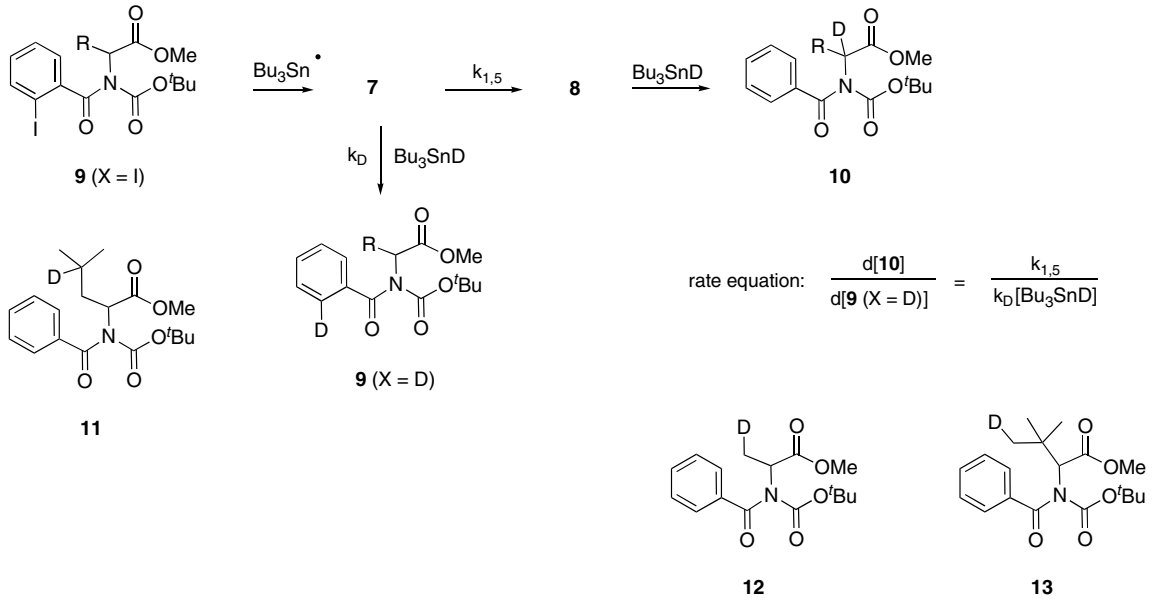
Scheme 3.

with 2-iodobenzoyl chloride (X = I) in the presence of triethylamine to afford the *N*-(2-iodobenzoyl)amino acid methyl esters in moderate yield. These amides were further reacted with sodium hydride and bis(*tert*-butyloxycarbonyl) anhydride (Boc_2O) to afford the precursors (**9**, X = I). An analogous procedure, utilizing benzoyl chloride, was used to prepare the 'reduced' compounds (**9**, X = H) as NMR standards.

With iodides (**9**, X = I) in hand, we next turned our attention to the determination of translocation rate data. Absolute rate constants for the 1,5-hydrogen transfer reactions in benzene were determined under pseudo first-order conditions (5 equiv Bu_3SnD) through the use of competition kinetics as depicted in Scheme 4.

Initial experiments were conducted using the leucine derivative. When **9c** (X = I) was reacted with Bu_3SnD (0.1 M) as described above, ^2H NMR spectroscopy revealed three main signals. Two of these corresponded to the directly reduced product (**9c**, X = D) and the translocated product (**10c**) at 7.6 and 5.2 ppm, respectively.[19] The third peak (1.5 ppm) corresponded to the product **11** of 1,7-hydrogen transfer, while the fourth peak (0.9 ppm) was consistent with small amounts of the product arising from 1,6-H transfer and too small for a value of $k_{1,6}$ to be determined in this system.

Given a best estimate for k_D of $6.7 \times 10^8\ M^{-1}\ s^{-1}$ at 80 °C,[20,21] integration of these signals and application of the appropriate integrated rate equation (Eq. 1) provided an estimate for the rate constant for 1,5-hydrogen transfer and formation of the α-leucinyl radical **8c** ($k_{1,5}$) of $3.1 \times 10^7\ s^{-1}$ at 80 °C, while applying analogous principles, $k_{1,7}$ in this system is estimated to be $1.9 \times 10^7\ s^{-1}$ at 80 °C.



Scheme 4.

$$[\mathbf{10c}]/[\mathbf{9c}(\mathrm{X}=\mathrm{D})] = k_{1,5}/(k_{\mathrm{D}}[\mathrm{Bu_3SnD}]) \qquad (1)$$

Of interest is the observation that when hydrogen atoms in the side-chain are available for abstraction, 1,*n*-hydrogen transfer becomes competitive with formation of the α-carbon centred radical **8**. While this is not surprising based on the observations of Easton,[15] this finding is somewhat disappointing given our initial objectives.

When the remaining systems of interest were examined in the manner described above, apart from glycine **9a** and phenylglycine **9e**, signals in addition to those for **9** (X = D) and **10** were observed in the relevant ^{2}H NMR spectra. These proved to correspond to **12**, the product from 1,6-hydrogen transfer in the case of alanine (**9b**), as well as **13**, the product from 1,7-hydrogen transfer in the *tert*-leucine system (**9d**), respectively.[19]

The data in Table 1 indicate that the rate constant for 1,5-H transfer is dramatically increased in the case of phenylglycine **7e**, consistent with the increased ability of the phenyl substituent to stabilize the forming α-centred radical **8e**. What is not immediately clear is the ordering amongst alkyl-substituted systems (**7b**–**7d**), with the bulkiest group (^{t}Bu) providing the largest rate constant for 1,5-transfer. We suggest that this observation is the result of release of steric compression during the formation of radicals **8**. We also expect that entropy plays an important role in these translocation reactions and therefore factors such as the number of available abstracting hydrogen atoms at each site will be important. This suggestion is consistent with the observation; 1,6-abstraction in the alanine-derived radical **7b** is faster than the analogous process in the leucine system **7c**, while the same trend is observed for 1,7-abstractions involving *tert*-leucine and leucine.

Table 1. Rate constant data[a] for 1,*n*-hydrogen atom transfers in amino acid radicals **7** in benzene at 80 °C

Entry	Radical	$k_{1,5}$ ($\times 10^7$ s^{-1})	$k_{1,6}$ ($\times 10^7$ s^{-1})	$k_{1,7}$ ($\times 10^7$ s^{-1})
1	**7a**	1.0	—	—
2	**7b**	1.9	1.5	—
3	**7c**	2.2	Trace[b]	0.9
4	**7d**	3.1	—	1.9
5	**7e**	4.9	—	—

$[Bu_3SnD] = 0.05$ M.
[a] Average of three experiments.
[b] Trace amount of product observed—see text.

Acknowledgements

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20. Assuming a kinetic isotope effect of 1.5. See: Garden, S. J.; Avila, D. V.; Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996**, *61*, 805–809.
21. A referee pointed out (correctly) that the value of k_D of 6.7×10^8 M^{-1} s^{-1} at 80° is most appropriate for *p*-substituted aryl radicals. While two *ortho* substituents have been shown to affect the rates of reaction of aryl radicals (for example, see: Brunton, G.; Gray, J. A.; Griller, D.; Barclay, L. R. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1978**, *100*, 4197–4200), other substitution patterns have been shown to have only minor influence on reactivity. Indeed, Ingold showed that the *o*-(3-phenylpropyl)phenyl radical reacts perhaps as little as 5% more slowly with Bu_3SnD than similar *p*-substituted systems do, although there is some uncertainty in this value. Given that the 95% (random error) confidence limit in k_D is about 11% of the value of k_D (see: Ref. 20), and given that we are communicating rate constant estimates, we felt that the value of 6.7×10^8 M^{-1} s^{-1} at 80° is likely to be as good as any other value for aryl radicals at this point in time and for our purposes.