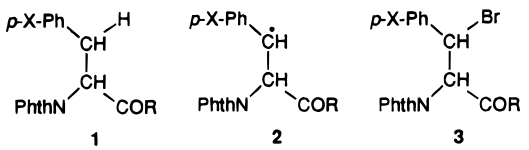
Anchimeric Assistance in Hydrogen Atom Transfer Reactions on the Side Chains of Amino Acid Derivatives

Christopher J. Easton* and Martin C. Merrett

Research School of Chemistry
Australian National University
Canberra, ACT 0200, Australia

Received September 1, 1995
Revised Manuscript Received December 19, 1995

Only a limited range of examples of neighboring group participation in atom transfer reactions have been reported. Anchimeric assistance has been observed in hydrogen atom abstractions, in the vicinal bromination of alkyl bromides,[1,2] and in reactions of *tert*-butoxy radical with Et_4Si, Et_4Ge, and Et_4Sn.[3] Results of studies by Wilt *et al.*,[4] of reactions of β-haloalkylsilanes with stannanes, have also been shown[3] to illustrate neighboring group participation in halogen atom transfer reactions. In each of these systems alkyl radical production is facilitated by a substituent on carbon adjacent to the incipient radical center, through 1,3-participation. We now report strong evidence for anchimeric assistance by an amido substituent, in hydrogen atom transfer reactions, through 1,4-participation. The present work stems from our earlier observations[5] that nucleophilic substitution reactions of **3a**−**f** to give alcohols are substantially affected through neighboring group participation by the ester and amide groups, particularly in the latter case where the amido substituent can interact more extensively with an electron deficient center developing in a reaction transition state.[6] In that work, **3a**−**f** were prepared, each as a 1:1 mixture of the diastereomers, by treatment of **1a**−**f** with NBS. The reverse transformations, of **3a**−**f** to **1a**−**f**, have now been accomplished using Ph_3SnH. As these reactions may be assumed to proceed *via* hydrogen and halogen atom transfer, respectively, to give the corresponding radicals **2a**−**f**, they



(a) X = H, R = OMe
(b) X = H, R = NH*t* Bu
(c) X = OAc, R = OMe
(d) X = OAc, R = NH*t* Bu
(e) X = NO_2, R = OMe
(f) X = NO_2, R = NH*t* Bu

provided the opportunity to probe for anchimeric assistance in atom transfer reactions.

The relative rates of reaction of **1a**−**f** to give **3a**−**f** were determined in standard competitive experiments, by measuring the relative rates of consumption of the starting materials and of formation of the products, and in a similar manner the relative rates of reduction of **3a**−**f** were also determined (Table 1). The effect of the aromatic ring substituents on the reactions of **1a**−**f** is similar to that previously reported for radical bromination of series of substituted toluene derivatives,[7] with **1a** and **1c**, and **1b** and **1d** reacting much faster than the corresponding nitro-substituted analogues **1e** and **1f**, respectively. This is consistent with the transition state proposed for radical bromination, in which hydrogen transfer to electrophilic bromine atom occurs with the development of an electron deficient center at the site of hydrogen abstraction.[7] In the processes involving Ph_3SnH, the relative rates of reaction reflect the ease with which **3a**−**f** transfer a bromine atom to the triphenyltin radical. In these processes, the effect of the nitro substituent is the reverse of that seen in the reactions with NBS, with the nitro-substituted compounds **3e** and **3f** reacting much faster than **3a**−**d**. The relative reactivity of **3a**−**f** is to be expected, however, as the transition state for a reaction of this type involves transfer of the halogen to the nucleophilic stannyl radical with the development of an electron rich center at the site of halogen abstraction.[8]

Table 1. Relative Rates of Reaction[a] of the Amino Acid Derivatives **1a**−**f** and **3a**−**f**

compd	k_{rel}[b]	compd[c]	k_{rel}[d]
1a	8	**3a**	1[e]
1b	40	**3b**	1
1c	9	**3c**	1.2
1d	34	**3d**	1.4
1e	1[e]	**3e**	4
1f	5	**3f**	4

[a] Relative rates of reaction determined in duplicate experiments varied by less than 20%. [b] Reaction with NBS in CCl_4 at reflux under N_2, initiated using a 250 W mercury lamp. [c] Data refers to reaction of the *threo* diastereomer in each case. The diastereoselectivity was less than 1.1 in the reactions of **3a**, **3b**, and **3e** and low in the reactions of **3c**, **3d**, and **3f**, but not possible to accurately quantify in the latter cases due to decomposition of the *erythro* isomers. [d] Reaction with Ph_3SnH in benzene at reflux under N_2, initiated using either AIBN or a 250 W mercury lamp. [e] Assigned as unity within each column.

Whether the carboxyl group is protected as an ester or an amide has very little effect on the relative rates of reaction of **3a**−**f** with Ph_3SnH, yet in the reactions with NBS, each of the amides **1b**, **1d**, and **1f** reacted approximately 5 times faster than the corresponding ester **1a**, **1c**, and **1e**, respectively. These effects are not consistent with steric constraints resulting from the greater bulk of the amido substituent relative to the ester group, as such factors would be expected to be at least as severe in the reactions of **3a**−**f**, where the large bromine atom is transferred to the bulky triphenyltin radical. The most obvious interpretation of the results is that the amido substituent of **1b**, **1d**, and **1f**, being more electron rich than the ester group of **1a**, **1c**, and **1e**, facilitates reaction by interacting directly with the electron deficient center in the bromination transition state (Figure 1). The analogous effect would not be expected in the reactions of **3a**−**f**, where any interaction between the carboxyl group and the electron rich center developing in the transition state would be unfavorable and would therefore be avoided.

Consistent with this interpretation, there was little diastereoselectivity in the reactions of **3a**−**f** with Ph_3SnH, indicating that the energetics of these processes are little affected by geometrical constraints on interactions between substituents. To examine the possibility of stereoselectivity in the hydrogen transfer

(1) Skell, P. S.; Tuleen, D. L.; Readio, P. D. *J. Am. Chem. Soc.* **1963**, *85*, 2849−2850. Skell, P. S.; Shea, K. J. In *Free Radicals*, Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 2, Chapter 26, p 809. Shea, K. J.; Lewis, D. C.; Skell, P. S. *J. Am. Chem. Soc.* **1973**, *95*, 7768−7776.
(2) Thaler, W. *J. Am. Chem. Soc.* **1963**, *85*, 2607−2613.
(3) Jackson, R. A.; Ingold, K. U.; Griller, D.; Nazran, A. S. *J. Am. Chem. Soc.* **1985**, *107*, 208−211.
(4) Wilt, J. W.; Belmonte, F. G.; Zieske, P. A. *J. Am. Chem. Soc.* **1983**, *105*, 5665−5675.
(5) Easton, C. J.; Hutton, C. A.; Roselt, P. D.; Tiekink, E. R. T. *Tetrahedron* **1994**, *50*, 7327−7340. Easton, C. J.; Hutton, C. A.; Merrett, M. C.; Tiekink, E. R. T. *J. Chem. Soc., Perkin Trans. 1*, submitted for publication.
(6) Winstein, S.; Goodman, L.; Boschan, R. *J. Am. Chem. Soc.* **1950**, *72*, 2311.
(7) Walling, C.; Rieger, A. L.; Tanner, D. D. *J. Am. Chem. Soc.* **1963**, *85*, 3129−3134. Friedrich, S. S.; Friedrich, E. C.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1969**, *34*, 900−905.
(8) Kuivila, H. G.; Walsh, E. J. *J. Am. Chem. Soc.* **1966**, *88*, 571−576. Migira, T.; Machida, T.; Nagai, Y. *Abstracts, 21st Annual Meeting of the Chemical Society of Japan*, Tokyo, 1968; Vol. III, p 1955. Sakurai, H. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 2, Chapter 25, p 768.

0002-7863/96/1518-3035$12.00/0

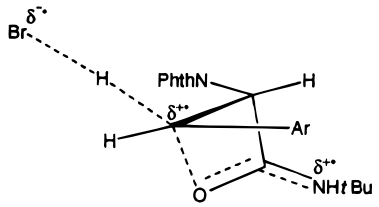
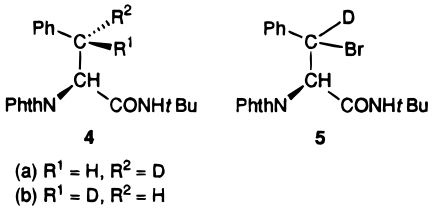
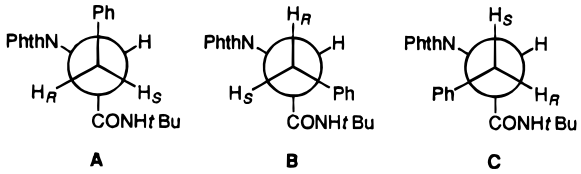


Figure 1. Neighboring group participation by the amido group in the reactions to give the radicals **2b**, **2d**, and **2f**.

reactions, the deuterides **4a** and **4b**[9] were treated with NBS. The (2*S*,3*S*)-deuteride **4a** gave a 1:1 mixture of the diastereomers of **5**, with each diastereomer containing 79% deuterium, whereas the diastereomer **4b** gave **5**, with 66% deuterium retention.



These results correlate with a deuterium isotope effect of 2.7 for the hydrogen atom transfer[10] and a stereoselectivity of 1.4 for abstraction of the pro-*R* hydrogen. This selectivity is not simply a result of steric effects. The ^{1}H NMR spectra of **4a** and **4b** and the respective coupling constants, $J_{\alpha,\beta}$, of 9.8 and 5.8 Hz indicate that the preferred conformation of the *S*-enantiomer of **1b** is **A**. This is the only staggered conformation which will give rise to the large coupling constant between the α-proton and the pro-*R* β-hydrogen. In this conformation, any steric interactions affecting the hydrogen atom transfer would be expected to result in stereoselective loss of the pro-*S* hydrogen, as this site is the less hindered to the approach of the bromine atom and loss of this hydrogen would relieve steric interactions between the phenyl and phthalimido groups. The stereoselectivity is consistent with neighboring group participation by the amido substituent. Considering the conformations **B** and **C** of **1b** which have the correct orientation to undergo



hydrogen atom transfer with direct interaction between the amide group and the developing electron deficient center, the conformer **B** would be preferred on steric grounds and stereoselective loss of the pro-*R* hydrogen from this conformer would be expected.

Several alternative explanations for the kinetic effects observed in the reactions of **1a**−**f** and **3a**−**f** were considered, but these are inconsistent with the stereoselectivity observed in the reactions of **4a** and **4b**. In principal, the phthalimido group of **1a**−**f** could be involved in neighboring group participation, but this would be expected to result in stereoselective loss of the pro-*S* hydrogen from **1b**. This would occur from the conformer **A**, whereas loss of the pro-*R* hydrogen would involve the conformer **C**. Not only is the conformer **C** of much higher ground-state energy, reaction *via* that conformer would also involve the development of additional steric interactions between the phenyl and amido substituents in the reaction transition state. Another possible interpretation of the results is that the amido substituent of **1b**, **1d**, and **1f** coordinates to the bromine atom involved in the hydrogen atom abstraction [Br∴NH(tBu)COR], thereby facilitating reaction. Similar three-electron-bonded species have been proposed as intermediates, for example, in the reaction of amino acids with hydroxyl radical [HO∴NH_2-$CHRCO_2^-$][11] and in the radical-induced oxidation of sulfides [RR′S∴OCOR″],[12] and sulfide coordination of the bromine atom [R_2S∴Br] has been demonstrated.[13] A third alternative is that the reactions of **1b**, **1d**, and **1f** proceed *via* the corresponding *N*-bromoamides and involve intramolecular 1,4-hydrogen transfer to the amidyl radicals. In these cases, stereoselective loss of the pro-*S* hydrogen from **1b** would be expected, however, as this would involve less steric interactions between the phenyl and phthalimido substituents. To confirm this expectation, the *N*-bromoamides of **4a** and **4b** were prepared by treatment with *tert*-butylhypobromite and photolyzed at reflux in CCl_4. The bromoamide derived from the (2*S*,3*S*)-deuteride **4a** gave a mixture of the diastereomers of **5**, with each diastereomer containing 28% deuterium, whereas the bromoamide of the diastereomer **4b** gave **5**, with 85% deuterium retention. These results correlate with a deuterium isotope effect of 1.5 for the intramolecular 1,4-hydrogen atom transfer[10,14] and a stereoselectivity of 3.8 for abstraction of the pro-*S* hydrogen. Clearly this stereochemical outcome is different to that observed in the reactions of **4a** and **4b** with NBS and precludes the involvement of amidyl radicals as intermediates in the reactions of **1b**, **1d**, and **1f** with NBS.

In conclusion, all of the above evidence indicates that the reactions of **1a**−**f** with NBS involve anchimeric assistance in hydrogen atom abstraction by the bromine atom, through neighboring group participation by an adjacent protected carboxyl group. It appears that this may be a more specific phenomenon than the examples of 1,3-participation in atom transfer reactions reported previously.[1−4] While 1,3-participation occurs in reactions involving either hydrogen or halogen atom abstraction, with correspondingly electron rich or deficient transition states, and is also reflected in the bridging of the product radicals as determined by EPR spectroscopic studies,[15] neighboring group effects observed in the present work are apparently limited to hydrogen transfer reactions and the stabilization of electron deficient reaction transition states.

JA953021F

(9) Compounds **4a** and **4b** were prepared as previously described for the corresponding methyl esters,[16] each in approximately 98% diastereomeric excess and with approximately 99% D_1 incorporation.

(10) Based on the assumption that the isotope effects for loss of the pro-*R* and pro-*S* hydrogens are identical.

(11) Mönig, J.; Chapman, R.; Asmus, K.-D. *J. Phys. Chem.* **1985**, *89*, 3139−3144.

(12) Glass, R. S.; Hojjatie, M.; Wilson, G. S.; Mahling, S.; Göbl, M.; Asmus, K.-D. *J. Am. Chem. Soc.* **1984**, *106*, 5382−5383. Asmus, K.-D.; Göbl, M.; Hiller, K.-O.; Mahling, S.; Mönig, J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 641−646. Mahling, S.; Asmus, K.-D.; Glass, R. S.; Hojjatie, M.; Wilson, G. S. *J. Org. Chem.* **1987**, *52*, 3717−3724. Glass, R. S.; Petsom, A.; Hojjatie, M.; Coleman, B. R.; Ducheck, J.; Klug, J.; Wilson, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 4772−4778.

(13) Asmus, K.-D.; Bahnemann, D.; Bonifacic, M.; Gillis, H. A. *Faraday Discuss.* **1978**, *63*, 213−225.

(14) Although examples of intramolecular 1,4-hydrogen atom transfer are rare,[17] the reactions of the *N*-bromoamides of **1b**, **4a**, and **4b** were shown to be intramolecular by carrying out the photolyses to give the bromides **3b** and **5** in the presence of other potentially reactive substrates.

(15) Krusic, P. J.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 846−860. Cooper, J.; Hudson, A.; Jackson, R. A. *Tetrahedron Lett.* **1973**, 831−834. Lyons, A. R.; Symons, M. C. R. *J. Chem. Soc., Faraday Trans. 2* **1972**, *68*, 622−630. Norman, R. O. C.; Storey, P. M. *J. Chem. Soc. B* **1971**, 1009−1013. Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 6459−6460; **1974**, *96*, 6715−6720.

(16) Easton, C. J.; Hutton, C. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3545−3548.

(17) For examples, see: Brunton, G.; Griller, D.; Barclay, L. R. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 6803−6811. Brunton, G.; Gray, J. A.; Griller, D.; Barclay, L. R. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1978**, *100*, 4197−4200. Casarini, D.; Grossi, L.; Lunazzi, L.; Placucci, G. *J. Org. Chem.* **1985**, *50*, 703−705. Gilbert, B. C.; Parry, D. J.; Grossi, L. *J. Chem. Soc., Faraday Trans. 1* **1987**, *83*, 77−83. Vener, E. J.; Cohen, T. *J. Org. Chem.* **1992**, *57*, 1072−1073.