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Anchimeric Assistance in Hydrogen-Atom Transfer to Bromine*

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The free-radical benzylic brominations of series of phenylalanine derivatives and *O*-phenylalkyl benzoates and *N*-phenylalkylamides with *N*-bromosuccinimide exhibit anchimeric assistance by neighbouring ester and amido groups. Rate enhancement occurs through electron donation to the electropositive carbon centre that develops in the transition state of the hydrogen-atom transfer to bromine. The extent of the effect depends on the electron demand at the benzylic position and the electron-donating ability of the neighbouring group.

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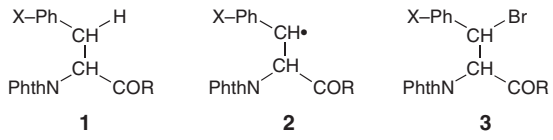
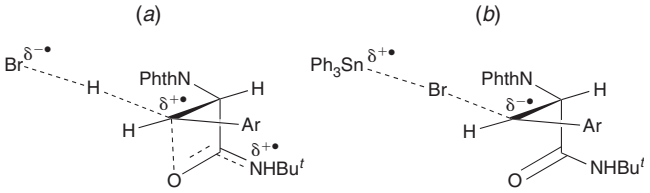
Neighbouring-group participation and anchimeric assistance commonly occur in ionic processes.[1] By contrast, only a limited range of examples have been found in free-radical reactions, and the majority of these involve 1,3-participation, where the formation of an alkyl radical is affected by a substituent on carbon adjacent to the incipient radical centre. Accordingly, anchimeric assistance has been observed in hydrogen-atom abstractions, during the vicinal halogenation of alkyl halides[2–4] and in reactions of the *tert*-butoxy radical with tetraethyl-silane, -germanium, and -stannane,[5] and in halogen-atom transfers in the reactions of β-haloalkylsilanes and vicinal dihalides with stannanes.[4–6] Neighbouring-group participation is also reflected in the bridging of the product radicals as determined through product analyses[4] and EPR (electron paramagnetic resonance) spectroscopic studies.[7]

Several years ago we reported 1,4-neighbouring-group participation by an amido substituent in hydrogen-atom transfer reactions from the side chains of amino acid derivatives.[8] These studies stemmed from our earlier observations that nucleophilic substitution reactions of the bromides **3a**–**3f** (Scheme 1) to give alcohols are substantially affected by neighbouring-group participation by the ester and amide groups, particularly in the latter case where the more electron-donating amido substituent can interact more extensively with an electron-deficient carbon centre developing in a reaction transition state.[9] In analogous free-radical reactions of the phenylalanines **1a**–**1f** with *N*-bromosuccinimide to give the bromides **3a**–**3f** via the radicals **2a**–**2f**, respectively, the amides **1b**, **1d**, and **1f** underwent reaction faster than the corresponding esters **1a**, **1c**, and **1e**. This enhanced reactivity of the amides **1b**, **1d**, and **1f** was attributed to the



a X = H, R = OMe
b X = H, R = NHBu^t
c X = 4-OAc, R = OMe
d X = 4-OAc, R = NHBu^t
e X = 4-NO_2, R = OMe
f X = 4-NO_2, R = NHBu^t
g X = 4-OMe, R = OMe
h X = 4-OMe, R = NHBu^t
i X = 3,4-$(OMe)_2$, R = OMe
j X = 3,4-$(OMe)_2$, R = NHBu^t

Scheme 1.



Scheme 2.

greater electron-donating ability of an amido substituent, relative to an ester group, to interact with and stabilize the electron-deficient carbon centre developing in the transition state of each hydrogen abstraction (Scheme 2*a*). No such rate enhancement was observed in the reductions of the bromides **3a**–**3f** with triphenyltin hydride to give **1a**–**1f** via the radicals **2a**–**2f**, respectively. This is as expected since the transition state for halogen-atom transfer to a stannyl radical

* Dedicated to Professor Lew Mander on the occasion of his 65th birthday.

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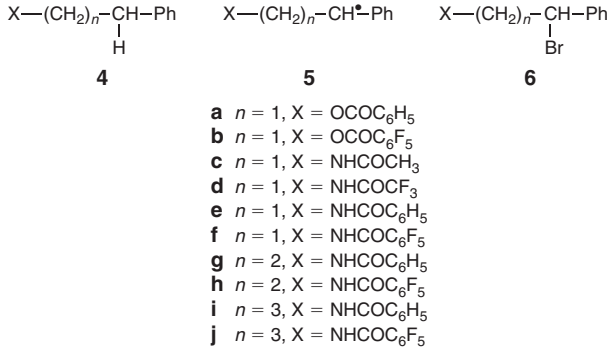


Scheme 3.

involves the development of an electron-rich centre at the site of halogen abstraction, which is unlikely to be facilitated by the presence of electron-donating groups (Scheme 2*b*).[8]

Hutton[10] has made good use of the nucleophilic substitution reactions of β-bromophenylalanine derivatives in the stereocontrolled synthesis of β-hydroxyphenylalanines. He found that the stereoselectivity was reduced by electron-donating substituents on the aryl ring, presumably because these decreased the extent of neighbouring-group participation by lowering electron demand at the benzylic position. This prompted us to investigate the effect of electron-donating substituents on the analogous free-radical processes, by examining reactions of **1g**–**1j**. We also studied reactions of **4a**–**4j** (Scheme 3) to determine if the anchimeric assistance seen in the radical reactions of **1a**–**1f** is a more general phenomenon.

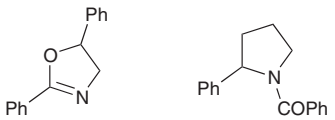
The esters **1g** and **1i** were obtained as reported previously.[10,11] The amide **1h** was prepared by treatment of *O*-methyltyrosine[12] with phthalic anhydride and then triethylamine, ethyl chloroformate, and *tert*-butylamine (see Accessory Materials). In a similar manner, 3,4-dimethoxyphenylalanine[13] was used to prepare the amide **1j** (see Accessory Materials). The amino acid derivatives **1g**–**1j** were treated with *N*-bromosuccinimide in carbon tetrachloride at reflux under nitrogen, while the solutions were irradiated with a 250 W mercury lamp, to give the corresponding bromides **3g**–**3j**, each as a 1 : 1 mixture of diastereomers (the esters **3g** and **3i** have been described previously;[10] the amides **3h** and **3j** and the bromination method are described in the Accessory Materials). As was previously observed for **3a**–**3f**, the yields of the bromides **3g**–**3j** were all greater than 90%. The relative rates of reaction of **1g**–**1j** were determined in standard competitive experiments (see Accessory Materials) and compared to those of **1a**–**1f**[8] (Table 1), by measuring the relative rates of consumption of the starting materials and of formation of the products.

The esters **4a**, **4b** and the amides **4c**–**4j** were prepared by acylation of the corresponding alcohol and amines, as described previously for **4a**, **4c**–**4g** and **4i**.[14] Characterization data for **4b**, **4h**, and **4j** are included as Accessory Materials. Treatment of **4a**–**4j** with *N*-bromosuccinimide, as described above for the reactions of **1g**–**1j**, afforded the corresponding bromides **6a**–**6j** (see Accessory Materials) in yields ranging from 58 to 86%. The crude yields appeared

Table 1. Relative rates of reaction[A] of the phenylalanine derivatives 1a–1j with *N*-bromosuccinimde

Compound	k_{rel}[B]
1a	1[C]
1b	4.5
1c	1.1
1d	4.3
1e	0.13
1f	0.63
1g	10
1h	33
1i	18
1j	49

[A] Reaction with *N*-bromosuccinimide in carbon tetrachloride at reflux under nitrogen, initiated using a 250 W mercury lamp.
[B] Relative rates of reaction were determined as the average of the results of at least duplicate experiments which varied by less than 10%. Data obtained for compounds **1a**–**1f** are derived from the literature.[8]
[C] Assigned as unity.



7 **8**

Scheme 4.

Table 2. Relative rates of reaction[A] of the esters 4a, 4b and the amides 4c–4j with *N*-bromosuccinimde

Compound	k_{rel}[B]
4a	0.36
4b	0.20
4c	0.80
4d	0.34
4e	1[C]
4f	0.60
4g	4.5
4h	2.9
4i	6.1
4j	3.8

[A] Reaction with *N*-bromosuccinimide in carbon tetrachloride at reflux under nitrogen, initiated using a 250 W mercury lamp.
[B] Relative rates of reaction were determined as the average of the results of at least duplicate experiments which varied by less than 10%.
[C] Assigned as unity.

to be almost quantitative when measured by ^{1}H NMR spectroscopy using *N*-*tert*-butylbenzamide as an internal standard in the reaction mixtures, but some decomposition of the bromides **6c**, **6e**, **6g**, and **6i** was observed during their isolation and purification, particularly with **6e** and **6i**, which cyclized to give the oxazoline **7**[15] and the pyrrolidine **8**[16] (Scheme 4), in yields of 75 and 55%, based on **4e** and **4i**, respectively. The relative rates of reaction of **4a**–**4j** (Table 2) were determined in standard competitive experiments, as performed with **1a**–**1j**. The pairs of fluorinated and non-fluorinated compounds **4a** and **4b**, **4c** and **4d**, **4e** and **4f**, **4g** and **4h**, and **4i** and

4j were always compared directly, so that the effects of the electron-withdrawing fluorines could be accurately assessed.

The relative rates of reaction of the phenylalanine derivatives **1a**–**1j** correspond to the relative rates of formation of the radicals **2a**–**2j**, since this is the first committing step on the pathway to give the bromides **3a**–**3j**. Notably, the rates do not reflect the stability of the radicals **2a**–**2j**. Radical stabilization energies calculated for model benzylic radicals indicate that both nitro and methoxy substituents in the *para* position increase radical stability.[17] However, in the reactions of **1a**–**1j**, the nitro substituents of **1e** and **1f** decrease reactivity relative to that of **1a** and **1b**, respectively, while the methoxyphenylalanines **1g** and **1h** are more reactive. Thus, the relative reactivity of **1a**–**1j** appears to be determined largely by the electron-donating and -withdrawing ability of the aryl substituents, indicating that the hydrogen-atom abstractions to give **2a**–**2j** proceed by electron-deficient carbon-centred transition states (Scheme 2). For the esters **1a**, **1c**, **1e**, **1g**, and **1i**, the ratios of the relative reaction rates correlate with σ^+ Hammett substituent parameters[18] with a reliability coefficient (R^2) of 0.9975 and a ρ value of -1.25. The ρ value is reduced to -1.05 for the amides **1b**, **1d**, **1f**, **1h**, and **1j**, indicating that there is less electron demand at the benzylic position in the transition states for the reactions of these species. This is consistent with that demand being decreased through neighbouring-group participation by the amido substituents of these compounds. Conversely, the extent of neighbouring-group participation by the amido group is enhanced by electron-withdrawing substituents on the aryl ring and decreased by electron-donating groups. Consequently, the nitro-substituted amide **1f** is almost five times more reactive than the ester **1e**, while the dimethoxyphenylalaninamide **1j** is less than three times more reactive than **1i**.

Anchimeric assistance is also evident in the reactions of **4a**–**4j** to give the corresponding bromides **6a**–**6j**. The fluorinated ester **4b** and amides **4d**, **4f**, **4h**, and **4j** react less readily than the corresponding non-fluorinated analogues **4a**, **4c**, **4e**, **4g**, and **4i**. Presumably this reflects the electron-withdrawing ability of the fluorines but it is not a simple inductive effect, because the substituents of **4i** and **4j**, in particular, are too remote from the reaction centre to then make a difference. Further, the inductive field parameters (σ^I) of the benzamido (0.13), acetamido (0.31), benzoyloxy (0.26), and triflamido (0.38) groups[18] do not correlate with the relative reactivity of the benzamide **4e** (1.0), acetamide **4c** (0.80), benzoate **4a** (0.36), and triflamide **4d** (0.34). Instead, fluorination appears to decrease the electron-donating ability and extent of neighbouring-group participation of the ester and amido groups in the hydrogen-atom transfers to give the radicals **5a**–**5j**. The amides **4c** and **4e**, and **4d** and **4f** are more reactive than the analogous esters **4a** and **4b**, respectively, due to the greater anchimeric assistance provided by the amido groups. The acetamide **4c** and the triflamide **4d** show the greatest effect of the fluorines because the electron density of the amido group is most affected in this case, where the fluorines are closest and most able to directly exert their inductive effect.[17]

The anchimeric assistance observed in the reactions of the phenylalaninamides **1b**, **1d**, **1f**, **1h**, and **1j** formally corresponds to 1,4-participation through either the amide oxygen or nitrogen. The reactions of **4a**–**4f**, **4g**, **4h**, and **4i**, **4j** could involve either 1,3- or 1,5-, 1,4- or 1,6-, and 1,5- or 1,7-participation, respectively. Although it is not practical to distinguish between these possibilities, there is likely to be a preference for 1,5-neighbouring-group effects. This is seen by analogy in the decomposition of the bromides **6e** and **6i**, to give the oxazoline **7** and the pyrrolidine **8**, respectively.

In conclusion, all of the above evidence indicates that anchimeric assistance in hydrogen-atom transfer to bromine is a general phenomenon. The neighbouring-group effects arise from stabilization of carbon-centred electron-deficient transition states and do not necessarily reflect properties of the intermediate radicals. Either way, the radical reactions show polar characteristics similar to those of their ionic counterparts.

Accessory Materials

Experimental procedures for the individual and competitive brominations and for the preparation of **1h** and **1j** and characterization of compounds **1h**, **1j**, **3h**, **3j**, **4b**, **4h**, **4j**, and **6a**–**6j** are available from the corresponding author or, until July 2009, the *Australian Journal of Chemistry*.

Acknowledgment

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