for 1,3-dinitronaphthalene, possibly due to its very low concentration or its fast conversion to the long-lived 4MC⁻. There are kinetic and spectroscopic evidence for the existence of short-lived 3MC⁻ in reactions of 1-chloro(bromo)-2,4-dinitronaphthalene with OH^-,[2e] 1-methoxy-2,4-dinitronaphthalene with MeO^-,[41a] or 1-(dialkylamino)-2,4-dinitronaphthalene with MeO^-[41b] or NR_2H.[41c]

The relative stabilities of the Meisenheimer complexes are shown in Table II, and comparison with data in Figure 6 shows that the most stable MC⁻ forms at the carbon atom that has the highest spin-orbital density opposite to the oxygen of OH•. If this carbon atom is bonded to a H, a long-lived MC⁻ is formed (compounds **3**, **6–8**, Figure 6), but if there is a nitro or cyano group at this position, there is overall nucleophilic substitution with a short-lived MC⁻ as intermediate (compounds **4**, **5** Figure 6), and no long-lived MC⁻ is observed. In 2,4-dinitrobenzonitrile, positions 1 and 5 have almost the same spin-orbital densities, and the energies of the corresponding MC⁻ are very similar. The CTC⁻ collapses to the two MC⁻, and 1MC⁻ loses the cyano group to form the corresponding phenol.[37]

Conclusions

Molecular-orbital calculations on nitroarenes support the hypothesis that compounds with more than one nitro group react with OH^- to form charge-transfer complexes of finite life and that these complexes have considerable radical character. They collapse initially to Meisenheimer complexes at the carbon atom with the lowest charge densities, but these complexes may isomerize via the charge-transfer complexes to more stable Meisenheimer complexes. The situation is different if addition is at a carbon that carries a good leaving group which can be eliminated, to give overall substitution.[2]

The AM1 method predicts geometries of nitroarenes[2f] and their Meisenheimer complexes in good agreement with experiment. There are large systematic errors in predicted reaction enthalpies, but relative values for related compounds are in reasonable agreement with experiment. The key point is that the AM1 method predicts the position of overall nucleophilic addition and substitution to a variety of nitroarenes. Qualitative theories of organic reactivity, based on inductive, mesomeric, and steric effects[4], are only partially successful in these predictions and fail to account for the observed single-electron transfer from basic or nucleophilic anions to a variety of electrophiles, including polynitroarenes and nitrogen heterocycles. There is now considerable experimental evidence that many reactions regarded as two-electron transfers actually occur by single-electron transfer via short-lived charge-transfer complexes.[42]

Acknowledgment. Support by the National Science Foundation (Organic Chemical Dynamics Program) and the donors of the Petroleum Research Found, administered by American Chemical Society, is gratefully acknowledged. A National Science Foundation Grant for the use of the Cray X-MP/48 at the University of Illinois Urbana-Champaign is gratefully acknowledged. We are especially grateful to Professor M. J. S. Dewar for unpublished results and his interest in the research.

Supplementary Material Available: Tables giving geometries, net atomic charges, dipole moments, spin-orbital densities, and orbital energies for 30 compounds discussed in the text (32 pages). Ordering information is on any current masthead page.

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Selective Reaction of Glycine Residues in Hydrogen Atom Transfer from Amino Acid Derivatives

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Abstract: Relative rates of reaction of the *N*-benzoylamino acid methyl esters **1a–4a** with *N*-bromosuccinimide and of **1a–4a** with di-*tert*-butyl peroxide are reported. The selective reaction of glycine derivatives in these and other reactions of *N*-acylamino acid derivatives is attributed to the relative stability of intermediate radicals produced by hydrogen atom transfer. Radicals formed by hydrogen abstraction from *N*-acylglycine derivatives may adopt planar conformations which are relatively free of nonbonding interactions and in which there is maximum delocalization of the unpaired electron, whereas radicals produced by similar reactions of derivatives of other amino acids are relatively unstable because of nonbonding interactions. In accord with this hypothesis, methyl pyroglutamate (**5a**) reacts at a faster rate than *N*-benzoylglycine methyl ester (**1a**) in reactions with either *N*-bromosuccinimide or di-*tert*-butyl peroxide. Anomalous rates of reaction of *N*-benzoylproline methyl ester (**6a**) are rationalized in terms of the regioselectivity of hydrogen atom transfer. Evidence for the mechanisms of reactions of **1a–6a** is derived from product studies and by comparison of the relative rates of reactions of **1a–6a** with those of the deuteriated amino acid derivatives **1b**, **2b**, **3b**,**c**, **5b**, and **6b**,**c**.

The preferential reactivity of glycine residues observed in the photoalkylation of peptides and proteins has been attributed to the formation of α-centered radicals by selective hydrogen atom transfer from glycine derivatives.[2] Irradiation experiments with polycrystalline and single crystal samples of amino acid derivatives have also displayed selective reaction of glycine residues.[3] Two main types of radicals are produced by irradiation, as shown by EPR spectroscopy. One of these gives EPR spectra that are broad and anisotropic. These radicals are thought to be sulfur-centered, mainly because similar spectra have been observed for a number of thiols and disulfides. The other type of radical, which displays

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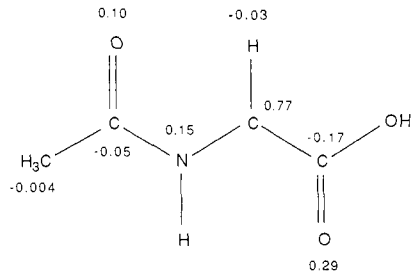
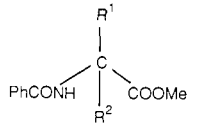


Figure 1. Distribution of the unpaired spin density in the radical formed by hydrogen atom abstraction from the α-position of *N*-acetylglycine.

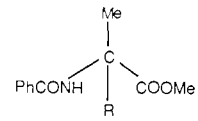
a doublet resonance in EPR spectra, is derived by hydrogen atom abstraction from the α-position of glycine derivatives. While the reactivity of amino acid residues is affected by the tertiary structure and the location of the amino acid in peptides and proteins, glycine residues are intrinsically more reactive than other amino acid derivatives.[2,3]

Radicals formed by hydrogen transfer from the α-position of *N*-acylglycine derivatives are stabilized by extensive delocalization of the unpaired electron. Molecular orbital calculations of the distribution of unpaired spin density in the radical formed by abstraction of an α-hydrogen from *N*-acetylglycine have shown it to be distributed in p orbitals perpendicular to the plane of the molecule (Figure 1).[4] While the regioselective formation of α-centered radicals by hydrogen atom transfer from *N*-acylamino acid derivatives is consistent with the degree of delocalization of the unpaired electron in the product radicals, the selective hydrogen atom abstraction from *N*-acylglycine derivatives is contrary to the expectation that tertiary radicals should form in preference to secondary ones.[5] Glycine residues afford secondary radicals by α-C–H bond homolysis, whereas analogous reactions of derivatives of other amino acids such as alanine and valine produce tertiary radicals.

In our preliminary investigation of this anomaly[6] we studied reactions of the amino acid derivatives **1a–3a** and the deuteriated analogues **1b–3b** with *N*-bromosuccinimide (NBS). NBS was chosen as the reagent because the initial reaction of reactive substrates in brominations with NBS involves hydrogen atom abstraction by bromine atom, a reaction in which there is relatively extensive C–H bond homolysis in the transition state and which is, therefore, relatively sensitive to the stability of the product radical.[5,7] We proposed that the particular reactivity of glycine residues in free-radical reactions could be attributed to the stability of the radicals produced by atom-transfer reactions. Thus, radicals formed by hydrogen abstraction from glycine derivatives may adopt conformations which are relatively free of nonbonding interactions and in which there is maximum delocalization of the unpaired electron, whereas radicals derived by analogous reactions of derivatives of other amino acids such as alanine and valine are destabilized by nonbonding interactions. To examine this hypothesis, we have now studied reactions of *N*-benzoylsarcosine methyl ester (**4a**), methyl pyroglutamate (**5a**), *N*-benzoylproline methyl ester (**6a**), and the deuteriated analogues **5b**, **6b**, and **6c** with NBS. For comparative purposes and in order to check for major deviations from proposed mechanistic schemes, reactions of **1a–6a** and **6b,c** with di-*tert*-butyl peroxide (DTBP) have also been studied. Reactions with DTBP involve hydrogen atom transfer from substrate to *tert*-butoxy radical. There is comparatively less C–H bond homolysis in the transition state of reactions involving hydrogen atom abstraction by *tert*-butoxy radical than in those involving hydrogen transfer to bromine atom. Reactions with DTBP are, therefore, less susceptible to radical-stability effects and more susceptible to polar and steric effects.[5]



1a $R^1 = R^2 = H$
1b $R^1 = R^2 = D$
1c $R^1 = Br$, $R^2 = H$



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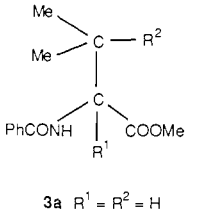
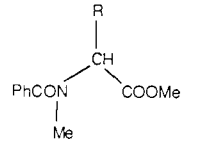
2b R = D



3a $R^1 = R^2 = H$
3b $R^1 = D$, $R^2 = H$
3c $R^1 = H$, $R^2 = D$
3d $R^1 = R^2 = Br$



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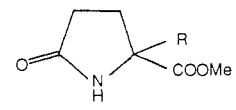
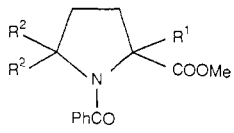
4b R = Br



5a R = H
5b R = D



6a $R^1 = R^2 = H$
6b $R^1 = D$, $R^2 = H$
6c $R^1 = R^2 = D$

Methods

Relative rates of reaction of the amino acid derivatives **1a,b**, **2a,b**, **3a,b**, **4a**, **5a,b**, and **6a–c** with NBS and of **1a–6a** and **6b,c** with DTBP were determined by measuring the relative rates of their consumption from mixtures. For any two substrates X and Y, the ratio of their rates of reaction can be measured by comparing the concentration of each substrate after reaction ($t = 1$) relative to the original ($t = 0$) concentration of that substrate.[8–10]

$$k_X/k_Y = \ln ([X]_{t=1}/[X]_{t=0})/\ln ([Y]_{t=1}/[Y]_{t=0})$$

This method applies only when the reactions of X and Y are irreversible and provided neither X nor Y is produced during the reaction. In the present work, single enantiomers of the amino acid derivatives **2a,b** and **3a,b** were used, and reaction mixtures were analyzed on a Chrompack XE-60-S-VAL-S-A-PEA GLC column or a Regis Pirkle Covalent L-Phenylglycine HPLC column, each of which resolved the enantiomers of **2a,b** and **3a,b**. The fact that no epimerization of **2a,b** or **3a,b** was observed in these reactions indicates that the reactions are irreversible. Although the glycine derivative **1a** reacted with DTBP to produce the racemic alanine derivative **2a**,[11] the relative rates of consumption of the glycine derivative **1a** and the alanine derivative **2a** could be determined by using the (2*S*)-alanine derivative **2a** and measuring the enantiomeric excess of **2a** after reaction to determine the quantity of unreacted substrate. In all of the systems studied, no reaction occurred in the absence of ultraviolet irradiation. This observation is consistent with the expectation that the reactions are free-radical processes.

Where it was feasible, products of reactions were examined to gain insight into the reaction mechanisms. Reactions of **1a**, **3a**, and **4a** with NBS to give the α-bromoglycine derivative **1c**,[12] the dibromovaline derivative **3d**,[13] and the α-bromosarcosine derivative

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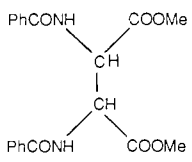
4b,[13] respectively, have been reported. Treatment of the glycine derivative **1a** with DTBP is known to produce diastereoisomers of the dimer **7** in addition to the alanine derivative **2a**.[11] Reaction of methyl pyroglutamate (**5a**) with DTBP has been reported to produce diastereoisomers of the dimer **8**.[14]

Reaction of the sarcosine derivative **4a** with *tert*-butoxy radical was studied directly by irradiating a mixture of **4a** and DTBP in the cavity of an EPR spectrometer. A range of solvents was examined for preparing mixtures of **1a–3a**, **5a**, or **6a** with DTBP; however, solutions suitable for study by EPR spectroscopy could not be obtained due to the low solubility of the amino acid derivatives in solutions containing DTBP.

Results

Reaction of the alanine derivative **2a** and of methyl pyroglutamate (**5a**) with NBS afforded, in each case, a red oil, which could not be resolved with numerous chromatographic systems. Treatment of the proline derivative **6a** with NBS (3 molar equiv) gave *N*-benzoyl-3-bromo-2-(methoxycarbonyl)pyrrole (**9**) and the 4-bromopyrrole **10**. When less than 3 equiv of NBS was used, the starting material **6a** and *N*-benzoyl-2-(methoxycarbonyl)-pyrrole (**11**) were detected in product mixtures. The assignment of structures of the bromopyrroles **9** and **10** rests heavily on the correlation of observed ^{13}C NMR shifts with those predicted by the use of additivity factors and the data available for a variety of pyrazoles.[15]



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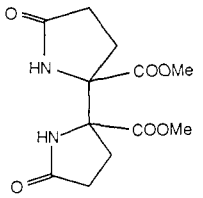

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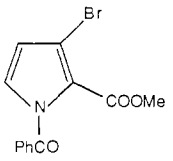

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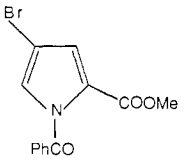

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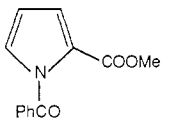

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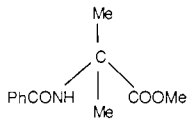

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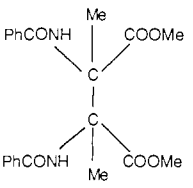

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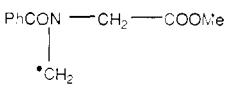

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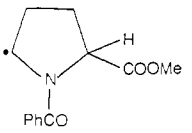

22

Treatment of the alanine derivative **2a** with DTBP afforded the α-methylalanine derivative **12** and diastereoisomers of the dimer **13**. Mixtures of products were obtained from reactions of the derivatives of valine **3a**, sarcosine **4a**, and proline **6a** with DTBP, from which discrete compounds could not be isolated.

Irradiation of a mixture of the sarcosine derivative **4a** and DTBP in the cavity of an EPR spectrometer gave rise to two signals of approximately equal intensity. One signal appeared as a triplet, consistent with formation of the radical **14** [$a(H_\alpha)$ = 17.5 G, g = 2.0030].[16] The other signal is consistent with formation of the radical **15**, appearing as a doublet [$a(H_\alpha)$ = 16.5 G, g = 2.0030].[16] The same doublet signals was observed when a mixture of the bromosarcosine derivative **4b**, hexabutylditin, and DTBP was irradiated. Under these conditions the expected product radical is **15**, produced by bromine atom transfer from **4b**.[17]

Table I. Relative Rates of Reaction of the Amino Acid Derivatives **1a–6a**, **1b–3b**, **5b**, and **6b,c** with NBS and of **1a–6a** and **6b,c** with DTBP

	NBS	DTBP
1a	1.0[a]	1.0[a]
1b	0.32 ± 0.03	
2a	0.33 ± 0.05	0.24 ± 0.02
2b	0.18 ± 0.02	
3a	0.04 ± 0.01	0.19 ± 0.03
3b	0.01 ± 0.002	
4a	0.37 ± 0.05	0.40 ± 0.03
5a	3.1 ± 0.7	2.4 ± 0.2
5b	2.1 ± 0.3	
6a	1.4 ± 0.1	1.9 ± 0.4
6b	1.2 ± 0.1	2.2 ± 0.2
6c	0.42 ± 0.04	0.7 ± 0.2

[a] Assigned as unity for each reagent.

Relative rates of reaction of the amino acid derivatives **1a,b**, **2a,b**, **3a,b**, **4a**, **5a,b**, and **6a–c** with NBS, and of **1a–6a** and **6b,c** with DTBP are presented in Table I. The error limits represent the standard deviation of the sample population. The relative rates of reaction of the valine derivatives **3a,b** compared to those of the glycine derivative **1a** were determined indirectly from competitive experiments using the glycine derivative **1a** and the alanine derivative **2a**, and **2a** and the valine derivatives **3a,b**. The errors shown for the relative rates of reaction of **3a,b** are the cumulative errors. No allowance was made for incomplete deuterium incorporation in the amino acid derivatives **1b–3b**, **5b**, and **6b,c**. The most significant effect of residual hydrogen on the rate of reaction would be expected with the deuteriated methyl pyroglutamate (**5b**), where the extent of deuterium incorporation was only 62%. The general correlation between the relative rates of reaction of **1a–6a** with NBS and with DTBP indicates a similarity in reaction pathways for these two reagents, and major deviations from the pathways discussed below would appear to be unlikely.

Discussion

The deuterium isotope effects reflected in the relative rates of reaction of the amino acid derivatives **1a–6a**, **1b–3b**, **5b**, and **6b,c** (Table I) and the fact that no epimerization of enantiomers of **2a** or **3a** was observed in reactions with either NBS or DTBP indicate that hydrogen transfer to bromine atom and *tert*-butoxy radical is the irreversible rate-determining step in reactions of the amino acid derivatives **1a–6a** with NBS and DTBP, respectively. Subsequent reactions of product radicals are unlikely to affect the relative reactivities of **1a–6a**.[5] The isotope effects reflected in the relative rates of reaction of **1a–3a** and the deuteriated analogues **1b–3b** with NBS indicate that each of the amino acid derivatives **1a–3a** reacts by α-C–H bond homolysis. Thus the relative rates of reaction of **1a–3a** with NBS indicate the ease of formation of the corresponding α-centered radicals **16–18**. The production of **1c** in the reaction of **1a** may be attributed to the reaction of the radical **16** by bromine-atom incorporation. A mechanism of formation of the dibromovaline derivative **3d** from **3a** via the α-centered radical **18** has been proposed.[13]

The formation of **2a** and **7** in the reaction of **1a** with DTBP[11] indicates that this reaction of **1a** involves hydrogen atom transfer to *tert*-butoxy radical to give the radical **16**. Similarly, the production of **12** and **13** in the reaction of **2a** with DTBP can be

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attributed to the reaction of **2a** with *tert*-butoxy radical to give **17**. Subsequent reaction of **17** by dimerization affords **13**, while coupling of **17** with methyl radical produced by β-scission of *tert*-butoxy radical leads to the formation of **12**. Although discrete products could not be isolated from the reaction of **3a** with DTBP, a previous study of the relative rates of reaction of **3a** and the deuteriated analogues **3b** and **3c** with DTBP has indicated that **3a** reacts only in part by hydrogen atom transfer to *tert*-butoxy radical to give the α-centered radical **18**.[13] It follows that while the relative rates of reaction of **1a** and **2a** with DTBP reflect the ease of formation of the corresponding radicals **16** and **17**, the rate of formation of **18** by reaction of **3a** with *tert*-butoxy radical is slower than the overall relative rate of reaction of **3a** with DTBP given in Table I.

On this basis there is a good correlation between the relative rates of formation of the α-centered radicals **16–18** through reaction with bromine atom and with *tert*-butoxy radical. With each species the rate of formation of the α-centered radical **16** by hydrogen atom transfer from the glycine derivative **1a** is faster than the rate of reaction of the alanine derivative **2a** to give **17**, which is in turn faster than the rate of production of the α-centered radical **18** by hydrogen transfer from the valine derivative **3a**. Even on a per hydrogen basis **1a** is more reactive than either **2a** or **3a**. When regarded in the context that the selectivity for the formation of tertiary alkyl radicals in preference to secondary radicals is typically a factor of 20 in reactions involving hydrogen transfer to bromine atom and a factor of 4 in reactions with *tert*-butoxy radical,[5,7] the relative rates of formation of **16–18** in these reactions are peculiar. To the extent that thermodynamic criteria control the pathways and rates of free-radical reactions, these results indicate that, in direct contrast to expectation, the secondary radical **16** is marginally more stable than the tertiary radical **17**, and both **16** and **17** are considerably more stable than **18**.

We attribute this peculiar stability of the radical **16** to a particularly favorable geometry. Stabilization of the captodative[18] radicals **16–18** will result from overlap of the semioccupied p orbital with the π orbitals of the amido and methoxycarbonyl substituents. There will be maximum overlap of these orbitals in planar conformations of the radicals **16–18** (Figure 2). The radical **17** will be destabilized compared to **16** by nonbonding interactions associated with planar conformations of **17**, and **18** will be even less stable owing to more severe nonbonding interactions. These destabilizing influences outweigh the normal thermodynamic preference for the production of tertiary radicals. A recent EPR study has also indicated that relatively small deviations from planarity can significantly diminish the importance of the captodative effect.[19]

The formation of the monobromide **1c** in high yield in the reaction of the glycine derivative **1a** with NBS and the lack of subsequent reaction of **1c** under these conditions[12] is consistent with our rationale for the reactivity of **1a**. The radical **19** produced by hydrogen atom abstraction from **1c** would be less stable than **14** because of nonbonding interactions (Figure 2).

From the production of the α-bromosarcosine derivative **4b** in the reaction of **4a** with NBS, it appears that this reaction involves hydrogen transfer from **4a** to bromine atom to give the α-centered radical **15**. The EPR study of the reaction of **4a** with *tert*-butoxy radical indicates that in this reaction hydrogen transfer from **4a** occurs to give either radical **14** or **15**. This variation in selectivity can be attributed to the susceptibility of reactions involving *tert*-butoxy radical to polar effects.[13] The EPR spectrum showed

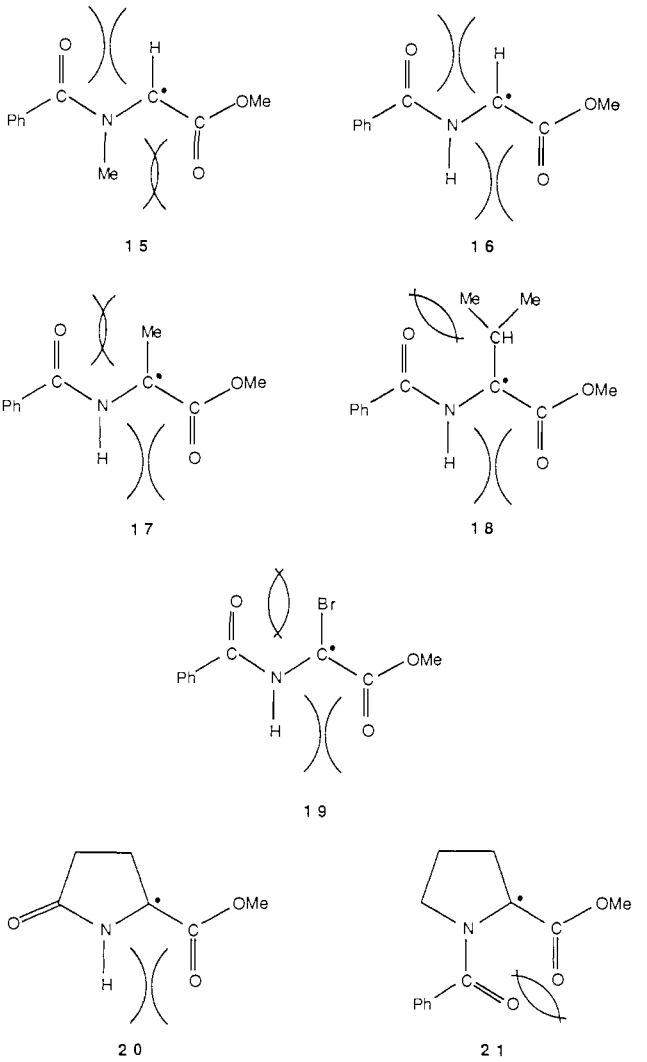

Figure 2. Nonbonding interactions associated with planar conformations of the amido- and methoxycarbonyl-substituted radicals **15–21**.

that the steady-state concentrations of **14** and **15** were approximately equal, indicating that their rates of formation were comparable.[20] The relative rate of reaction of **4a** with NBS (Table I) is a measurement, therefore, of the relative rate of production of **15**, whereas the relative rate of production of **15** by reaction of **4a** with DTBP is approximately half of the overall relative rate of reaction.

The relative rates of production of the α-centered radicals **15** and **17** in reactions with bromine atom and with *tert*-butoxy radical are very similar. This supports the hypothesis that the rate of hydrogen atom transfer from amino acid derivatives is affected by the extent of nonbonding interactions in the product radicals, since the degree of nonbonding interactions in planar conformations of **15** and **17** is also very similar (Figure 2).

The deuterium isotope effect reflected in the relative rates of reaction of methyl pyroglutamate (**5a**) and the deuteriated analogue **5b** with NBS and the production of the dimer **8** in the reaction of **5a** with DTBP indicate that with each reagent **5a** reacts by hydrogen transfer from the α-position to give the radical **20**. That the rates of reaction of **5a** with bromine atom and with *tert*-butoxy radical are faster than the corresponding rates of reaction of the glycine derivative **1a** is consistent with the rationale proposed above. The radical **20** can adopt planar conformations which are relatively free of nonbonding interactions (Figure 2). Formation of the radical **20** is favored by the relief of ring strain and by the release of steric interactions between the methoxycarbonyl substituent and the β-hydrogens in **5a**.[20,21] It is possible

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that formation of the radical **20** is also favored entropically by the inflexibility of the ring in **5a**, holding the amido group in the planar orientation as required for stabilization of the product. Thus the radical **20** is more stable than the glycyl radical **16** and this is reflected in the relative rates of reaction of **1a** and **5a** with bromine atom and with *tert*-butoxy radical.

On the basis of the hypothesis presented above, reaction of *N*-benzoylproline methyl ester (**6a**) to give the α-centered radical **21** would be expected to be much slower than the rate of reaction of the glycine derivative **1a** to give **16**, because the nonbonding interactions are much more severe in **21** than in **16** (Figure 2). The anomalous relative rates of reaction of **6a** compared to **1a** with bromine atom and with *tert*-butoxy radical are due to the regioselectivity of reaction. With each species, the relative rates of reaction of **6a** and the deuteriated analogues **6b,c** show that the major reaction of **6a** occurs at the δ-position to form the radical **22** in preference to the radical **21**. The production of **9** and **10** in the reaction of **6a** with NBS provides little information on the regioselectivity of reaction, but it is not inconsistent with reaction via the radical **22**. While the rate of reaction of **6a** is faster than the rate of reaction of **1a**, the rate of formation of **21** is considerably slower than the rate of formation of **16**. In fact, steric interactions associated with planar conformations of the radical **21** are so severe that the predominant reaction of **6a** is to produce the radical **22**, instead of **21**. Analogous regioselectivity has been observed in an electrochemical reaction of *N*-(methoxycarbonyl)proline methyl ester.[22]

Conclusion

In summary, the relative rates of reaction of **1a–6a** and the deuteriated analogues **1b–3b**, **5b**, and **6b,c** with bromine atom and of **1a–6a** and **6b,c** with *tert*-butoxy radical indicate that the selective reaction of glycine residues in these and other free radical reactions of amino acid derivatives is due to the stability of radicals produced by atom-transfer reactions. Radicals produced by hydrogen transfer from *N*-acylglycine derivatives may adopt planar conformations which are relatively free of nonbonding interactions and in which there is maximum delocalization of the unpaired electron, whereas radicals produced by similar reactions of derivatives of other amino acids are relatively unstable because of nonbonding interactions. Presumably selective reactions of derivatives of pyroglutamic acid and proline have not been observed in biological systems due to the relatively rare natural occurrence of these amino acids when compared to that of glycine.[23] In view of the numerous methods that have been reported for the synthesis of amino acids through the elaboration of glycine derivatives, particularly α-halogenated glycine derivatives,[12,24] the selective bromination of glycine derivatives has considerable potential as a method for the selective modification of glycine residues in small peptides.[25]

Experimental Section

GLC analyses were carried out on either a Varian 3700, a Perkin-Elmer 990, or a Pye 104 gas chromatograph using a Chrompack XE-60-S-VAL-S-A-PEA column (50 m × 0.22 mm) or a 5% OV-17 on VarAport column (1.0 m × 3 mm). HPLC analyses were performed on either a Shimadzu (LC-4A) HPLC with a Rheodyne (7125) injector and a Shimadzu ultraviolet detector (SPD-2AS) or with a Waters Model 501 solvent delivery system and a U6K injector with a Waters Model 481 absorbance detector using a Regis Pirkle Covalent L-Phenylglycine column (25 cm × 4.6 mm), a DuPont Zorbax cyanopropyl column (25 cm × 9.4 mm), or a Waters Z-module with a μ-Porasil Radial-Pak cartridge (10 cm × 8 mm). Column eluates were monitored at 254 nm. EPR spectra were recorded on a Varian E9 EPR spectrometer. Radicals were generated directly in the spectrometer cavity by irradiating solutions with an Oriel 1000-W high-pressure mercury lamp. Mixtures of **4a** and DTBP (1:1, w/w) and of **4b**, DTBP, and hexabutylditin (1:1:1, w/w/w) were prepared and degassed by bubbling with nitrogen for 10–15 min before irradiation.

Glycine, (2*R*)-, (2*S*)-, and (2*R*,*S*)-alanine, (2*R*)- and (2*R*,*S*)-valine, sarcosine, (2*R*,*S*)-pyroglutamic acid, (2*R*,*S*)-proline, and (2*R*,*S*)-glutamic acid were purchased from Sigma Chemical Co. α-Deuteriated glycine, alanine, valine, proline, and glutamic acid were prepared by treatment of the corresponding nondeuteriated amino acids with acetic anhydride/D_2O.[26] Deuteriated alanine and valine were resolved by treatment of the respective *N*-acetylamino acid derivatives with Hog Renal Acylase 1.[27] Deuteriated pyroglutamic acid was prepared by cyclization of deuteriated glutamic acid.[28] 2,5,5-Trideuterioproline was prepared by the method of Leitch.[29] The amino acid derivatives **1a,b**,[30] (2*R*)-, (2*S*)-, and (2*R*,*S*)-**2a**,[31] (2*S*)-**2b**,[31] (2*R*)- and (2*R*,*S*)-**3a**,[32] (2*S*)-**3b**,[32] **4a**,[33] (2*R*,*S*)-**5a,b**,[34] and **6a–c**[35] were all prepared from the corresponding amino acids by using standard procedures. They were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy and had physical constants in agreement with those reported. Deuterium content of the amino acid derivatives was determined by mass spectrometry to be the following: **1b**, 90% D_2; **2b**, 83% D_1; **3b**, 85% D_1; **5b**, 62% D_1; **6b**, 83% D_1; and **6c**, 92% D_3.

Competitive Reactions of 1a–6a and the Deuteriated Analogues 1b–3b, 5b, and 6b,c with NBS. Mixtures of two amino acid derivatives, *tert*-butylbenzamide (internal standard), and NBS in carbon tetrachloride were irradiated with a 250-W mercury lamp at reflux under nitrogen. Aliquots were removed at intervals and analyzed by GLC and HPLC. Various mixtures of amino acid derivatives were studied, including **1a** and (2*R*,*S*)-**2a**, **1b** and (2*R*,*S*)-**2a**, **1a** and (2*S*)-**2b**, (2*R*)-**2a** and (2*S*)-**2b**, (2*R*,*S*)-**2a** and (2*R*,*S*)-**3a**, (2*R*)-**3a** and (2*S*)-**3b**, **1a** and **4a**, **1a** and (2*R*,*S*)-**5a**, **1a** and (2*R*,*S*)-**5b**, **1a** and (2*R*,*S*)-**6a**, **1a** and (2*R*,*S*)-**6b**, and **1a** and (2*R*,*S*)-**6c**. All experiments were carried out at least in triplicate and analyses were performed at least in triplicate. Results of different experiments were consistent, as were results obtained from aliquots taken from the same experiment at different times.

Competitive Reactions of 1a–6a and 6b,c with DTBP. Mixtures of two amino acid derivatives, *tert*-butylbenzamide, and DTBP in *tert*-butyl alcohol were irradiated in a Rayonet photochemical reactor equipped with 12 RPR 3500 lamps. Reaction mixtures were analyzed as described above for the reactions with NBS. Mixtures of amino acid derivatives that were studied include **1a** and (2*S*)-**2a**, (2*R*,*S*)-**2a** and (2*R*,*S*)-**3a**, **1a** and **4a**, **1a** and (2*R*,*S*)-**5a**, **1a** and (2*R*,*S*)-**6a**, **1a** and (2*R*,*S*)-**6b**, and **1a** and (2*R*,*S*)-**6c**.

Reaction of *N*-Benzoyl-(2*R*,*S*)-proline Methyl Ester 6a with NBS. A mixture of *N*-benzoyl-(2*R*,*S*)-proline methyl ester **6a** (0.5 g, 2.1 mmol) and NBS (1.14 g, 6.4 mmol) in carbon tetrachloride (80 ml) was heated at reflux while being irradiated with a 250-W mercury lamp, under nitrogen, for 1 h. The suspension was chilled in an ice/salt bath and then filtered and concentrated in vacuo. The residue was chromatographed on silica with ethyl acetate–hexane as eluent to give *N*-benzoyl-4-bromo-2-(methoxycarbonyl)pyrrole (**10**) and *N*-benzoyl-3-bromo-2-(methoxycarbonyl)pyrrole (9). **10** (96 mg, 14%): mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 3 H), 7.03 (d, J = 2 Hz, 1 H), 7.22 (d, J = 2 Hz, 1 H), 7.40–7.90 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 51.9, 99.3, 122.5, 126.4, 126.6, 128.9, 130.0, 132.6, 134.0, 159.7, 167.1; MS, *m/z* (relative intensity) 309 (92), 307 (96), 278 (5), 276 (6), 228 (10), 205 (10), 203 (9), 176 (100). (Anal. Calcd for $C_{13}H_{10}BrNO_3$: C, 50.86; H, 3.26; N,

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4.56. Found: C, 50.83; H, 3.05; N, 4.31.) **9** (190 mg, 29%): oil; ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 3 H), 6.39 (d, J = 4 Hz, 1 H), 7.14 (d, J = 4 Hz, 1 H), 7.45-7.53 (m, 3 H), 7.73-7.77 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 51.9, 109.4, 114.9, 123.8, 126.3, 128.9, 129.8, 132.5, 133.8, 160.0, 167.1; MS, m/z (relative intensity) 309 (35), 307 (36), 278 (3), 276 (3), 251 (3), 249 (3), 230 (100); precise mass calcd for $C_{13}H_{10}BrNO_3$ 306.9845, found 306.9840.

Reaction of *N*-Benzoyl-(2*R*,*S*)-alanine Methyl Ester (2a) with DTBP. A mixture of *N*-benzoyl-(2*R*,*S*)-alanine methyl ester (**2a**) (0.3 g, 1.5 mmol) and DTBP (4 mL, 19 mmol) in *tert*-butyl alcohol (30 mL), contained in a quartz tube under nitrogen, was irradiated in the Rayonet photochemical reactor. After 4 days the reaction mixture was concentrated and chromatographed on silica with ethyl acetate-hexane as eluent to give dimethyl 2,3-dibenzamido-2,3-dimethylbutanedioate (**13**) and *N*-benzoyl-2,2-dimethylglycine methyl ester (**12**). **13** (60 mg, 20%): mp 170-177 °C; ^{1}H NMR (DMSO-d_6) δ 2.00 (s, 6 H), 3.80 (s, 6 H), 6.80 (br, 2 H), 7.53-7.93 (m, 10 H); MS, m/z (relative intensity) 413 (0.4), 381 (2), 353 (7), 231 (22), 207 (38), 175 (8), 105 (100), 77 (50). (Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.1; H, 5.9; N, 6.8. Found: C, 63.9; H, 5.9; N, 6.6.) **12** (32 mg, 10%) was identical in all respects with an authentic sample obtained by derivatization of the corresponding amino acid.[36]

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Registry No. 1a, 1205-08-9; **1b**, 102770-12-7; (2*S*)-**2a**, 38767-73-6; (2*R*)-**2a**, 7260-27-7; (2*RS*)-**2a**, 38767-73-6; (2*S*)-**2b**, 118013-54-0; (2*R*)-**3a**, 1492-13-3; (2*RS*)-**3a**, 14599-03-2; (2*S*)-**3b**, 116297-93-9; **4a**, 71533-21-6; (2*RS*)-**5a**, 54571-66-3; (2*RS*)-**5b**, 117918-31-7; (2*RS*)-**6a**, 114051-14-8; (2*RS*)-**6b**, 117918-32-8; (2*RS*)-**6c**, 117918-33-9; **9**, 117918-26-0; **10**, 117918-27-1; **11**, 117918-28-2; **12**, 65563-98-6; (±)-**13** (diastereomer-1), 117918-29-3; (±)-**13** (diastereomer-2), 117918-34-0; **14**, 117918-30-6; **15**, 116453-15-7.

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Steric and Electrochemical Effects on Rates of Electron Transfer and S_N2 Reactions of 9-(Dialkylamino)fluorenide Ions with Alkyl Halides

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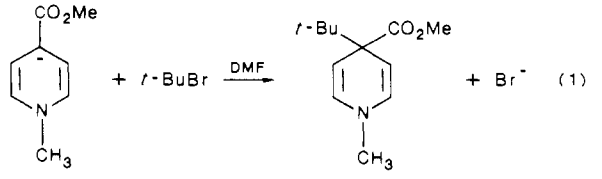
Abstract: Rate ratios for reactions of $PhCH_2Cl$ vs Ph_2CHCl with seven 9-(dialkylamino)fluorenide (9-R_2NFl^-) ions were measured in Me_2SO solution. Although the reaction sites in these ions are known to be highly congested and Ph_2CHCl is more sterically hindered than is $PhCH_2Cl$, the $k^{PhCH_2Cl}/k^{Ph_2CHCl}$ rate ratios for reactions with 9-R_2NFl^- ions in Me_2SO were all much lower (0.20-4.9) than for the less hindered 9-$MeFl^-$ or *p*-$MeOC_6H_4O^-$ ions (81 and 138, respectively). This suggested that the Ph_2CHCl reactions with 9-R_2NFl^- ions were occurring by single electron transfer (SET) mechanisms, despite the formation of high yields of S_N2-type products. This conclusion was supported by the observation of a close correspondence between SET rates (log k_{SET}), calculated by using the Marcus equation, and log k_{obsd} for reactions of 9-R_2NFl^- ions with both a known single electron acceptor, F_3CCH_2I, and with Ph_2CHCl and $(p\text{-}ClC_6H_4)_2CHCl$. Similar log k_{SET} vs log k_{obsd} comparisons for reactions of the 9-R_2NFl^- ions with $PhCH_2Cl$, c-$C_6H_{11}Br$, and *n*-BuBr revealed greater disparity.

The idea that, in principle, a concerted ("polar") S_N2 reaction can merge with a single electron transfer (SET) mechanism, wherein the product is formed by coupling of a geminate radical pair, has been recognized for many years.[1] In his recent definitive book on electron transfer reactions Eberson concludes, however, that it takes a very strong electron donor anion to effect a bimolecular aliphatic substitution reaction on an alkyl halide by an outer-sphere SET mechanism.[2] Nevertheless, he points out that this has been achieved for certain alkyl halides and that there is good reason to believe that this SET mechanism will merge with the concerted single electron shift S_N2 reaction, as has been suggested by several investigators.[3] Outer-sphere SET substitutions have been observed by Lund and Lund for reactions of *t*-BuBr with radical anions, $ArH^{\bullet-}$, and with carbanion **1**, which



(1)

1 **2**

was generated electrochemically from 4-(methoxycarbonyl)-*N*-methylpyridinium iodide. Similar substitutions were also observed for reactions of **1** with 1-adamantyl and neopentyl bromides, but the less hindered ethyl, *n*-butyl, and *sec*-butyl bromides appeared to react by borderline mechanisms.[3]

In earlier papers[4] we have shown that reactions of 9-substituted fluorenide ions, 9-GFl^-, with $PhCH_2Cl$ are subject to rate-retarding steric effects, as G becomes more bulky along the series, Me, Et,

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