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Reactivities of Amino Acid Derivatives Toward Hydrogen Abstraction by Cl• and OH•

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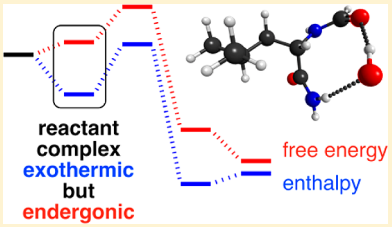
Supporting Information

ABSTRACT: In recent computational studies of hydrogen-atom abstraction from amino acid derivatives, two distinct rationalizations have been put forward for the relative inertness of the α-C−H. Of these, the proposal that the inertness is due to a "kinetic trap" associated with particularly stable complexes is shown to be unlikely because of unfavorable entropies. On the other hand, the proposed existence of deactivating polar effects at the α-position in Cl• abstractions is likely also to be applicable to OH• abstractions, but to a lesser extent.



INTRODUCTION

The carbon-centered radicals formed through hydrogen-atom abstraction from the α (and to a lesser extent the β) positions of the amino acid residues of proteins and peptides may undergo subsequent reactions, ultimately culminating in backbone cleavage.[1] It is therefore somewhat serendipitous that electrophilic free radicals (e.g., Cl• and OH•) appear to avoid abstraction from the α and β positions, instead preferring to react (where possible) with C−H moieties distal to these centers (see Figure 1),[2,3] producing radicals that are unlikely to lead to backbone cleavage. Indeed, it has even been suggested that a possible reason for nature selecting proteins as the building blocks of life is the innate resistance of this structural framework toward free-radical-induced degradation.[3] From the perspective of physical organic chemistry, this regioselectivity is peculiar, since abstraction from the α carbon usually affords radical products that are overwhelmingly more stable compared with radicals formed along the aliphatic side chain, partially due to the existence of a captodative effect.[4]

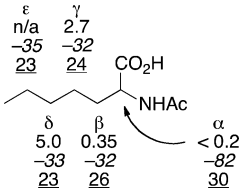


Figure 1. Experimental[3] relative rates for hydrogen abstraction by Cl• and corresponding calculated[5] free energies of reaction (in *italics*) and free energy barriers (underlined) (kJ mol^{-1}).

In light of this remarkable regioselectivity, a number of theoretical studies have attempted to shed light on the origin of this contrathermodynamic effect in the context of abstractions by Cl• and OH•. Two differing explanations have been put forward that are dependent on the nature of the abstracting radical.

For abstractions by Cl•, we have previously attributed the larger barrier associated with abstraction from the α position (see Figure 1) to the existence of a deactivating polar effect.[5] In addition, we proposed that the early transition structure found in that case is particularly sensitive to such a polar effect, because the influence of the profound stability of the captodatively stabilized α-radical product is reduced. In this regard, our findings are consistent with the longstanding experimentally held view that polar effects give rise to the regioselectivity of H abstraction by Cl•.[2,6]

On the other hand, for abstractions by OH• from *N*-formylleucinamide (**1**) (Figure 2), Scheiner and Kar concluded that the larger barrier associated with abstraction from the α position arises because of the formation of a particularly stable reactant complex at this position, which serves to act as a "kinetic trap".[7] The formation of such complexes has also been invoked in explaining the kinetics of H abstraction by OH• from other amino acids, including glycine and alanine,[8] methionine,[9] asparagine,[10] isoleucine,[11] and serine.[12]

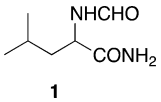


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Figure 2. *N*-Formylleucinamide (**1**), a model for leucine residues in peptides.

Although it is entirely possible that reactant complexes are important in determining the regioselectivity of H abstraction from amino acid derivatives by OH•, but not by Cl•, a unifying

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explanation for the relative inertness in the two types of abstractions would be more appealing. In addition, the previous OH• investigations were based on considerations of enthalpies rather than free energies, thereby precluding consideration of the entropic penalty to be paid for the formation of such complexes. Indeed, in our previous investigation, we noted that, although binding of Cl• to *N*-acetylglycine is favorable on enthalpic grounds, such a complex is unfavorable on the free energy surface and therefore unlikely to be significant in determing the regioselectivity of H abstraction. In light of this finding, we felt it important to investigate whether similar conclusions might be reached in the case of the reactions involving OH•. To this end, we have re-evaluated the H abstraction from **1** by both OH• and Cl•, in the context of calculated free energies, and we now present our findings.

COMPUTATIONAL DETAILS

We have used a theoretical approach that we have found previously to yield kinetics information of reasonable accuracy.[5,13]

Standard ab initio molecular orbital theory and DFT calculations[14] were carried out with Gaussian 09.[15] Gas-phase geometries of stationary points were obtained with the BHandH-LYP/6-31+G(d,p) procedure. We have briefly examined the conformational space of each relevant species, at the BHandH-LYP/6-31+G(d,p) level, in the same manner as in ref 5. Following each geometry optimization, harmonic frequency analysis was carried out to confirm the nature of the stationary point as an equilibrium structure or a transition structure. Improved single-point energies were evaluated using the B2K-PLYP procedure[16] in conjunction with the aug′-cc-pV(T+d)Z basis set, where aug′ denotes the use of diffuse functions only on non-hydrogen atoms. The frozen-core approximation was used in all B2K-PLYP calculations. In order to account for the effect of spin−orbit coupling, literature values of 3.52 and 0.83 kJ mol^{-1} were applied for the isolated Cl atom and OH radical, respectively.[17] We have assumed that the spin−orbit effect is quenched in the transition structure and in other regions of the reaction paths that we have examined.

To obtain the zero-point vibrational energies (ZPVEs) and thermal corrections for enthalpies (ΔH_{298}) and entropies (S_{298}) at 298 K, we used BHandH-LYP/6-31+G(d,p) harmonic vibrational frequencies and appropriate literature scale factors.[18] A harmonic-oscillator rigid-rotor model is assumed in these calculations. For nonstationary points on reaction paths, the vibrations that correspond to the reaction coordinate are removed from the evaluation of ZPVEs and ΔH_{298} and S_{298} values. For some nonstationary structures, harmonic vibrational analysis yields contentious low or imaginary frequencies. In those cases, the questionable frequencies are replaced by interpolated values obtained using formulas proposed by Truhlar and co-workers.[19]

The intrinsic reaction coordinate (IRC)[20] procedure was used to obtain reaction paths that connect transition structures with their adjacent minima. We employ the IRCmax method[21] to approximate a high-level reaction path, by carrying out high-level (B2K-PLYP) single-point energy calculations on a low-level (BHandH-LYP) IRC. Solvation corrections at each point on the reaction path were obtained at the M05-2X/6-31G(d) level using the SMD model, which has been shown to yield free energies of solvation for a wide range of neutral solutes with an overall uncertainty of ∼3 kJ mol^{-1}.[22] We find that this methodology produces standard free energies of solvation for OH• (−16.6 kJ mol^{-1}), water (−28.6 kJ mol^{-1}), and HCl (−5.4 kJ mol^{-1}) that are in good agreement with the corresponding experimental values[23] of −16.3, −26.4, and −8.2 kJ mol^{-1}. In order to best reflect experimental reaction conditions, we used the parameters for acetic acid for abstractions by Cl•, while for OH• abstractions the parameters for water were employed.

Rate constants (k) at 298 K are obtained from the calculated free energy barriers ($\Delta G^{\ddagger}$) using the standard Eyring expression: $k = (k_B T/h)\exp(-\Delta G^{\ddagger}/RT)$. These k values, together with the number of hydrogen atoms at each of the α, β, γ, and δ positions, were then used to obtain our theoretical estimates of relative yields. All relative energies are given in kJ mol^{-1}.

RESULTS AND DISCUSSION

Importance of Reactant Complexes. We first consider whether reactant complexes play an important role in determining the kinetics of H abstraction from *N*-formylleucinamide (**1**) by Cl• and OH•. In addition to the complexes formed between **1** and either Cl• or OH• that are directly relevant to abstraction from the α−δ positions, we have also considered complexes that may not directly lead to H abstraction but which nonetheless may act as kinetic traps for the abstractions. However, because the latter complexes are relevant to all the abstractions, they are unlikely to affect the *relative* propensities for abstraction at the various positions. Representative examples of the complexes are shown in Figure 3.

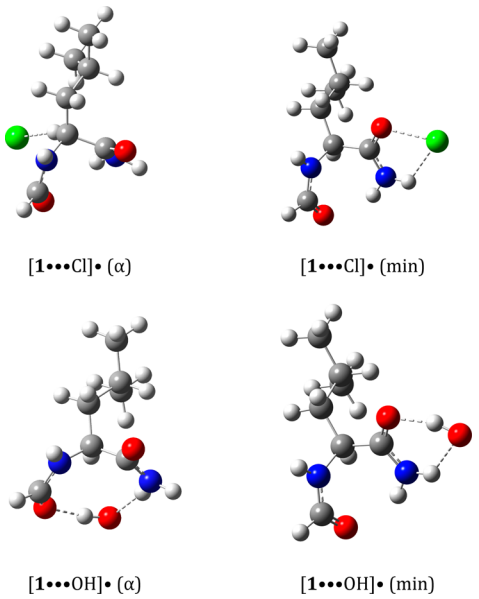

Figure 3. Geometries of complexes formed between **1** and Cl• or OH•.

Beginning with the interaction of Cl• with **1** (Table 1), we note that the complex of lowest energy (i.e., [**1**···Cl]•(min), Figure 3), which is not related to abstraction from any particular position, is predicted to be strongly bound on the enthalpic surface (ΔH_C(min) = −33.4 kJ mol^{-1}) but only weakly bound in terms of free energy ($\Delta G_{C,s}$(min) = −6.5 kJ mol^{-1}). The complexes that are directly relevant to abstractions by Cl• from the α−δ positions are all predicted to have positive free energies and thus would not form spontaneously; these are therefore unlikely to affect the regioselectivity of H abstraction by Cl•.

Turning our attention now to the complexes formed between **1** and OH•, we find that although the complex suggested by Scheiner and Kar to provide a kinetic trap hindering abstraction from the α-position has a favorable enthalpic complexation energy ($\Delta H_C(\alpha)$ = −35.0 kJ mol^{-1}), the inclusion of entropic contributions and solvation effects renders the binding unfavorable on the free energy surface ($\Delta G_{C,s}(\alpha)$ = +21.7 kJ mol^{-1}). Regarding the large and positive $\Delta\Delta G_{C,s}$ for both the minimum energy OH complex and the complex associated with α abstraction, we note that the proton of the OH• moiety in

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Table 1. Solution-Phase Free Energies of Complexation ($\Delta G_{C,s}$) between Cl$^\bullet$ and OH$^\bullet$ with *N*-Formylleucinamide (1) and Components Leading to These Values (298 K, kJ mol^{-1})[a]

	ΔE_C	$\Delta\Delta H_C$	ΔH_C	$-T\Delta S_C$	ΔG_C	$\Delta\Delta G_{C,s}$	$\Delta G_{C,s}$
				Cl$^\bullet$ [b]			
α	−1.3	1.4	0.1	22.3	22.3	0.1	22.5
β	−6.1	0.8	−5.3	21.5	16.2	5.6	21.8
γ	−11.1	1.7	−9.4	25.9	16.5	−4.8	11.7
δ	−2.9	1.1	−1.8	14.5	14.5	0.7	13.3
min[d]	−35.3	1.9	−33.4	29.3	−4.1	−2.4	−6.5
				OH$^\bullet$ [c]			
α	−41.4	6.4	−35.0	35.7	0.7	20.9	21.7
β	−4.8	−0.8	−5.5	34.5	29.0	3.3	32.3
γ	5.1	1.9	6.9	25.4	32.3	1.5	33.7
δ	−4.6	4.2	−0.3	19.3	19.0	1.9	20.9
min[d]	−37.9	6.2	−31.7	35.1	3.4	16.7	20.1

[a]ΔE_C = vibrationless gas-phase complexation energy (B2K-PLYP/aug′-cc-pV(T+d)Z//BHandH-LYP/6-31+G(d,p)). $\Delta\Delta H_C$ = correction for enthalpy at 298 K (inclusive of ZPVE). ΔH_C = complexation enthalpy at 298 K (ΔE_C + $\Delta\Delta H_C$). $-T\Delta S_C$ = entropic contribution. ΔG_C = gas-phase free energy of complexation (ΔH_C − $T\Delta S_C$). $\Delta\Delta G_{C,s}$ = solvation contribution. $\Delta G_{C,s}$ = solution-phase free energy of complexation (ΔG_C + $\Delta\Delta G_{C,s}$). [b]Acetic acid solvent for $\Delta\Delta G_{C,s}$. [c]Water solvent for $\Delta\Delta G_{C,s}$. [d]Minimum energy complex that is not specific to abstraction from any of the positions (see Figure 3).

these complexes is involved in hydrogen bonding with **1** (Figure 3). Thus, we can expect this proton to be solvated less strongly than in an isolated OH$^\bullet$. As a result of all of the above effects, the formation of the α complex is not spontaneous and is therefore unlikely to be important in determing the kinetics of H abstraction.

This finding contrasts with the conclusions reached previously based on the enthalpic surface,[7] which did not take into account the unfavorable entropic penalty (on the free energy surface) associated with the interaction of OH$^\bullet$ with **1**. It therefore seems that the relatively inert nature of the α-C−H in amino acid derivatives toward abstraction by OH$^\bullet$ must have an alternative explanation, and we now proceed to explore this further.

Barriers for Abstraction from Neutral *N*-Formylleucinamide. We have computed both the gas-phase (Table 2) and solution-phase (Table 3) reaction free energies and barriers for the abstraction by Cl$^\bullet$ and OH$^\bullet$ from the various positions of **1** (i.e., α–δ). Furthermore, in order to assist in elucidating the effects that give rise to the observed regioselectivity, we also provide the individual components that together result in the final free energy barriers. In the gas phase (Table 2), we find that the free energies of reaction (ΔG_g) become increasingly negative in the order $\delta \rightarrow \beta \rightarrow \gamma \rightarrow \alpha$, consistent with the expected relative stabilities of the carbon-centered radicals being formed: i.e., abstractions from CH_3 < CH_2 < CH leading to primary, secondary, and tertiary radicals, respectively. Formation of the α-carbon-centered radical, which is subject to captodative stabilizing effects, has the greatest thermodynamic driving force (−61.9 and −120.7 kJ mol^{-1} for abstractions by Cl$^\bullet$ and OH$^\bullet$, respectively).

If we compare the barriers calculated at the two tertiary positions for H abstractions by both Cl$^\bullet$ and OH$^\bullet$, we find that the barriers for abstraction from the α position are larger than those for the γ position. This ordering is in contrast to thermodynamics but, even in the absence of solvation effects,

Table 2. Gas-Phase Reaction Free Energies (ΔG_g) for Hydrogen Abstraction by Cl$^\bullet$ and OH$^\bullet$ from the α, β, γ, and δ Positions of 1, along with Corresponding Free Energy Barriers ($\Delta G^\ddagger_g$) and Their Components (298 K, kJ mol^{-1})[a]

	ΔG_g	$\Delta E^\ddagger_g$	$\Delta\Delta H^\ddagger_g$	$\Delta H^\ddagger_g$	$-T\Delta S^\ddagger_g$	$\Delta G^\ddagger_g$
			Cl$^\bullet$			
α	−61.9	8.5	−6.1	2.5	31.3	33.8
β	−21.1	−1.3	−9.9	−11.2	37.2	26.0
γ	−40.5	−6.5	−0.8	−7.3	34.0	26.7
δ	−17.3	2.3	−5.0	−2.8	30.2	27.5
			OH$^\bullet$			
α	−120.7	−2.6	0.6	−1.9	41.9	40.0
β	−80.0	−12.8	1.6	−11.2	41.7	30.5
γ	−99.4	−3.8	−0.2	−4.0	39.8	35.7
δ	−76.2	1.3	−0.3	1.0	40.3	41.3

[a]ΔG_g = gas-phase free energy of reaction (B2K-PLYP/aug′-cc-pV(T+d)Z//BHandH-LYP/6-31+G(d,p)). $\Delta E^\ddagger_g$ = vibrationless energy contribution to the gas-phase variational free energy barrier. $\Delta\Delta H^\ddagger_g$ = corrections for 298 K enthalpy barrier (incorporating ZPVE). $\Delta H^\ddagger_g$ = 298 K enthalpy barrier ($\Delta E^\ddagger_g$ + $\Delta\Delta H^\ddagger_g$). $-T\Delta S^\ddagger_g$ = entropic contribution. $\Delta G^\ddagger_g$ = gas-phase variational free energy barrier ($\Delta H^\ddagger_g$ − $T\Delta S^\ddagger_g$).

Table 3. Solution-Phase Free Energy Barriers ($\Delta G^\ddagger_s$) for Hydrogen Abstraction from the α, β, γ, and δ Positions of 1 by Cl$^\bullet$ and OH$^\bullet$, and Their Components, and Solution-Phase $\Delta G^\ddagger_s$ Values for Protonated 1 (298 K, kJ mol^{-1})[a]

	$\Delta E^\ddagger$	$\Delta\Delta H^\ddagger$	$-T\Delta S^\ddagger$	$\Delta G^\ddagger$	$\Delta\Delta G^\ddagger_s$	$\Delta G^\ddagger_s$	$\Delta G^\ddagger_s$(H$^+$-**1**)
				Cl$^\bullet$ [b]			
α	8.6	−5.4	30.2	33.5	−3.6	29.9	41.0
β	−2.7	−6.1	34.8	26.0	4.6	30.7	33.8
γ	−6.5	−0.8	34.0	26.7	−2.0	24.8	22.8
δ	0.2	−3.3	29.9	26.8	−0.1	26.6	26.9
				OH$^\bullet$ [c]			
α	−2.6	0.6	41.9	40.0	14.2	54.2	56.5
β	−12.8	1.6	41.7	30.5	26.5	57.0	64.1
γ	−6.9	1.2	39.5	33.8	11.0	44.8	50.3
δ	1.3	−0.3	40.3	41.3	12.9	54.2	58.4

[a]$\Delta E^\ddagger$ = vibrationless energy contribution to the solution-phase variational free energy barrier (B2K-PLYP/aug′-cc-pV(T+d)Z//BHandH-LYP/6-31+G(d,p)). $\Delta\Delta H^\ddagger$ = corrections for 298 K enthalpy barrier (incorporating ZPVE). $-T\Delta S^\ddagger$ = entropic contribution. $\Delta G^\ddagger$ = gas-phase free energy contribution to the solution-phase free energy barrier ($\Delta E^\ddagger$ + $\Delta\Delta H^\ddagger$ − $T\Delta S^\ddagger$). $\Delta\Delta G^\ddagger_s$ = solvation contribution. $\Delta G^\ddagger_s$ = solution-phase variational free energy barrier ($\Delta G^\ddagger$ + $\Delta\Delta G^\ddagger_s$). [b]Acetic acid solvent for $\Delta\Delta G^\ddagger_s$. [c]Water solvent for $\Delta\Delta G^\ddagger_s$.

already partially reflects experimental results in related systems.[3] We find that the transition structures for Cl$^\bullet$ abstraction are "early", with Cl···H distances >1.9 Å. On the other hand, the transition structures for abstraction by OH$^\bullet$ are not particularly early (HO···H ≈ 1.45 Å for abstractions from the α, β, and δ positions and 1.54 Å for γ-abstraction). Thus, one might expect reaction thermodynamics to play a smaller role in the Cl$^\bullet$ abstraction than in the OH$^\bullet$ abstraction. As we shall see, for the abstraction by Cl$^\bullet$, the contrathermodynamic behavior is consistent with a polar deactivating effect, where the σ-electron-withdrawing NHCHO and $CONH_2$ groups at the α carbon disfavor hydrogen abstraction by the electrophilic Cl$^\bullet$ radical. However, such a polar effect would appear to be less dominant in the OH$^\bullet$ abstraction, due to the presence of relatively strong secondary interactions.

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We now turn our attention to considering the effect of solvation on the H abstraction barriers (Table 3). First of all, we note that the locations of the solution-phase variational TSs along the reaction paths are in some cases identical with, and in other cases slightly different from, the gas-phase variational structures. This is reflected in the small differences in some cases in the gas-phase (Table 2) and solution-phase (Table 3) $\Delta E^{\ddagger}$ and $\Delta G^{\ddagger}$ values. We also note that the solvation contributions ($\Delta\Delta G^{\ddagger}_{s}$) at the α, γ, and δ positions are relatively close to one another, but the $\Delta\Delta G^{\ddagger}_{s}$ values for β abstractions are somewhat more positive, for both Cl$^{\bullet}$ and OH$^{\bullet}$ abstractions. In comparing the barriers associated with abstraction by Cl$^{\bullet}$ and OH$^{\bullet}$ from the α and γ positions, we see that abstractions from the former position are associated with barriers that are 5.1 and 9.4 kJ mol^{-1} higher, respectively, than from the latter position.

Effect of Protonation. The experimental studies were performed under acidic conditions, and hence the amino acid derivatives might be subject to various degrees of protonation, but our solvation corrections, obtained using a continuum model, do not explicitly account for such effects. Partial protonation of the carbonyl moieties, associated for example with hydrogen bonding,[24] might be expected to accentuate the extent of deactivation at the α position. Indeed, we previously found that full protonation of the amino group of norleucine results in an especially large deactivation at the α and adjacent positions for the abstraction by Cl$^{\bullet}$.[5] Partial protonation of an amido carbonyl is likely to have a less marked effect, but it might nonetheless further disfavor abstraction from the α position in comparison with the unprotonated substrate.

To this end, we have calculated the corresponding barriers for protonated **1** (Table 3, $\Delta G^{\ddagger}_{s}$(H^{+}-**1**)). The result is that, for the abstraction by Cl$^{\bullet}$, there is a clear deactivating effect at the α and (to a lesser extent) the β positions. We have further utilized the calculated solution-phase barriers for both **1** and H^{+}-**1** to estimate approximate relative yields of the chlorinated products at the various positions. For **1**, such estimation leads to 3, 4, 24, and 68% for the α, β, γ and δ products, respectively. For H^{+}-**1**, the corresponding values are 0 (α), 1 (β), 46 (γ), and 53% (δ). These compare reasonably well with the experimental relative yields[3] for chlorine abstraction from the closely related *N*-acetylleucine, for which the values for α, β, γ, and δ are 0, 0, 49, and 51%, respectively. For abstraction from protonated **1** by OH$^{\bullet}$, we find that the general trend for the barriers for H^{+}-**1** is not very different from that for neutral **1**. This is perhaps not unexpected, as the polar deactivating effect of OH$^{\bullet}$ is found experimentally to be somewhat less than that of Cl$^{\bullet}$.[3] Our calculated barriers for **1** correspond to approximate relative yields of 2 (α), 1 (β), 85 (γ), and 12 (δ) %, and for H^{+}-**1** they are 6 (α), 1 (β), 75 (γ), and 18% (δ).

Structural and Intermolecular Effects in the Barriers. To further elucidate the source of the observed variations in the abstraction barriers, we have divided each vibrationless barrier ($\Delta E^{\ddagger}$) into a structural-distortion component (ΔE_{dist}) and a fragment-interaction component (ΔE_{int}) (Table 4).[25] The ΔE_{dist} values indicate the energies required to distort the fully optimized reactant geometries to those in the transition structures, and ΔE_{int} represents the energy change for bringing together the distorted fragments from infinite separation to form the transition structure. To allow for a more thorough analysis, we have also included other constituents of the solution-phase free energy barriers for both neutral and protonated **1**.

Table 4. Structural-Distortion (ΔE_{dist}) and Fragment-Interaction (ΔE_{int}) Components of the Vibrationless Barriers for the Abstraction Reactions of 1 and H^{+}-1 by Cl$^{\bullet}$ and OH$^{\bullet}$, and Other Constituents of the Solution-Phase Free Energy Barriers (kJ mol^{-1})

	ΔE_{dist}	ΔE_{int}	$\Delta ZPVE^{\ddagger}$	$\Delta\Delta H^{\ddagger}_{298-0}$	$-T\Delta S^{\ddagger}$	$\Delta\Delta G^{\ddagger}_{s}$	$\Delta G^{\ddagger}_{s}$
				1, Cl$^{\bullet}$ [b]			
α	16.7	−8.1	−4.1	−1.3	30.2	−3.6	29.9
β	5.5	−8.2	−3.8	−2.3	34.8	4.6	30.7
γ	10.6	−17.1	1.3	−2.1	34.0	−2.0	24.8
δ	2.0	−1.9	−1.5	−1.9	29.9	−0.1	26.6
				H^{+}-**1**, Cl$^{\bullet}$ [b]			
α	12.6	−1.4	−3.7	−1.5	34.3	0.6	41.0
β	6.7	0.5	−3.5	−2.0	32.9	−0.8	33.8
γ	2.8	−12.6	−2.2	−2.0	32.6	4.3	22.8
δ	1.5	−2.1	−1.4	−2.0	31.5	−0.6	26.9
				1, OH$^{\bullet}$ [c]			
α	17.1	−19.7	4.9	−4.3	41.9	14.2	54.2
β	4.8	−17.5	6.3	−4.7	41.7	26.5	57.0
γ	6.6	−13.4	5.4	−4.2	39.5	11.0	44.8
δ	5.1	−3.8	3.8	−4.1	40.3	12.9	54.2
				H^{+}-**1**, OH$^{\bullet}$ [c]			
α	12.6	−13.3	3.7	−3.3	40.0	16.7	56.5
β	8.1	−1.6	2.1	−3.3	38.4	20.5	64.1
γ	5.3	−20.0	3.2	−2.9	38.5	26.2	50.3
δ	5.9	3.3	0.8	−2.5	36.2	14.6	58.4

[a] $\Delta ZPVE^{\ddagger}$ = zero-point vibrational energy contribution to barrier. $\Delta\Delta H^{\ddagger}_{298-0}$ = corrections for 298 K enthalpy barrier (excluding $\Delta ZPVE^{\ddagger}$). $-T\Delta S^{\ddagger}$ = entropic contribution. $\Delta\Delta G^{\ddagger}_{s}$ = solvation contribution. $\Delta G^{\ddagger}_{s}$ = solution-phase free energy barrier. [b] Solvent acetic acid for $\Delta\Delta G^{\ddagger}_{s}$. [c] Solvent water for $\Delta\Delta G^{\ddagger}_{s}$.

For the abstraction by Cl$^{\bullet}$, it is apparent that, for both **1** and H^{+}-**1**, ΔE_{dist} and ΔE_{int} represent the largest variations among the various factors. For the abstraction by OH$^{\bullet}$, there are also substantial variations in $\Delta\Delta G^{\ddagger}_{s}$. Abstraction from the most remote δ position gives ΔE_{dist} and ΔE_{int} values that are both very small in magnitude. Thus, the magnitude of the overall free energy barrier at the δ position is mainly governed by entropy and solvation. The α abstractions have notably more positive ΔE_{dist} values than the corresponding β, γ, and δ values. This can be attributed to the interruption of the intramolecular hydrogen bonding between the two α substituents in the α transition structures (Figure 4).

We now turn our attention to ΔE_{int}. It can be seen that, with the exception of OH$^{\bullet}$ abstraction from neutral **1**, ΔE_{int} values at the γ position are often notably more negative than those at

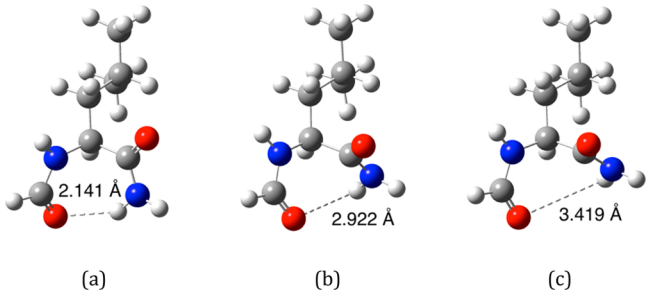

Figure 4. Structure of **1**: (a) fully optimized; (b) within the transition structure of α abstraction by Cl$^{\bullet}$; (c) within the transition structure of α abstraction by OH$^{\bullet}$.

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other positions. We find that abstraction from the γ carbon nicely positions the incoming Cl$^{\bullet}$ or (especially) OH$^{\bullet}$ radical for favorable secondary interactions with an α substituent (Figure 5). In the case of OH$^{\bullet}$ abstraction from **1**, the major

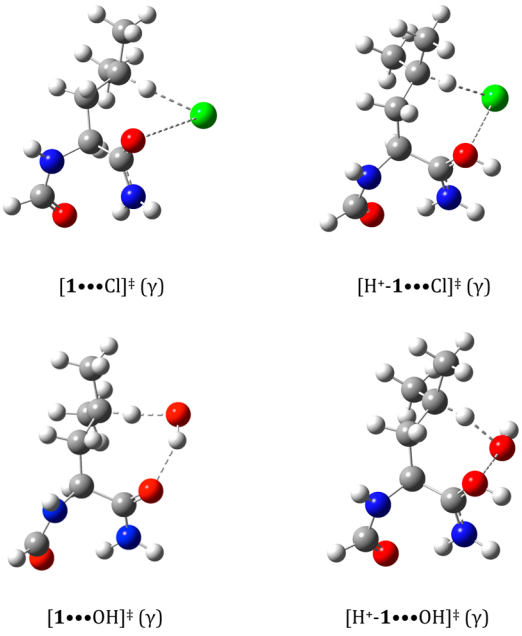

Figure 5. Geometry of the transition structures for abstraction from the γ position of **1** and H^{+}-**1** by Cl$^{\bullet}$ and OH$^{\bullet}$.

secondary interaction is hydrogen bonding with an amido-carbonyl oxygen. In other cases, however, the major secondary interaction is between the amido-carbonyl oxygen and the electronegative atom (Cl or O) of the attacking radical.

We can see that, upon protonation, i.e., going from **1** to H^{+}-**1**, ΔE_{int} values at α and β become less negative. This observation is consistent with a polar deactivating effect. Interestingly, for OH$^{\bullet}$ abstractions for neutral **1**, the α ΔE_{int} is actually the most negative among the four abstraction reactions, and this can be attributed to the hydrogen bonding between OH$^{\bullet}$ and the α substituents, which is in accord with previous findings.[7] Examination of the geometry of the corresponding transition structures at the β, γ, and δ positions reveals the existence of similar hydrogen-bonding interactions (see for example, [**1**···OH]‡(γ) in Figure 5), but they appear to contribute to a progressively smaller extent to ΔE_{int}.

CONCLUDING REMARKS

Our computational study suggests that the formation of reactant complexes is unlikely to be important in determining the regioselectivity of H abstraction from the various sites in amino acid residues. Specifically, while there exist reactant complexes in enthalpic terms, entropic and solvent effects render these complexes essentially unimportant. Instead, structural factors, polar effects, and solvent effects, together with secondary interactions, can be used to rationalize the variations in the barriers. The regioselectivity of hydrogen abstraction is likely to be affected by protonation of, or hydrogen bonding to, the substrate, but reactions remote from the α- and β positions are still favored.

ASSOCIATED CONTENT

Supporting Information

Optimized geometries of relevant species (Table S1) and ZPVEs, thermal corrections to enthalpies, entropies, solvation energies, and high-level single-point energies (Table S2). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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