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Dissociation energies of C_α–H bonds in amino acids – a re-examination†

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Johnny Hioe,[a] Marianne Mosch,[a] David M. Smith*[b] and Hendrik Zipse*[a]

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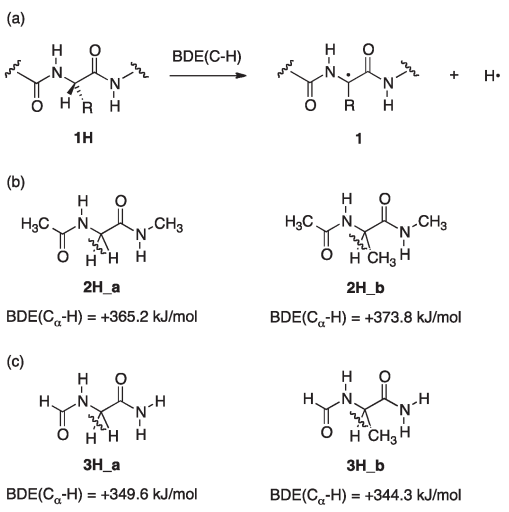
The C_α–H bond dissociation energies (BDE) in glycine and alanine peptide models have been assessed using selected theoretical methods from the G3 and, in part, G4 family. The BDE values (and thus the stability of the respective C_α peptide radicals) are shown to depend significantly on the level of theory, the size of the model system and the coverage of conformational space. For the largest dipeptide models chosen here, BDE(C_α–H) values of +363.8 kJ mol^{-1} (glycine) and +372.3 kJ mol^{-1} (alanine) have been obtained at G3B3 level. This reconfirms earlier findings that glycyl peptide radicals are more stable than radicals derived from alanine or any other amino acid carrying substituents at the C_α position.

Introduction

The abstraction of hydrogen atoms from amino acids, peptides and proteins is of outstanding relevance for processes as diverse as the oxidative damage to proteins and the catalysis of unusual substrate rearrangements through radical enzymes. The bond dissociation energies of the C–H bonds (BDE(C–H)) involved in these hydrogen transfer reactions thus represent important parameters in assessing the likelihood of these processes. Experimental data for individual C–H bonds in amino acids and peptides is still rather limited and the bulk of BDE data has thus been obtained from quantum chemical studies. As is described in Scheme 1 for the question of C_α–H bond energies, theoretical studies are typically not performed on complete proteins or peptides **1H**, but on smaller dipeptide or amino acid models instead.

Using theoretical methods designed for the description of open shell systems such as G3(MP2)-RAD, we have recently found the BDE(C–H) values in glycine dipeptide (BDE(C_α–H, **2H_a**) = +365.2 kJ mol^{-1}) to be significantly smaller than those in alanyldipeptide (BDE(C_α–H, **2H_b**) = +373.8 kJ mol^{-1}).[1–4] Together with BDE data for other dipeptide radicals this was taken to reflect steric interactions between the C_α substituents and the amide groups present on the N- and C-terminal side of the central amino acid radicals. Combining results obtained from B3LYP/6-31G(d) calculations for peptide model **3H** and earlier work by Rauk *et al.*,[5] Julian *et al.* predict BDE(C_α–H, **3H_a**) = +349.6 kJ mol^{-1} for glycine peptide **3H_a** and BDE(C_α–H, **3H_b**) = +344.3 kJ mol^{-1} for alanine peptide **3H_b**.[6] These values are practically identical to those reported earlier by Rauk *et al.*[13] These BDE values are not only significantly smaller than those obtained for dipeptide model **2H** at G3(MP2)-RAD level, but also imply lower BDE values for alanine residues as compared to glycine. This apparent contradiction may be due to various factors such as the choice of model system, the choice of theoretical method, and the strategy for calculating reaction energies. Using the examples of glycine and alanine we show in the following how these factors impact BDE(C–H) values for the C_α position in peptide models. Furthermore, we show that a carefully chosen



Scheme 1 (a) Definition of C_α–H bond dissociation energies (BDE(C_α–H)) in peptides; (b) BDE(C_α–H) values obtained for glycine and alanine dipeptide models **2H_a** and **2H_b** (ref. 1–4); (c) BDE(C_α–H) values obtained for glycine and alanine dipeptide models **3H_a** and **3H_b** (ref. 6 and 13).

[a]*Department of Chemistry, LMU München, Butenandtstrasse 5-13, 81377 München, Germany. E-mail: zipse@cup.lmu.de; Fax: +49 89 218077738*
[b]*Excellence Cluster, Engineering of Advanced Materials, University Erlangen-Nürnberg, Nägelsbachstrasse 49b, 91052 Erlangen, Germany and Rudjer Boskovic Institute, Bijenicka 54, 10000, Zagreb, Croatia. E-mail: David.Smith@irb.hr*

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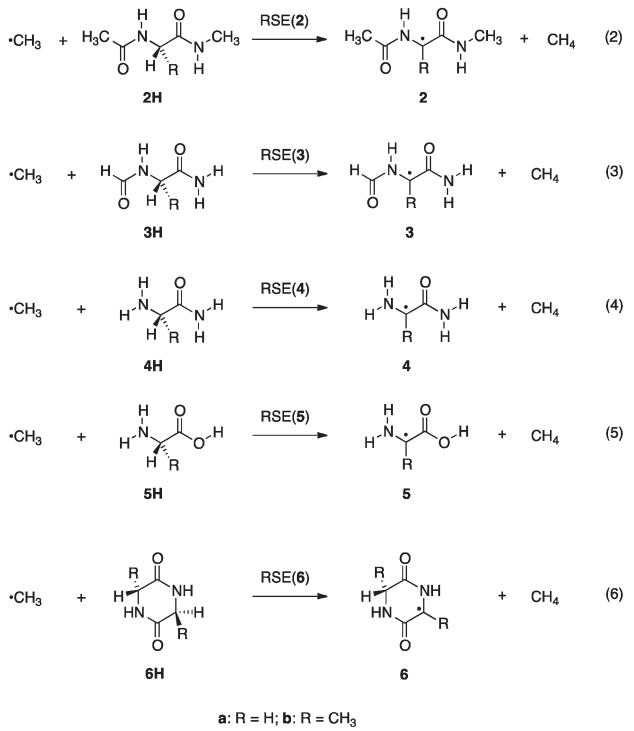

Scheme 2 Isodesmic reactions (2)–(6) for the calculation of radical stabilization energies of amino acid and peptide radicals 2–5 derived from glycine (**5H_a**, R = H) and alanine (**5H_b**, R = CH_3) and peptide anhydrides **6H**.

combination of the said factors is sufficient to allay any apparent inconsistency related to the relative stabilities of glycine and alanine peptide radicals.

Results

The calculation of C–H bond dissociation energies is most easily approached using hydrogen transfer reactions between the system of interest and a (thermochemically) well characterized reference system. For carbon-centered radicals the most often used reference system is methane (CH_4), whose C–H bond energy is accurately know as BDE(C–H) = +439.3 ± 0.4 kJ mol^{-1}.[7] The reaction energy for an isodesmic hydrogen transfer reaction with this reference system as shown, for example, for peptide radical **2_a** in Scheme 2, is often referred to as the radical stabilization energy (RSE) of radical **2_a** relative to methyl radical $^{\bullet}CH_3$. Summation of the RSE value for a particular radical with the (experimental) BDE(C–H) value of the reference system then yields the BDE(C–H) value for the system under investigation. The BDE(C–H) value in model peptide **2H_a**, for example, can thus be calculated using expression (1).

$$\mathrm{BDE(C\text{–}H,\ \mathbf{2H\_a})} = \mathrm{BDE(C\text{–}H,\ CH_4)} + \mathrm{RSE(\mathbf{2\_a})} \qquad (1)$$

The reaction energy calculated for hydrogen transfer between methyl radical ($^{\bullet}CH_3$) and peptide model **2H_a** amounts to RSE(**2_a**) = −74.1 kJ mol^{-1} at the G3(MP2)-RAD level of theory. The combination of this value with the BDE(C–

Table 1 RSE and BDE(C_α–H) values of amino acid/peptide models at various levels of theory using the isodesmic reaction (2)–(6) in Scheme 2

System	B3LYP/6-31G(d)		G3(MP2)-RAD		Other	
	RSE	BDE(C_α–H)	RSE	BDE(C_α–H)	RSE	BDE(C_α–H)
2_a	−101.6	+337.7	−74.1	+365.2	−75.5[a]	+363.8[a]
2_b	−98.9	+340.4	−65.5	+373.8	−67.0[b]	+372.3[b]
3_a	−100.4	+338.9	−75.9	+363.4	−77.6[a]	+361.7[a]
					−78.4[c]	+360.9[c]
3_b	−101.0	+338.3	−69.6	+369.7	−71.2[a]	+368.1[a]
4_a	−108.1	+331.2	−85.6	+353.7	−87.7[a]	+351.6[a]
					−88.9[c]	+350.4[c]
4_b	−113.7	+325.6	−87.1	+352.2	−89.9[a]	+349.4[a]
5_a	−118.8	+320.5	−95.8	+343.5	−96.0[d]	+343.3[d]
					−97.8[h]	+341.5[h]
					−99.0[a]	+340.3[a]
					−99.1[c]	+340.2[c]
					−101.4[e]	+337.9[e]
5_b	−130.8	+308.5	−102.5	+336.8	−106.4[a]	+332.9[a]
6_a	−98.3	+341.0	−77.9	+361.4	−80.1[a]	+359.2[a]
					−80.2[g]	+359.1[g]
						+340 ± 15[f]
6_b	−114.6	+324.7	−87.7	+351.6	−90.1[a]	+349.2[a]
					−91.2[g]	+348.1[g]
						+325 ± 15[f]

[a] G3B3. [b] IMOMO(G3B3, G3(MP2)-RAD). [c] G4-5H. [d] G3X(MP2)-RAD. [e] W1RO. [f] Experimental values in aqueous solution (ref. 11). [g] PCM/G3B3. [h] G2MP2.

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H) value in methane according to eqn (1) then yields a C_α–H bond dissociation energy of BDE(C_α–H, **2H_a**) = +365.2 kJ mol^{-1} for peptide model **2H_a**. Following this procedure BDE(C_α–H) values have been computed for all amino acid and peptide models in Scheme 2 and compiled in Table 1.

Choice of electronic structure method

The BDE(C_α–H) value obtained for glycine dipeptide **2H_a** at the G3(MP2)-RAD level is in good agreement with that obtained from the even more elaborate G3B3 scheme,[8] BDE(C_α–H, **2H_a**) = +363.8 kJ mol^{-1}. Both values are significantly larger than the value of BDE(C_α–H, **2H_a**) = +337.7 kJ mol^{-1} obtained with the more economical B3LYP/6-31G(d) approach. This is also found for all other amino acids, peptide models and peptide anhydrides **2H–6H** studied here. Previous studies[7] indicate that G3B3 and G3(MP2)-RAD methods predict BDE values with an accuracy of 3–5 kJ mol^{-1}. This implies that the BDE(C_α–H) data obtained at B3LYP/6-31G(d) level are too low by 20–30 kJ mol^{-1}.

BDE(C_α–H) data for glycine **5H_a** have also been evaluated with the G3X(MP2)-RAD and the more elaborate G4-5H and W1RO schemes (Table 1).[10,14,18] G3X(MP2)-RAD theory[18] differs from G3(MP2)-RAD in that geometry optimizations are performed at B3LYP/6-31G(2df,p) (instead of B3LYP/6-31G(d)) level, and in adding a basis set correction term at the (restricted open shell) Hartree–Fock level. Results obtained for **5H_a** with both methods are practically identical, which implies that the basis set used in geometry optimizations are not critical for obtaining accurate BDE data. G4-5H theory is a variant of G4 theory[15] whose performance in the description of hydrogen transfer reactions is particularly good, while the even more expensive W1RO theory[16,17] is expected to deliver sub-kcal mol^{-1} accuracy in predicting the thermochemistry of a wide variety of systems. Both approaches yield effectively the same BDE data as obtained at the G3B3 level, thus confirming the quality of these predictions. The subsequent discussion will thus focus on the G3B3 results exclusively.

Choice of model system

The value of BDE(C_α–H, **2H_a**) = +363.8 kJ mol^{-1} for glycine dipeptide model **2H_a** is significantly smaller than that calculated for the alanine-based dipeptide model **2H_b** with BDE(C_α–H, **2H_b**) = +372.3 kJ mol^{-1}. This implies that glycyl radical **2_a** is more stable than alanine radical **2_b** by +8.5 kJ mol^{-1}. On moving from dipeptide **2H** to the smaller peptide models, this difference is found to diminish to +6.4 kJ mol^{-1} in dipeptide model **3H** and reverse to −2.2 kJ mol^{-1} in peptide model **4H**. Finally, in the bare amino acids the BDE(C_α–H) in alanine (**5H_b**) amounts to BDE(C_α–H, **5H_b**) = +332.9 kJ mol^{-1}, which is 7.4 kJ mol^{-1} less than in glycine with BDE(C_α–H, **5H_a**) = +340.3 kJ mol^{-1}. We note in passing that the BDE(C_α–H) value obtained here for glycine **5H_a** at G3B3 level is slightly higher than the value of BDE(C_α–H, **5H_a**) = +331 kJ mol^{-1} based on G2(MP2) theory reported by Rauk.[5]

As is shown in a pictorial manner in Fig. 1, the move to smaller and smaller peptide models and, eventually, to amino acids is accompanied by a cross-over in the relative stabilities of glycyl and alanyl radicals, the larger model systems predicting lower BDE(C_α–H) values for glycine as compared to alanine. This trend is due to two opposing effects of the C_α substituents at the radical stage: (a) an inductively stabilizing effect onto the C_α radical center; and (b) steric repulsion with the amide substituents at the N- and C-terminal side. The alanyl radical **5_b** is more stable than glycyl radical **5_a** due to the electron-donating effect of the methyl group attached to the radical center. Extension of the peptide models on the N- and C-terminal side as in **3H** and **2H** now adds steric effects large enough to overcompensate the beneficial electronic effect and thus leads to higher stability of the glycyl peptide radicals. This is also fully in line with earlier conclusions by Radom *et al.* on the stability of peptide ester radicals.[9] The conformational consequences of these interactions will be discussed below.

Choice of reference system

The stabilization energies reported in Table 1 and Fig. 1 are all based on the reference system CH_4/$^{\bullet}CH_3$. In order to test whether different reference systems lead to substantially

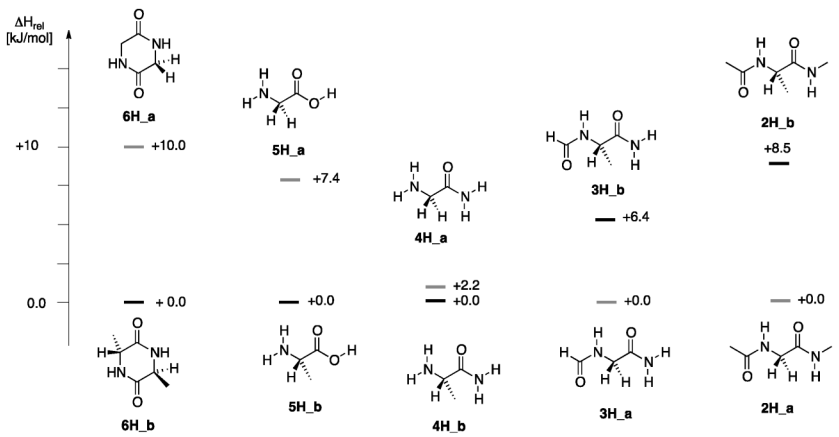

Fig. 1 Relative C_α–H BDE between glycine and alanine at G3B3 level of theory.

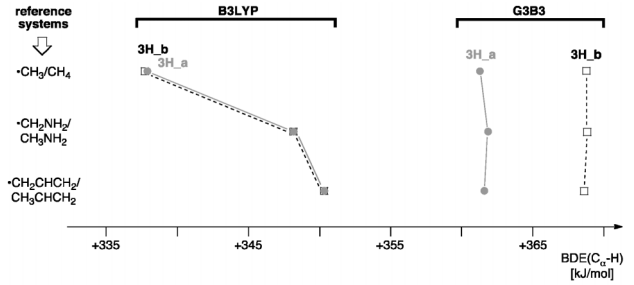

Fig. 2 (a) Influence of reference system and theoretical method on the BDE(C_α–H) values for glycine and alanine dipeptide models **3H_a** and **3H_b**.

different results, BDE(C_α–H) values in glycine and alanine dipeptide models and anhydrides **2H–6H** were recalculated using the CH_3NH_2/$^\bullet CH_2NH_2$ and the propene/allyl radical reference systems. Experimental BDE(C–H) values are known for both of these systems, and both bond energies are closely similar to those in the peptide models studied here. It should be added that the experimental bond energy in CH_3NH_2/$^\bullet CH_2NH_2$ of BDE(C–H, exp.) = +392.9 $\pm$ 9.4 kJ mol^{-1} can be closely matched at G3B3 level with BDE(C–H, G3B3) = +392.4 kJ mol^{-1} using the isodesmic equation approach with the CH_4/$^\bullet CH_3$ reference system. This is also found for the bond strength of the allylic C–H bond in propene with BDE(C–H, exp.) = +368.6 $\pm$ 2.9 and kJ mol^{-1} BDE(C–H, G3B3) = +368.8 kJ mol^{-1}.

As shown schematically in Fig. 2 the BDE(C_α–H) values obtained at G3B3 level for dipeptide models **3H_a** and **3H_b** are closely similar for all three reference systems, the BDE(C_α–H) in **3H_b** being larger by *ca.* 6 kJ mol^{-1} than that in **3H_a**. This is distinctly different for the B3LYP level, where the BDE(C_α–H) values are found to vary by more than 10 kJ mol^{-1} in absolute terms as a function of the reference system and where glycine and alanine dipeptides **3H_a** and **3H_b** are predicted to have essentially the same BDE(C_α–H) values. Similar observations can also be made for all other dipeptide models and amino acids in Table 1/Fig. 1 (see SI† for full details).

Conformational selection

The reaction enthalpies obtained for isodesmic reactions (2)–(6) (and thus the BDE(C_α–H) values) depend significantly on the conformers chosen for reactants and products. The BDE values listed in Table 1 have been obtained using Boltzmann-averaged enthalpies over all relevant conformers. It is important to note at this point that conformational preferences are rather different for closed-shell dipeptides and their respective C_α radicals. For peptide models **3H_a**/**b** and radicals **3_a**/**b** the required information on conformational energies has been compiled in Table 2. For both radicals **3_a** and **3_b** the extended C_5 conformation is found to be most stable, while the closed-shell parent dipeptides **3H_a** and **3H_b** prefer the folded C_7 conformation. For these latter systems, the C_5 conformation represents the second best conformer, located +1.9 kJ mol^{-1} (in **3H_a**) and +4.2 kJ mol^{-1} (in **3H_b**) higher in energy. That the C_5/C_7 energy difference is not identical in these dipeptide models is due to the steric effects induced by the C_α methyl substituent present in **3H_b**. These results are consistent with previous studies of C_α-peptide radicals.[3] Table 3 compiles BDE(C_α–H) values of peptide models **3H_a**/

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Table 2 Relative energies of dominant conformers for peptide **3H_a**/**b** and peptide radical **3_a**/**b**

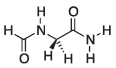
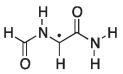
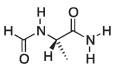
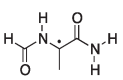
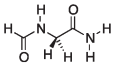
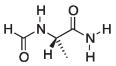
	Backbone geometry	Peptide bond conformations	$\Delta H_{298,\mathrm{rel}}$ B3LYP [kJ mol^{-1}]	$\Delta H_{298,\mathrm{rel}}$ G3B3 [kJ mol^{-1}]
 **3H_a**	C_7	Trans	+0.0	+0.0
	C_5	Trans	+0.1	+1.9
	C_7	Cis	+12.4	+14.4
	C_5	Cis	+15.4	+20.0
 **3_a**	C_5	Trans	+0.0	+0.0
	C_5	Cis	+7.6	+9.2
	β_2	Trans	+27.3	+26.2
	α_L	Trans	+29.0	+30.8
	α_R	Cis	+40.9	+40.5
 **3H_b**	$C_{7,ax.}$	Trans	+0.0	+0.0
	C_5	Trans	+4.3	+4.2
	$C_{7,eq.}$	Trans	+10.2	+9.4
	α'	Cis	+15.2	+17.3
	C_5	Cis	+18.9	+21.5
	α_R	Cis	+24.3	+24.3
	β_2	Trans	+26.4	+25.3
	$C_{7,eq.}$	Cis	+27.3	+26.8
 **3_b**	C_5	Trans	+0.0	+0.0
	C_5	Cis	+6.9	+5.2
	β_2	Cis	+17.8	+15.7
	C_7	Trans	+20.0	+19.4
	β_2	Trans	+20.5	+17.8
	α_L	Cis	+28.5	+25.5

Table 3 Cα–H BDE of conformational restricted peptide model **3H_a/b**

	Backbone geometry	Peptide bond conformations	BDE B3LYP [kJ mol^{-1}]	BDE G3B3 [kJ mol^{-1}]
 **3H_a**	C_5	Trans	+338.5	+360.0
	C_5	Cis	+330.8	+351.2
 **3H_b**	C_5	Trans	+334.4	+364.1
	C_5	Cis	+326.6	+352.1
	C_7	Trans	+358.7	+387.8
	β_2	Trans	+332.7	+360.9

b using a restricted conformational space with $CH_4/^{\bullet}CH_3$ as the reference system. For glycine model **3H_a** the BDE(C_α–H) value of +360.0 kJ mol^{-1} obtained through locking the system in a C_5 conformation is almost identical to that obtained with full Boltzmann averaging (+361.7 kJ mol^{-1}, G3B3 data from Table 1). Differences are somewhat larger for the alanine system **3H_b**, where the system in its C_5 conformation has a clearly lower BDE(C_α–H) value of +364.1 kJ mol^{-1} as compared to that obtained with Boltzmann averaging of +368.1 kJ mol^{-1}. Significantly larger variations in BDE(C_α–H) values are observed when locking the dipeptide systems in the C_7 conformation, which is particularly unfavorable for dipeptide radicals. Similar trends can also be observed at the B3LYP level of theory (Table 3). This implies that relative glycine/alanine dipeptide BDE(C_α–H) values also depend on the conformational selection made for radicals as well as for closed-shell parents.

Comparison to experimental studies

The BDE(C_α–H) values obtained for glycine- and alanine anhydride (**6H_a** and **6H_b**) at G3(MP2)-RAD and G3B3 level in the gas phase are significantly larger than the experimental values obtained with photoacoustic calorimetry in aqueous solution ($BDE_{exp.}$(C_α–H, **6H_a**) = 340 ± 15 kJ mol^{-1}; $BDE_{exp.}$(C_α–H, **6H_b**) = 325 ± 15 kJ mol^{-1}).[11] This might only partially be due to aqueous solvation effects. The application of a continuum solvation model (PCM) for water, at the B3LYP/6-31G(d) level, lowers the BDE(C_α–H) value of **6H_a** by only 0.13 kJ mol^{-1} and that of **6H_b** by 1.1 kJ mol^{-1}, respectively. The deviations between experiment and theory may, in part, also be due to the large uncertainties of the measurements in water.[11]

Table 4 Rate constants for hydrogen abstraction by thiyl radicals[12] and BDE(C_α–H) values for selected peptide models

System	Rate constant [M^{-1} s^{-1}]	C–H BDE [kJ mol^{-1}]
6H_a	8.0×10^4	+359.2[a]
N-Ac-Gly-NH_2	3.2×10^4	+363.8[a] (**2H_a**)
N-Ac-Ala-NH_2	1.0×10^4	+372.3[b] (**2H_b**)
N-Ac-Pro-NH_2	0.18×10^4	+391.5[b] (Proline)[c]

[a] G3B3. [b] IMOMO(G3B3/G3(MP2)-RAD). [c] Taken from ref. 3.

Kinetic studies by Schöneich *et al.* measuring C_α–H-abstraction rate constants from peptides N-Ac-Gly/Ala-NH_2 by thiyl radicals have established that the abstraction from glycine N-Ac-Gly-NH_2 is approximately three times faster than from alanine N-Ac-Ala-NH_2, which may be rationalized by lower BDE(C_α–H) values in glycine as compared to alanine.[12]

In contrast to the B3LYP values for peptide models **3H_a/3H_b** published earlier,[5b] the G3B3 results obtained here for peptide models **2H_a/2H_b** containing the full acetyl group on the N-terminal position predict lower BDE(C_α–H) values for glycine as compared to alanine by about 7–8 kJ mol^{-1} (regardless of the choice of reference system). Glycine anhydride **6H_a** is shown in the same experimental study to react with the thiyl radical faster than either the glycine or alanine dipeptide models. This observation can also be rationalized by the G3B3 data in Table 1, which shows lower bond energies for **6H_a** as compared to **2H_a**. With additional consideration of BDE(C_α–H) values for the dipeptide proline model reported earlier at the G3B3 level,[3] the kinetic data reported by Schöneich *et al.* can be correlated rather well with the respective bond energies (Table 4, Fig. 3). This is in remarkable contrast to the poor correlation obtained earlier with B3LYP BDE(C_α–H) values for the smaller dipeptide models **3H_a/3H_b** by Rauk.

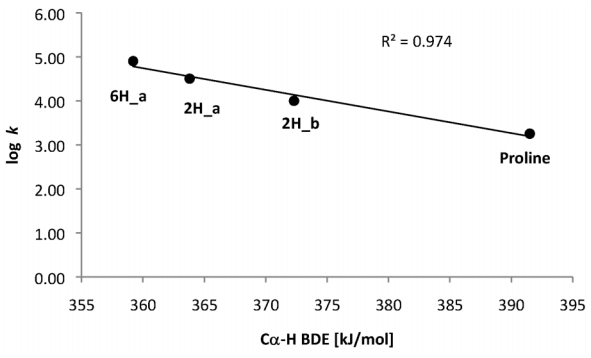


Fig. 3 Correlation of BDE(C_α–H) values obtained at the G3B3 level with rate data for H-abstraction.[12]

Conclusions

BDE(C_α–H) values in amino acids and peptide models can be computed quite reliably using an appropriate combination of electronic structure methods, sufficient conformational sampling and an experimentally well-characterized reference system. Results obtained using the G3(MP2)-RAD and G3B3 schemes are in good agreement with those obtained with benchmark quality methods such as W1RO, while this is not so for calculations obtained from hybrid density functional methods such as B3LYP. The choice of reference system is much less critical when one of the G3-level methods is used. Some care is required in selecting conformations for high-level calculations, as the conformational preferences of radicals and non-radicals differ substantially. Importantly, our results confirm that glycyl peptide radicals are more stable than analogous radicals derived from alanine (or other α-amino acids) and thus resolve an apparent inconsistency, which had emerged from previous work in the literature.

Notes and references

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