Pergamon

Tetrahedron Letters, Vol. 38, No. 44, pp. 7721-7724, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10085-5

Are α-Centered Peptide Radicals Stabilized by a Capto-Dative Effect?[1,2]

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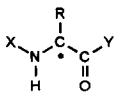
Abstract: The kinetics of the thermal C-C-cleavage reaction of the dimer of sarcosine anhydride **5** has been investigated between 295 and 333 °C in mesitylene. From the temperature dependence and from the release of strain on dissociation the cyclic α-peptide radical **6** was calculated to have a radical stabilization enthalpy (RSE) of -6.3 ± 1.3 kcal / mol thus indicating the absence of a synergistic capto-dative effect. © 1997 Elsevier Science Ltd.

α-Centered peptide radicals **1** (X = –C=O, Y = NH–) are involved in the catalytic activity of some enzymes[5] but also play an important role in oxidative damages of proteins[6] and are responsible for protein degradation, protein- DNA crosslinking[6k], fragmentation[6g] etc. which have significant biological, pathological and medical consequences.[6]

The ready formation of these radicals has been attributed to their capto-dative[2] substitution pattern.[7] This was supported by C–H bond strength arguments based on ab initio calculations and isodesmic reactions[6h,i] and by experimental C-C-bond strengths[7] as obtained from the thermolysis of dimers of the model radicals **2**.[7] The *ab*



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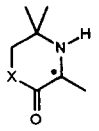


2 X = O, NH

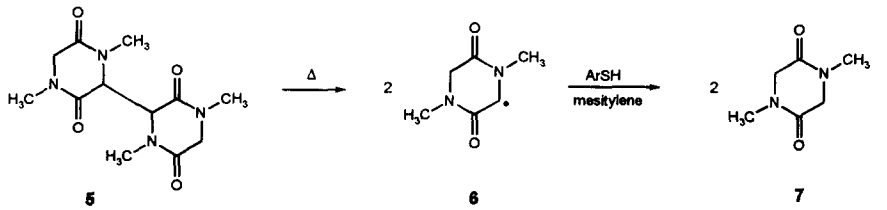
initio CH-bond strengths, however, suffer from their large uncertainties and from their relative and not absolute nature. Radicals **2**, on the other hand, for which we calculated radical stabilization enthalpies RSE[8] = -15.9 kcal / mol (X = NH) and -18.2 kcal / mol (X = O) from the data in the literature,[7] are not appropriate models for peptide radicals **1** (X = –C=O, Y = NH–) because the radical centers in **2** are flanked by a *free amino* group and not by an amide type nitrogen. Radicals flanked by both a free amino group and a capto functionality (–$COOCH_3$,[8a] -COR,[8b] –CN[8c]) are the only typical radicals for which a synergistic capto-dative stabilization[2] has been experimentally shown to exist, so far.[1,8,9]

In recent years we have developed a protocol for the determination of radical stabilization enthalpies (RSE) of monosubstituted[10] and disubstituted[8] alkyl radicals **4** from the activation enthalpies $\Delta H^{\ddagger}$ or dissociation enthalpies of C-C-cleavage reactions of the dimers **3**, which can be obtained from the temperature dependence of the reaction rates or equilibrium constants.[8]

3 **4**

From the difference of the RSE's of a disubstituted radical XYRC• **4** and the sum of the RSE's of the corresponding two monosubstituted radicals XR_2C• and YR_2C• the synergistic stabilization of **4** is obtained. α-Amino-α-carbonyl radicals **4** (X = $-NR_2$, Y = –COR) have a *synergistic stabilization* of -9.7 kcal / mol,[8b] α-amino-α-cyano alkylradicals **4** (Y = –CN) of -6.1 kcal / mol,[8c] and α-amino-α-ethoxycarbonyl radicals (Y = $-COOC_2H_5$) of -6.7 kcal / mol.[8a]

We now report a kinetic investigation of the thermolysis of the more soluble *meso* form of the two diastereomers of the dimers of sarcosine anhydride **5**[11] between 295-333 °C in mesitylene.[13] It is cleaved into two cyclic peptide radicals **6** which are trapped quantitatively by *p*-thiocresol forming sarcosine anhydride **7** in a quantitative yield. **6** has been used frequently as a model for peptide radicals.[6a-g,14]



5 **6** **7**

The kinetics were followed by the ampoule technique under N_2 reference with GC-analysis of **5** and **7** and first order kinetics were obtained. The activation parameters were calculated by the Eyring equation (Table 1).

Table 1 Activation parameters of the homolytic bond dissociation reaction of an equilibrium mixture of *meso*- and D,L-**5**[13] into **7** from kinetic measurements in mesitylene with an excess *p*-thiocresol as scavenger.

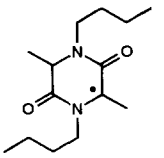
	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$ [a]	RSE	BDE(C-H) [b]
5	53.4 ± 1.3 kcal/mol	14.0 ± 2.4 cal / (mol ∃ K)	45.4 ± 2.0 kcal/mol	-6.3 ± 1.3 kcal/mol	92.4 kcal/mol

a) 315°C, the temperature at which the half life time is 1 hour. b) BDE(C-H) = 98.7 kcal / mol[15] + RSE

MM2 force field calculations predict an average excess of 10.4 kcal / mol strain energy in the equilibrium mixture of *meso*- and D,L-**5**[13] over two moles of **7** *released* on bond dissociation. Taking this quantity into account and neglecting the geminal interactions of the α-carbamoyl and the α-acylamino substituents in the radical precursor **5** which are probably small,[8] a radical stabilization enthalpy RSE = -6.3 ± 1.3 kcal / mol results for **6** and a C-H-bond dissociation enthalpy of BDE(C-H) = 92.4 kcal / mol in the 3-position of **7**. In qualitative agreement with *ab initio* calculation[6h,i] and with a small RSE of α-carbamoyl alkyl radicals[16], the α-acylamino-α-carbamoyl radical **6** is thermochemically substantially less stabilized than the α-amino-α-cabonyl radicals (RSE = -21.8 kcal / mol)[8b], α-acylamino-α-ethoxycarbonyl (RSE = -14.8 kcal / mol)[8a] and α-amino-α-cyano radicals (RSE = -13.8 kcal/mol)[8c].

An RSE of -6.3 kcal / mol is also in good agreement with the relatively high ESR aH_{β}^{Me}-hfc of 17.5 Gauss for the N-substituted alanine anhydride radical **8**.[9] From this hfc and an observed linear aH_{β}^{Me}-hfc / RSE relationship[17a] an RSE = -8.6 kcal / mol for **8** can be calculated. aH_{α} - hfcs of α-centered glycine radicals in peptides range between 18 and 19 Gauss[18] suggesting an RSE of approximately -6.6 kcal / mol.[17b] In

contrast the hfcs of the capto-dative stabilized radicals **2** (aH_β^{Me} = 10.9 G,[7b] X=O and aH_β^{Me} = 11.73 G,[7a] X =NH) lead to values of RSE = -19.3 kcal / mol and RSE = -17.9 kcal / mol, respectively.[17a]



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This result supports our previous suggestion[8] that a synergistic capto-dative effect is due to homo-amide resonance between an amino group and the carbonyl or nitrile capto group in capto-dative radicals and depends essentially on the availability of the lone pair on nitrogen for conjugation with the capto group.

The RSE = -6.3 kcal / mol of **6** is a good approximation for the RSE of α-centered peptide radicals despite the cis-conformation of **6**. It is expected that the RSE of such a radical center in a peptide chain, which has a trans-conformation is slightly different.[6e]

Financial support by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* is gratefully acknowledged. We thank Dr. M. Keller for the X-ray analyses and Professor A. L. J. Beckwith for stimulating discussions.

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11. **5** was synthesized by dehydrodimerization of 4.0 g (28 mmol) 1,4-dimethylpiperazine-2,5-dione **7** with 5.9 g (40 mmol) di-*tert*-butylperoxide in 80 ml degased *tert*-butanol. After 2 h irradiation with a 125 W high pressure mercury lamp under a nitrogen flow the D,L-isomer precipitated. *Meso*-**5** was isolated by removal of the solvent. After recrystallization from MeOH the two separated diastereomers were obtained in an overall yield of 1.4 g (5 mmol, 70 %). The configuration of the diastereomers was determined by X-ray diffraction analysis of D,L-**5** which had previously been erroneously identified as the *meso*-diastereomer.[12] *meso-3,3'-Bis-(1,4-dimethylpiperazine-2,5-dione)* : ^{1}H NMR(400 MHz, $CDCl_3$, TMS): δ = 2.97 ppm (s, 6H, NCH_3), 2.99 (s, 6H, NCH_3), 3.84 (d, J = 18 Hz, 2H, CH_2), 4.02 (d, J = 18 Hz, 2H, CH_2), 4.45 (s, 2H, CH). - ^{13}C NMR(100 MHz, $CDCl_3$, TMS) : δ = 33.42 ppm (NCH_3), 33.77 (NCH_3), 51.52 (CH_2), 64.62 (CH), 163.09 (CO), 163.94 (CO). - MS (EI, 70 eV) : m/z (%) = 282 (3) [M^+], 141 (46) [M/2], 113 (44) [M/2-CO], 43 (17), 42 (60). D,L-*3,3'-Bis-(1,4-dimethylpiperazine-2,5-dione)* : mp. 305°C. - ^{1}H NMR(400 MHz, $CDCl_3$, TMS): δ = 2.95 ppm (s, 6H, NCH_3), 2.96 (s, 6H, NCH_3), 3.83 (d, J = 18 Hz, 2H, CH_2), 3.99 (d, J = 18 Hz, 2H, CH_2), 4.42 (s, 2H, CH). - ^{13}C NMR(100 MHz, $CDCl_3$, TMS) : δ = 33.79 ppm (NCH_3), 33.89 (NCH_3), 51.43 (CH_2), 64.66 (CH), 163.63 (CO), 164.06 (CO). - MS (EI, 70 eV) : m/z (%) = 282 (3) [M^+], 141 (46) [M/2], 113 (44) [M/2-CO], 43 (17), 42 (60). - $C_{12}H_{18}N_4O_4$ (282.3) : calc. C: 51.06, H: 6.43, N: 19.85; found C: 50.55, H: 6.34, N: 19.45.

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13. At these temperatures a fast equilibrium between *meso*- and D,L-**5** was observed, so that the kinetics were performed from the equilibrium mixture of the dimer **5** ($K_{300°C}$ = [D,L-**5**]/[*meso*-**5**] = 0.59 ± 0.01; experimentally determined by GC). Isomerisation experiments in CD_3OD at temperatures far below the temperature of the homolytic bond dissociation of **5** (< 215°C) led to an exchange of all α-H atoms by deuterium. Addition of pyridine led to an acceleration of the isomerization and therefore we conclude that the isomerisation was due to a deprotonation-reprotonation reaction.

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17. (a) RSE*[kcal/mol]* = 1.61∃aH_β^{Me}*[Gauss]*-36.8(±1.4); (b) RSE*[kcal/mol]* = 1.65∃aH_α*[Gauss]*-37.1(±1.3). See ref. 9.

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(*Received in Germany* 5 *August* 1997; *accepted* 5 *September* 1997)