Homolytic Bond Dissociation Energies for the Cleavage of α-N–H Bonds in Carboxamides, Sulfonamides, and Their Derivatives. The Question of Synergism in Nitrogen-Centered Radicals

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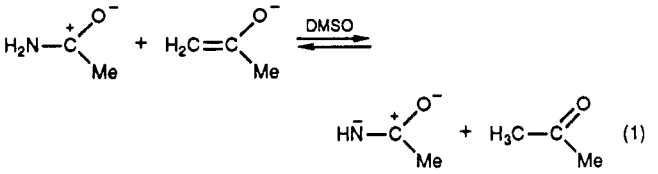
Estimates of homolytic bond dissociation energies (BDEs) of the N–H bonds of acetamide, benzamide, and benzenesulfonamide by measurements of their equilibrium acidities and the oxidation potentials of their conjugate bases in dimethyl sulfoxide (DMSO) solution place them within experimental error of that of ammonia (107 kcal/mol). The BDE for urea is 4 kcal/mol higher, but those for cyanamide and thiourea are lower by 8 and 18 kcal/mol, respectively. *N*-Methyl substitution in acetamide fails to affect the BDE, but *N*-phenyl substitution lowers it by 8 kcal/mol. Introduction of *N*-methoxyl and *N*-hydroxyl groups into acetamide lower the N–H BDE by 17 and 19 kcal/mol, respectively. Identical effects are observed for like substitutions into benzamide. The introduction of an *N*-NH_2 group into CH_3CONH_2, $PhCONH_2$, $PhSO_2NH_2$, $(H_2N)_2C{=}O$, and $(H_2N)_2C{=}S$ lowers the N–H BDE by 25, 26, 24, 23, and 20 kcal/mol, respectively. The results are discussed in terms of the relative stabilization energies of the corresponding radicals.

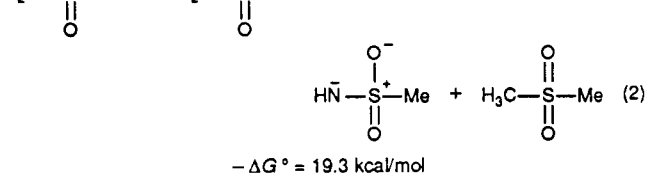
In the previous paper we have shown that nitrogen acids are usually more acidic by 17 ± 5 kcal/mol than analogous carbon acids but that carboxamides are unusual in this regard. In DMSO solution carboxamides are more acidic than their carbon acid analogues, the ketones, by only 1–2 kcal/mol. In the gas phase the difference is larger (7–8 kcal/mol), but still only about half as large as between other NH and CH analogues.[1] The small difference in acidities between carboxamides and ketones was attributed to repulsions between the lone pairs on the oxygen atom of the carbonyl group and those on the nitrogen atom in the carboxamide ion, an effect that is destabilizing and strongly acid weakening (eq 1), together with resonance stabilization of the carboxamide.



(1)

$-\Delta G^\circ = 0.72$ kcal/mol

The relationship is different between the analogous sulfonamide and sulfone because the resonance delocalization effect in the $CH_2{=}S(O_2^-)CH_3$ ion is much less important than in the $CH_2{=}C(O)^-Me$ ion (eq 2).



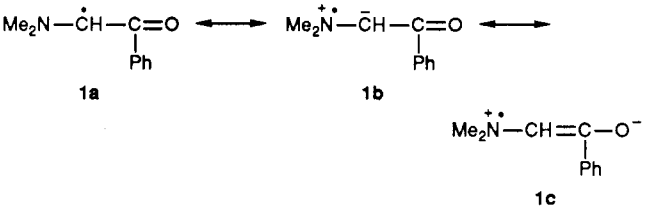
(2)

$-\Delta G^\circ = 19.3$ kcal/mol

In a separate study we have estimated, by eq 3, the effects of α-substituents on the homolytic bond dissociation energies (BDEs) of the acidic C–H bonds of α-substituted acetophenones, $PhCOCH_2G$, relative to that in $PhCOCH_3$.[2]

$$\Delta BDE = 1.37\Delta pK_{HA} + 23.1\Delta E_{ox}(A^-) \quad (3)$$

The ΔBDEs estimated are believed to be equivalent, within a $PhCOCH_2G$ family, to the relative radical stabilization energies (RSEs) of the corresponding $PhC(=O)\dot{C}HG$ radicals.[2] The effects of α-MeO or α-R_2N groups on the acidity (pK_{HA}) of acetophenone are small (1.5–2.5 kcal/mol), but the effects of these substituents on the oxidation potentials of the corresponding anions, $E_{ox}(A^-)$, are large (10–19 kcal/mol). These large effects can be attributed to stabilization of the radicals being formed by loss of an electron from the anion. Delocalization of the odd electron into the adjacent MeO or Me_2N group was believed to be augmented synergistically by the PhCO group as represented by valence bond symbolism by resonance contributors **1a–c**.[2]



1a **1b** **1c**

The nitrogen analogues of α-hydroxy- and α-aminoacetophenones are benzohydroxamic acids, PhCONHOH, and benzohydrazide, $PhCONHNH_2$, respectively. It was of interest to extend the study to these and related substrates to see whether or not synergism between the HO and H_2N donors and the PhCO acceptor would also serve to stabilize the nitrogen-centered radicals being formed on oxidation of the anions derived from these carboxamide derivatives.

Results and Discussion

Homolytic Bond Dissociation Energies of the N–H Bonds in Amides. The homolytic bond dissociation energies (BDEs) for several carboxamides and related amides are given in Table I, together with the pK_{HA} and $E_{ox}(A^-)$ values from which the BDEs were estimated. Similar data for a number of analogous ketones are included for comparison.

The cyclic voltammograms for the parent amide ions listed in Table I were difficult to obtain. The CV waves for these were broad (110–170 mV) and could be reproduced only by careful polishing of the electrode after each run. (Amides **7**, **9**, and **11** were noteworthy in that they gave narrower waves.) Despite these problems, an ex-

(1) Bordwell, F. G.; Hughes, D. L.; Fried, H. E.; Lynch, T.-Y.; Satish, A. V.; Whang, Y. *J. Org. Chem.*, preceding paper in this issue.
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Table I. Homolytic Bond Dissociation Energies in Dimethyl Sulfoxide for Carboxamides and Related Compounds at 25 °C

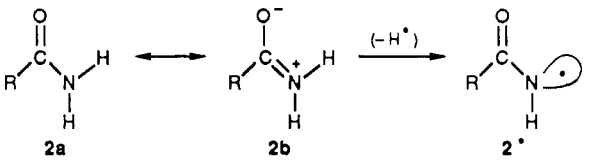
no.	compound	pK_{HA}[a]	$E_{ox}(A^-)$[d]	BDE[e]	ΔBDE[g]
1.	NH_3	(~41)[b]		107[f]	(0.0)
2.	$PhSO_2NH_2$	16.1	1.175	105	2
3.	$CNNH_2$	17.0	0.868	99	8
4.	H_2NCONH_2	26.9	0.788	111	-4
5.	H_2NCSNH_2	21.0	0.361	93	14
6.	$PhCONH_2$	23.5	0.824	107	0
7.	$PhCSNH_2$	16.9	0.499	90	17
8.	CH_3CONH_2	25.5	0.725	107	0
9.	CH_3CSNH_2	18.5	0.434	91	16
10.	$CH_3CONHMe$	25.9	0.658	107	0
11.	$CH_3CONHPh$	21.5	0.605	99	8
12.	CH_3COCH_3	26.5	0.049	94	11[h]
13.	$PhCOCH_3$	24.7	0.268	93	12[h]
14.	$PhCOCH_2Me$	24.4	-0.065	88	17[h]
15.	$PhCOCH_2Ph$	17.7	0.105	82	23[h]
16.	$PhCOCH_2NMe_3^+$	14.6[c]	0.903	97	-4[i]

[a] Reference 5 unless otherwise noted. [b] Extrapolated (ref 6). [c] Reference 7. [d] Measured by cyclic voltammetry with a Ag/AgI reference electrode in DMSO relative to the ferrocene-ferrocenium couple under the conditions previously reported (ref 8); referenced to the standard hydrogen electrode by adding -0.125.[8] [e] Estimated by using the empirical equation: $BDE = 1.37pK_{HA} + 23.1E_{ox}(A^-) + 56$ (ref 9) unless otherwise noted. [f] Reference 10. [g] $BDE(NH_3) - BDE(HA)$; assumed to be equal to radical stabilization energies (RSEs). [h] Relative to the BDE of the C-H bond in CH_4 (105 kcal/mol[10]). [i] Relative to the BDE of the acidic C-H bond in $PhCOCH_3$.

cellent correlation was found between irreversible potentials, $E_{ox}(A^-)$, and the reversible $E_{1/2}$ values obtained by a second harmonic alternating current technique (SHACV) for six carboxamides of varied structure. We are therefore confident that the ΔBDEs in Table I (and Table II) are accurate to within the usual limits of ±3 kcal/mol estimated by using the empirical equation given in footnote *e* in Table I.

We will assume that the ΔBDEs in Table I can be equated to radical stabilization energies (RSEs), and will discuss the results, in part, in these terms. We realize that the assumption of ΔBDE = RSE is not valid, in general. For example, it may not apply to a comparison of A–B vs A–C bonds, where B and C are atoms of different kinds, because the difference in BDEs would depend not only on the stabilities of the A•, B•, and C• radicals being formed, but also on the ground state energies of the A–B and A–C molecules. Within a family of weak acids, HA_1, HA_2, HA_3, etc., however, the differences in ground-state energies are expected to be small compared to the difference in energies of the radicals, A_1•, A_2•, A_3•, etc., being formed. Furthermore, we are keeping the nature of the bonded atoms constant, and the BDEs are often based primarily on the oxidation potential of A^-, which should give a good measure of radical stability.

Examination of Table I shows that acetamide, *N*-methylacetamide, and benzamide appear to have BDEs equal to that of ammonia. This is surprising at first sight, since one might have expected the C=O moiety to stabilize the corresponding RCONH• radical. Carboxamides are known to exist in a planar conformation with a rotational barrier of the order of 15–20 kcal/mol. The rotational barrier can be attributed to orbital overlap between the lone pair on nitrogen and the π-bond of the carbonyl group and/or to electrostatic effects.[3] When held in this conformation the odd electron in the radical (**2**•) is in an orbital orthogonal to the C=O π-bond, and orbital overlap is minimal.



2a **2b** **2•**

Wiberg and Laidig have discounted the importance of resonance contributor **2b**. We note that both the change from sp^3 hybridization in NH_3 toward sp^2 hybridization in $=NH_2^+$, and the accumulation of a positive charge on nitrogen, expected if contributor **2b** is important, would be bond strengthening rather than bond weakening. Thus, changes in hybridization, and the accompanying changes in atom electronegativity, are known to affect BDEs strongly. For example, in hydrocarbons the BDEs of C–H bonds increase from 98 to 110 to 132 along the series CH_3CH_3, $H_2C{=}CH_2$, $HC{\equiv}CH$.[10] The effect of charge can be seen by comparing the change in the α-C–H BDE of 72 in $PhCOCH_2NMe_2$[2] to 97 in $PhCOCH_2NMe_3^+$ (Table I). Also, calculations by Pasto indicate that the BDE of $H{-}CH_2NMe_3^+$ is 4 kcal/mol higher than that of $H{-}CH_3$.[11] The failure of the BDEs of carboxamide N–H bonds to increase is consistent with the unimportance of contributor **2b**. On the other hand, it is possible that some degree of orbital overlap exists in radical **2**•, but is offset by the effects of rehybridization.

The apparent failure of an α-C=O group to stabilize a nitrogen-centered radical of type RCONH• is in sharp contrast to the strong stabilization provided by an analogous carbon-centered radical. Thus, the carbonyl groups in acetone and acetophenone weaken the α-C–H bonds by 11 and 12 kcal/mol, respectively, relative to the C–H bond in methane (Table I). Here delocalization of the odd electron in the radical being produced by homolysis plays an important stabilizing role, which is enhanced further by 5 and 11 kcal/mol, respectively, in α-methyl- and α-phenylacetophenones (Table I). In contrast, the BDE of the N–H bond in acetamide is unaffected by *N*-methyl substitution but is decreased by 8 kcal/mol by *N*-phenyl substitution. The latter effect points to strong delocalization of the odd electron on nitrogen in the radical into the adjacent phenyl ring.

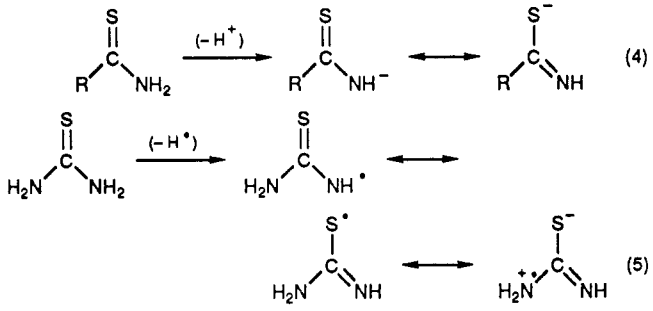
The BDE of benzenesulfonamide is within experimental error of that of ammonia, but that of cyanamide is 8 kcal/mol lower (Table I). These effects of α-$PhSO_2$ and α-CN groups on N–H BDEs are similar to those observed previously on C–H BDEs.[4]

The observation that urea is less acidic by 2.3 kcal/mol than acetamide is somewhat surprising since replacement of the CH_3 group in CH_3CONH_2 by NH_2 to give H_2NCONH_2 would have been expected to be acid strengthening in view of the greater field/inductive effect of NH_2 vs CH_3 (0.33 vs 0.00).[12] For example, $H_2NCH_2CONH_2$ is more

(3) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935–5943.
(4) Bordwell, F. G.; Bausch, M. J.; Branca, J. C.; Harrelson, J. A., Jr. *J. Phys. Org. Chem.* **1988**, *1*, 225–241.
(5) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
(6) Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 2964–2968.
(7) Bordwell, F. G.; Van Der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1883–1885.
(8) Bordwell, F. G.; Harrelson, J. A., Jr.; Satish, A. V. *J. Org. Chem.* **1989**, *54*, 3101–3105.
(9) Bordwell, F. G.; Cheng, J.-P.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 1229–1231.
(10) McMillen, D. F.; Golden, D. M. *Ann. Rev. Phys. Chem.* **1982**, *33*, 483–532.
(11) Pasto, D. J.; Krasnansky, R.; Zereher, C. *J. Org. Chem.* **1987**, *52*, 3062–3072.

acidic than $MeCH_2CONH_2$ by 1.4 kcal/mol.[13] The higher pK_{HA} suggests a lower ground-state energy for urea than acetamide.[14]

Replacements of the C=O bond in urea, acetamide, and benzamide by a C=S bond cause increases in acidity of 8.1, 9.0, and 9.6 kcal/mol, respectively. In a given family of acids, such as remotely substituted fluorenes[17] or a series of hydrocarbons giving highly delocalized anions,[8] increases in acidity are usually accompanied by shifts to more positive potentials for the corresponding conjugate bases.[8] An opposite effect was observed for the C=O to C=S structural change; the $E_{ox}(A^-)$ values for $H_2N(=S)NH^-$, $PhC(=S)NH^-$, and $CH_3C(=S)NH^-$ were shifted to more *negative* potentials by 9.8, 7.4, and 6.7 kcal/mol, respectively, relative to those of the corresponding carboxamide conjugate bases. These changes in oxidation potentials lead to lowering the BDEs of the N–H bonds in the corresponding thioamides of 14, 17, and 16 kcal/mol. A large increase in ground-state energy is believed to be at least partially responsible for both the effects on acidities and on BDEs. The C=S bond in molecules appears to be at least 35 kcal/mol weaker than the C=O bond.[18] This increase in ground-state energy leads to an appreciable lowering of the heterolysis energy of the N–H bond, a decrease in pK_{HA}, and a consequent decrease in the homolysis energy of this bond.[14] This effect is augmented by the inherent greater ability of sulfur than oxygen to stabilize a negative charge or odd electron.[20a] The latter effects can be represented in valence-bond symbolism by eqs 4 and 5. Evidence for the superior ability of sulfur vs oxygen to accommodate a negative charge is suggested



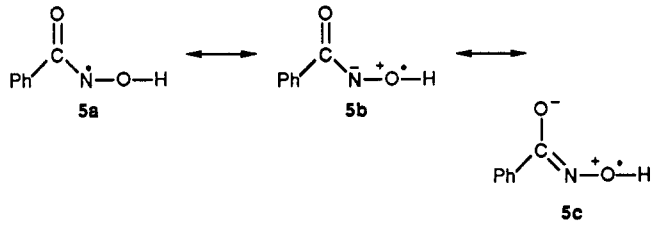
by the 10.7 kcal/mol higher acidity of PhSH than PhOH in DMSO and 8.5 kcal/mol in the gas phase; this is apparently a consequence of a decrease in lone pair–lone pair interactions in the larger S^- ion.[20b] The superior ability of sulfur vs oxygen to stabilize an odd electron is indicated by the roughly 15 kcal/mol more negative oxidation potential for ArS^- ions vs ArO^- ions of the same basicity.[21]

Table II. Homolytic Bond Dissociation Energies for Hydroxamic Acids and Hydrazides in Me_2SO at 25 °C

compound	pK_{HA}[a]	$E_{ox}(A^-)$[b]	BDE[c]	ΔBDE[d]
CH_3CONH_2	25.5	0.725 (110)	107	(0.0)
$CH_3CONHOH$	16.0	0.452 (100)	88	19
$CH_3CONHOMe$	17.0	0.464 (60)	90	17
$CH_3CONHNH_2$	21.8	−0.140 (90)	82	25
$PhCONH_2$	23.35	0.824 (100)	107	(0.0)
PhCONHOH	13.7	0.578 (60)	88	19
$PhCONHOCH_2Ph$	14.35	0.600 (60)	89	18
$PhCONHNH_2$	18.9	−0.068 (80)	81	26
$PhCONHNMe_2$	19.7	−0.016 (50)	82	24
$PhCOCH_3$	24.7	0.268 (60)	93	(0.0)
$PhCOCH_2OMe$	22.85	−0.175 (70)	80	13
$PhCOCH_2NMe_2$	23.55	−0.572 (65)	72	21
$PhSO_2NH_2$	16.1	1.175 (120)	105	(0.0)
$PhSO_2NHOH$	15.4			
$PhSO_2NHNH_2$	17.1	0.048 (135)	81	24
$PhSO_2NHNMe_2$	15.8	0.213	80	25
$(H_2N)_2C{=}O$	26.9	0.788 (170)	111	(0.0)
$(H_2NNH)_2C{=}O$	23.3	−0.370 (140)	88	23
$(H_2N)_2C{=}S$	21.0	0.361 (160)	93	(0.0)
$H_2NNH)_2C{=}S$	16.6	−0.078 (70)	72	20

[a] From ref 1 and earlier papers from this laboratory; in this paper hydroxamic acids were shown to be NH acids. [b] Measured by cyclic voltammetry using a Ag/AgI reference electrode under the conditions previously described. Referenced to the SHE_{aq} electrode by adding −0.125 V;[8] wave widths are given in parentheses. [c] Estimated by using the equation given in footnote *e* of Table I. [d] ΔBDE = [BDE(parent) − BDE(derivative)].

Homolytic Bond Dissociation Energies of the N–H Bonds in Hydroxamic Acids and Carbohydrazides: The Question of Synergism. If the conclusion that resonance involving the amino and carbonyl groups in carboxamides is unimportant can be extended to hydroxamic acids and carbohydrazides, it follows that resonance contributors of type **5c**, upon which the captodative and like postulates are based,[22] should be unimportant. In



other words, there should be little or no synergistic stabilization of these nitrogen-centered analogues of carbon-centered α-MeO- and α-(dimethylamino)phenacyl radicals (**1a–1c**) for which we have postulated synergism between the donor and PhCO acceptor groups.[2] The data providing information concerning this question are summarized in Table II.

Examination of Table II, which summarizes the pK_{HA} and $E_{ox}(A^-)$ data from which the BDEs were calculated, shows that substitution of one of the hydrogen atoms on nitrogen of CH_3CONH_2 and $PhCONH_2$ by OH increases the acidities by 13 and 13.2 kcal/mol, respectively, and makes the oxidation potentials of the anions more negative

(12) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1–83 (p 16).
(13) Fried, H. E. Ph.D. Dissertation, Northwestern University, 1978.
(14) Equilibrations and acidity measurements in several systems have shown that the more stable isomer has the higher pK_{HA}. Examples include 1,1,3-triphenyl- and 1,1,3-triphenylazapropenes,[15] and *cis*- and *trans*-1,3-dithiane 1,3-disulfoxides.[16] It follows that we can expect structural changes that lower the ground state energy to increase the pK_{HA} and vice versa.
(15) O'Donnell, M. J.; Bennett, W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L.; Bordwell, F. G.; Mrozack, S. R.; Cripe, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 8521–8525.
(16) Fried, H. E., unpublished results.
(17) Bordwell, F. G.; Bausch, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 1979–1985.
(18) Kouyman, E. C. In *Organic Sulfur Chemistry*; Janssen, M. J., Ed.; Interscience, New York, 1967; p 2, lists the C=S and C=O BDEs as being 45 and 73 kcal/mol stronger than the C–S and C–O BDEs, respectively. If we assume that the latter have average values of 65 and 86 kcal/mol, this places the BDEs of the C=S and C=O bonds at 110 and 159 kcal/mol. (The latter value is about 20 kcal/mol lower than the value given in most other tables.) The C=S bond in S=C=S has a BDE of 128 kcal/mol vs 192 kcal/mol for the C=O bond in O=C=O.[19a] Charton, M., estimates the difference to be 35 kcal/mol.[19b]
(19) (a) Roberts, J. D.; Caserio, M. C. *Basic Principles of Organic Chemistry*, 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1977; Table 4.3, p 77. (b) Charton, M. *The Chemistry of Double-bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1989; Chapter 5, Table I.
(20) (a) Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A., Jr. *J. Am. Chem. soc.* **1988**, *110*, 5904–5906. (b) Taft, R. W.; Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 463–469.
(21) Cheng, J.-P. Ph.D. Dissertation, Northwestern University, 1987.
(22) Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148–154.

Table III. *E* Values for Amide Ions in Dimethyl Sulfoxide at 25 °C.

amide	pK_{HA}	$E_{ox}(A^-)^a$ (exp)[b]	$E_{1/2}$[c]	conditions for $E_{1/2}$
$CH_3CONHOH$	16.0	−0.322[a] (−0.298)	−0.311	SHACV, Pt electrode 88°/178° AC amplitude 100 mV frequency 30 Hz
$CH_3CONHOMe$	17.0	−0.300 (−0.286)	−0.324	SHACV, Pt electrode, 92°/182° AC amplitude 100 mV frequency 45 Hz
CH_3CSNH_2	18.5	−0.333 (−0.316)	−0.349	SHACV, Pt electrode 88°/178° AC amplitude 70 mV frequency 40 Hz
$CH_3CON(Me)OH$	19.6	−0.649 (−0.650) reversible by CV at 300 mV/S	−0.776 −0.711 (CV)	SHACV, Pt electrode 28°/118° AC amplitude 50 mV frequency 40 Hz
$CH_3CONHNH_2$	21.8	−0.946 (−0.890)	0.964	SHACV, Pt electrode, 94°/184° AC amplitude 100 mV frequency 45 Hz
CH_3CONH_2	25.5	−0.055 (−0.025)	−0.125	SHACV, Pt electrode 90°/180° AC amplitude 100 mV frequency 45 Hz

[a] IR-compensated CV measured under an argon blanket at a scan rate of 100 mV/s by N. G. Harvey at Duke University using a Ag/$AgNO_3$ reference electrode, a Pt wire auxiliary electrode in DMSO solution with anion concentrations of 5 to 7 mM. Reported vs ferrocenium/ferrocene couple. [b] Measured in this laboratory under similar conditions. [c] Measured by N. G. Harvey at Duke University by the SHACV technique under similar conditions. The total errors in *E* values for scan rates of 25–1000 mV/s is ±30 mV.

by 6.3 and 5.7 kcal/mol, respectively. The net result is a lowering of the BDE by 19 kcal/mol in each instance, relative to the parent. Similar substitution of MeO and $PhCH_2O$ groups for an *N*–H hydrogen atom in $PhCONH_2$ have slightly smaller effects (ΔBDEs = 17–18 kcal/mol). In terms of radical stabilization energies (RSEs), the MeO group is apparently stabilizing the nitrogen-centered radical **5** by about 4 kcal/mol more than it stabilizes the analogous carbon-centered radical **1** (Table II). Similar results were obtained when α-NH_2 or α-NMe_2 groups were substituted for one of the *N*-H hydrogen atoms in CH_3CONH_2 and $PhCONH_2$. For $CH_3CONHNH_2$ the ΔBDE is 25 kcal/mol, and for $PhCONHNH_2$ and $PhCONHNMe_2$ the ΔBDEs are 26 and 24 kcal/mol, respectively. These values are to be compared to that of 21 kcal/mol for ΔBDE of $PhCOCH_2NMe_2$ (Table II). It is clear from these results that OH, OR, NH_2, and NMe_2 groups are more effective at stabilizing adjacent nitrogen-centered than analogous carbon-centered radicals by about 4 kcal/mol, despite the absence of synergism. If we restrict our attention to contributors **5a** and **5b** versus **1a** and **1b**, this is understandable since the nitrogen atom, because of its greater electronegativity, would be expected to accommodate the negative charge in **5b** more effectively than does carbon atom in **1b**.

The ΔBDEs for the benzenesulfonohydrazides, $PhSO_2NHNH_2$ and $PhSO_2NHNMe_2$ (24 and 25 kcal/mol, respectively), are at least as large as those for the corresponding benzohydrazides. This is a significant result because the $PhSO_2$ and PhCO groups differ greatly in their effect on adjacent carbon-centered radicals. The $PhSO_2$ group can be destabilizing,[9] or at best mildly stabilizing, whereas the PhCO group is strongly stabilizing. The close similarity in their effect, or lack thereof, in $PhSO_2\dot{N}$–NH_2 and $PhCO\dot{N}$-NH_2 radicals rules out the operation of synergistic effects between the donor an acceptor functions in nitrogen-centered radicals, and casts doubt on our earlier conclusion that synergism is operative in the analogous carbon-centered radicals. The experimental observations with the $PhCO\dot{C}HOMe$ and $PhCO\dot{C}HNR_2$ radicals were that both the acceptor and donor functions exert strong stabilizing effects on the radical, but the effects were no more than additive.[2] This ruled out the captodative effect, which is defined as a greater than additive effect.[22] The case for synergism was based on the assumption that a saturation effect should make the observed effect *less* than additive.[2] Although saturation (and steric) effects are clearly evident for the introduction of the third substituent in a series,[23] the case is less convincing when only two substituents are present. In view of the present results, we conclude that synergism is of little or no importance in stabilizing either carbon- or nitrogen-centered radicals joined to donor and acceptor functions.

Additional evidence of the independence of action of donor and acceptor groups attached to a nitrogen radical is provided by the final four entries in Table II. The "acceptor" $H_2NC{=}O$ moiety in urea *strengthens* the N–H bond in the attached NH_2 group by 4 kcal/mol, relative to NH_3 (Table I). Attachment of NH_2 groups to nitrogen in urea weakens the α-N–H bond by 23 kcal/mol, an effect comparable to that in acetamide. In contrast, the H_2N-$C{=}S$ moiety in thiourea *weakens* the N–H bond in the attached NH_2 group by 14 kcal/mol (Table I). Yet, despite the marked difference in the acceptor properties of the $H_2NC{=}O$ and $H_2NC{=}S$ moieties, the effect of attaching NH_2 groups to nitrogen in thiourea is essentially the same as that in urea, a 20 kcal/mol weakening of the N–H bond.

Summary and Conclusion

Estimates of homolytic bond dissociation energies (BDEs) of N-H bonds in carboxamides indicate that α-PhCO groups do not stabilize nitrogen-centered radicals in contrast to their strong stabilizing effect on carbon-centered radicals. α-$PhSO_2$ groups also show little or no ability to stabilize adjacent nitrogen radicals, but α-CN groups exert strong stabilizing effects. Replacement of the C=O bond in carboxamides by C=S bond causes increases in acidities of the N–H bonds by 8–10 kcal/mol and weakening of the N–H bonds by 14–17 kcal/mol as a consequence of large increases in ground-state energies and the superior ability of sulfur than oxygen in stabilizing a negative charge or odd electron. Comparisons of N–H and C–H ΔBDEs in PhCONHG and $PhCOCH_2G$ compounds, where G = OR or NR_2, indicate that the stabilizing effects of these groups on adjacent nitrogen-centered radicals are about 4 kcal/mol greater than on adjacent carbon-centered radicals. It is concluded from these and related data that the acceptor PhCO and donor G groups are exerting their influence independently rather than synergistically, here, and also

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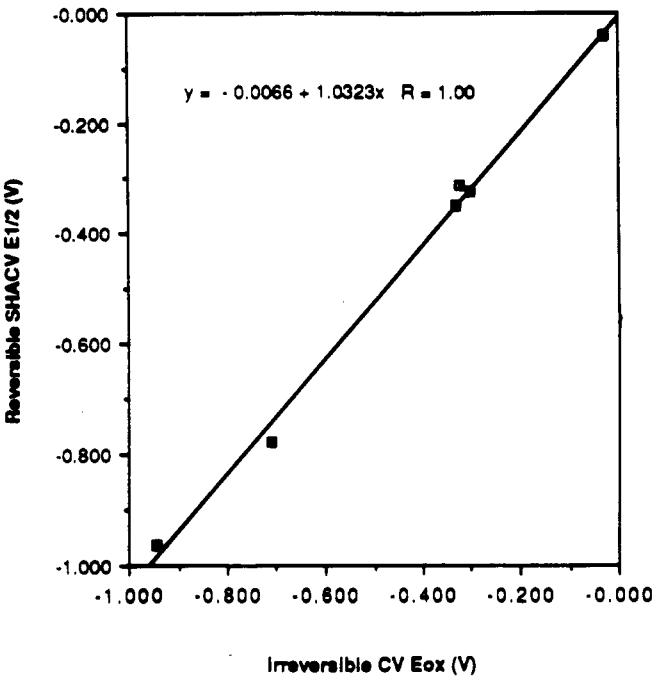

Figure 1. Plot of reversible oxidation potentials ($E_{1/2}$) obtained from second harmonic alternating current cyclic voltammograms vs irreversible cyclic voltammograms for six amides (Table III). (Courtesy of N. G. Harvey, Duke University.)

in the analogous carbon-centered radicals studied previously.[2]

Experimental Section

Materials and Acidities. The sources and properties, including pK_{HA} values in DMSO, for these compounds have been described in earlier publications.[1,4]

Electrochemistry. Research in the laboratory of Professor E. M. Arnett at Duke University has shown that there is a very good correlation (R^2 = 0.998; slope = 1.0) between the irreversible cycliic voltammetric (CV) potentials that we have reported in DMSO for substituted fluorenide ions and the reversible second harmonic alternating current (SHACV) oxidation potentials measured in his laboratory.[24] Since the nitranions obtained from parent carboxamides and sulfonamides listed in Table I were among the worst anions that we have seen with regard to fouling the electrode during oxidation potential measurements, and giving broad CV waves, it was important to check our $E_{ox}(A^-)$ values for these with those obtained by the SHACV technique. On the other hand, the anions derived from hydroxamic acids, carbohydrazides, and their derivatives are all better behaved electrochemically than are the anions derived from the parent carboxamides. The waves are narrow and sharp, and the $E_{ox}(A^-)$ values, although irreversible, are readily reproducible to within ±30 mV by independent investigators. The much greater stability of the radicals being formed on oxidation explains the improved electrochemical behavior. The results of SHACV measurements for acetamide, thioacetamide, acetohydroxamic acid, *N*- and *O*-methylhydroxamic acids, and acetohydrazide are summarized in Table III.

A comparison of the CV values given in Table III shows that our CV values are all slightly less negative than those measured in Arnett's laboratory, and that these, in turn, are usually less negative than the $E_{1/2}$ values by about 30 mV, as expected. A plot of the reversible SHACV data vs the CV data, both measured by N. G. Harvey, reveals a remarkably good correlation (Figure 1). Note that the correlation covers a range of 0.84 V (19 kcal/mol) and includes representatives from several types of amides.

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(24) Private communication from E. M. Arnett and J.-P. Cheng.

Hydroxylated Metabolites of Loratadine: An Example of Conformational Diastereomers Due to Atropisomerism

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The structures of two metabolites of the nonsedating antihistamine loratadine (1) were confirmed by synthesis. The metabolites **3a** and **3b**, which are hydroxylated in the bridgehead, were each prepared from tricyclic ketone **8** in seven steps. Each of these compounds was found to exist as a pair of conformational diastereomers which interconvert slowly at room temperature. These conformers arise due to the restricted conformational mobility inherent to the diaryl[*a*,*d*]cycloheptane ring system.

Introduction

Loratadine (1) is a potent nonsedating H_1-antihistamine[1] presently in clinical use.[2] A study aimed at identifying the metabolites of loratadine revealed that the compound is first hydrolyzed to the piperidinylidene amine **2** and then hydroxylated at several positions. These hydroxylated derivatives may be conjugated and are ultimately excreted in the urine in their free or conjugated form.[3] Two of the major hydroxylated derivatives were isolated and tentatively identified as hydroxy metabolites **3a** and **3b**. In order to confirm the structural assignments of these hydroxylated metabolites and also evaluate their pharmacological profile, alcohols **3a** and **3b** were prepared.

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