Donor-Acceptor Effects on the Stability of Radicals Derived from α-Dialkylamino Ketones

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Abstract: The bond dissociation energies (BDEs) for the acidic C-H bonds in $CH_3COCH_2NMe_2$ and $CH_3COCH_2NEt_2$ ketones, estimated in DMSO from pK_{HA} and oxidation potential data, are 3-4 kcal/mol higher than that for the acidic C-H bond in $PhCOCH_2NMe_2$. It is suggested that the electronic and steric effects of the Ph group dictate a *Z* structure for the precursor enolate ion and the generation of a radical that is strongly stabilized by electrostatic effects, which are responsible for the apparent synergistic effects of the PhCO and NMe_2 groups in stabilizing the $PhCO\dot{C}HNMe_2$ radical. This suggestion was supported by the observation that the BDEs of the acidic C-H bonds in ketocyclic analogues of the α-dialkylamino open-chain ketones, wherein the enolate ion is locked in an *E* structure, have higher BDEs by 9-11.5 kcal/mol.

It has been known for many years that electron donor and acceptor groups attached to a radical center often stabilized the radical to an extent greater than the effect of either of the individual substituents,[1] presumably because of conjugation involving both substituents.[1a] In recent years, there has been considerable controversy as to whether these effects are additive, less than additive, or more than additive. Viehe and his associates have concluded on the basis of electron spin resonance (ESR) data and qualitative theoretical arguments that the effects are more than additive, i.e., synergistic, and have coined the term "captodative" to define this condition.[1c] On the other hand, Rüchardt and his associates have concluded on the basis of a combination of kinetic and thermodynamic data that the effects are no more than additive.[2]

In an earlier paper, we made estimates of the homolytic bond dissociation energies (BDEs) of the acidic C-H bonds in α-alkoxy- and α-(dialkylamino)acetophenones ($PhCOCH_2G$ (G = OR, NR_2)) relative to the BDE of the parent ketone (G = H) by eq 1. These ΔBDEs can be equated to the relative stabilization

$$\Delta BDE = 1.37\Delta pK_a + 23.06\Delta E_{OX}(A^-) \qquad (1)$$

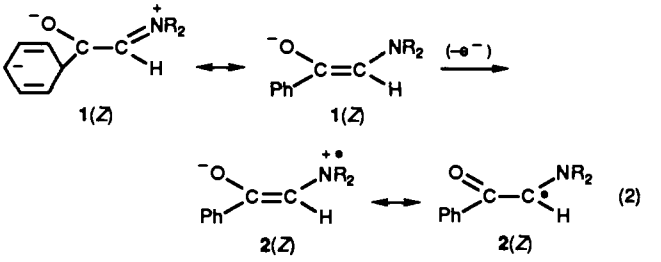
energies (RSEs) of the corresponding radicals since the relative oxidation potentials of the anions provide a good measure of relative radical stabilities when combined with the ΔpK_{HA} term, which allows the comparison to be made at the same anion basicity.[3]

It was surprising to find that when G = MeO and Me_2N, the ΔBDEs were 13 and 21 kcal/mol, respectively, because these values are essentially identical with the gas-phase BDEs for $MeOCH_2$-H and Me_2NCH_2-H, relative to methane,[4] implying that the stabilizing effect of the Me_2N and MeO groups on the $PhCOCH_2^\bullet$ radical is as large as that on the $CH_3^\bullet$ radical. Since the $PhCOCH_2^\bullet$ radical is about 12 kcal/mol more stable than the $CH_3^\bullet$ radical, a smaller effect resulting from "saturation" was anticipated. We concluded that a synergistic effect between the PhCO and NMe_2 (or MeO) moieties was operative in the $PhCO\dot{C}HNMe_2$ and $PhCO\dot{C}HOMe$ radicals.[3] A later study showed that these synergistic effects appeared to be strongly attenuated by steric effects in tertiary radicals of the type $R_2N\dot{C}(Ph)CN$.[5] In the present paper, we have extended the study to $RCOCH_2NR_2$ ketones and their cyclic analogues.

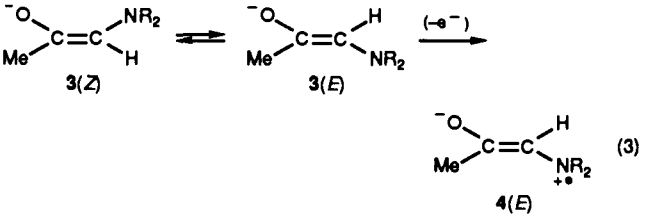
Results and Discussion

The results of the present studies on the equilibrium acidities of α-dialkylamino ketones and their oxidation potentials and those of their conjugate bases are shown in Table I.

The first three entries in Table I provide estimates of the effect of α-NMe_2 and α-NEt_2 groups on stabilities of $CH_3CO\dot{C}HG$ radicals. The RSEs (ΔBDEs) are large (17 and 18 kcal/mol, respectively) but 3-4 kcal/mol smaller than that for the corresponding $PhCO\dot{C}HNMe_2$ radical. On the other hand, the effects of α-Me and α-Ph donors on acetone and acetophenone are within 1 kcal/mol of one another (5 kcal/mol for α-Me and 10 kcal/mol for α-Ph).[6] Consideration of the structures of precursor enolate ions and the resulting radicals offers a plausible explanation for the enhanced effects on BDEs of α-NR_2 (and α-OR) substituents in $PhCOCH_2G$ relative to the CH_3COCH_2G compounds. The Ph moiety in the acetophenone derivative causes the *Z*-enolate **1** to be favored over the *E* isomer by virtue of both steric and



electronic effects. The radical formed from the *Z*-enolate is stabilized by the favorable electrostatic interaction of the oppositely charged cis oxygen and nitrogen atoms. In the enolate ion derived from the acetone derivative, however, the differences in stabilities between the *Z* and *E* isomers will be less, and the *E*-, as well as the *Z*-enolate **3** may be present. As a consequence, the less



stabilized radical **4**(*E*) may then be formed to an appreciable

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(2) (a) Birkhofer, H.; Beckhaus, H.-D.; Rüchardt, C. In *Substituent Effects in Radical Chemistry*; Viehe, H. G., Janousek, Z., Merényi, R., Eds.; Reidel: Dordrecht, The Netherlands, 1986; 199-218. Birkhofer, H.; Hadrich, J.; Beckhaus, H. D.; Rüchardt, C. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 573-575.

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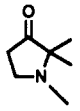
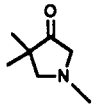
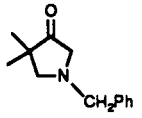
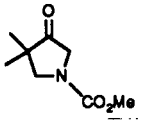
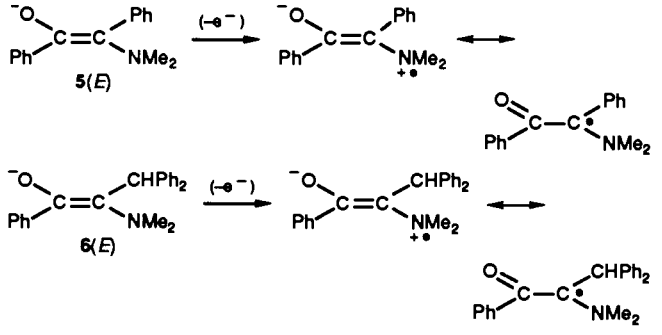
Table I. Acidities and Homolytic Bond Dissociation Energies in DMSO for α-Dialkylamino Ketones and Related Ketones

compd	pK_{HA}[a]	$E_{OX}(A^-)$[b]	$E_{OX}(HA)$[c]	$pK_{HA\bullet+}$[d]	BDE[e]	ΔBDE
CH_3COCH_3	26.5	0.076 (100)	3.30 (170)	−28	94	(0.0)
$CH_3COCH_2NMe_2$	26.0	−0.631 (100)	1.55 (175)	−11	77	17
$CH_3COCH_2NEt_2$	26.0	−0.665 (105)	1.29 (60)	−7.0	76	18
$PhCOCH_3$	24.7	0.143 (60)	3.06 (190)	−24	93	(0.0)
$PhCOCH_2NMe_2$	23.5_5	−0.572			72	21
$PhCOCH(Ph)\text{-}c\text{-}C_5H_{10}N$	21.5	−0.382 (60)	1.44 (100)	−9.3	76.5	16.5
$PhCOCH(CHPh_2)NMe_2$	25.8	−0.348 (80)	1.41 (115)	−3.8	83.2	10
	25.8	−0.151			88	
	24.8	−0.019 (80)	1.28 (90)	2.9	89	(0.0)
	26.2	−0.115 (70)	2.97 (175)	−25.7	89	(0.0)
	27.7	−0.793 (65)	1.60	−13	78	11
	26.4	−0.617 (95)	1.49 (100)	−9.1	77.5	11.5
	22.0	−0.265 (45)	2.91 (96)	−31	80	9

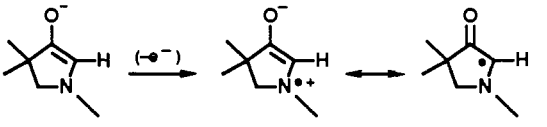
[a] Average of equilibrium measurements in DMSO against two or more indicators. [b] Measured by cyclic voltammetry (eV) with a Ag/AgI reference electrode in DMSO relative to the ferrocene/ferrocenium couple under the conditions previously reported (Bordwell, F. G.; Harrelson, J. A., Jr.; Satish, A. V. *J. Org. Chem.* **1989**, *54*, 3101–3105) and referenced to the standard hydrogen electrode by adding −0.125 V. Numbers in parentheses are wave widths ($E_p - E_{1/2}$ (mV)); $E_{OX}(A^-)$ values are reproducible to about 50 mV (~1 kcal/mol). [c] Measured by cyclic voltammetry in acetonitrile. [d] Calculated with eq 4. [e] Estimated with use of the equation BDE (kcal/mol) = $1.37pK_{HA} + 23.1E_{OX}(A^-) + 56$ (Bordwell, F. G.; Cheng, J.-P.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 1229–1231). Estimates of BDEs via this equation have been shown to be within ±2 kcal/mol of the values chosen as best by McMillen and Golden[4] for 9-methylanthracene, 9,10-dihydroanthracene, diphenylmethane, and cyclopentadiene; recent values reported for fluorene, acetone, thiophenol, diphenylamine, 2-benzylpyridine, 4-benzylpyridine, and *N*-methylaniline are also within ±2 kcal/mol of our estimates.

extent. We reasoned on this basis that replacement of the hydrogen atom in these enolate ions by a large group, such as Ph or $CHPh_2$, should favor the *E* isomer and decrease the RSE (or ΔBDE). The BDE data for $PhCOCH(Ph)\text{-}c\text{-}C_5H_{10}N$ and $PhCOCH(CHPh_2)NMe_2$ in Table I provide a test for this idea. The introduction of a Ph or $CHPh_2$ group no doubt forces the enolate ions for steric reasons to adopt *E* structures **5**(*E*) and **6**(*E*).



The RSE for the radical derived from **5**(*E*) remains surprisingly large (16.5 kcal/mol), however. Evidently, the loss of electrostatic stabilization in this radical is largely compensated by the delocalization of the odd electron by the Ph group. On the other hand, the Ph_2CH group offers no compensating stabilizing effect, and the RSE from the radical formed from **6**(*E*) drops by 11 kcal/mol in accord with our expectations.

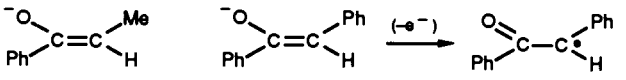
This interpretation is supported by the data obtained for the cyclic systems shown in Table I. Here too the RSEs have been decreased sharply (to 9–11.5 kcal/mol). The enolate ions in the cyclic systems are required by the ring structure to adopt an *E* structure, e.g., **7**, the enolate ion derived from 1,4,4-trimethyl-



pyrrolidin-3-one. As a consequence, the stabilizing electrostatic effect in the resulting radical **8** is diminished. (Note, however, that the change from the model $PhCO\dot{C}H_2$ to $PhCO\dot{C}HNR_2$ involves a change from a primary radical to a secondary radical, whereas for the corresponding change from the cyclic model, both radicals are secondary.)

These results suggest that a *Z* structure for the enolate ion and stabilization of the incipient radical by electrostatic effects are responsible for the synergistic effects observed in the $PhCO\dot{C}HOR$ and $PhCO\dot{C}HNR_2$ radicals.

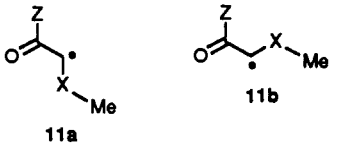
It is of interest in this connection to look at the effects of Me and Ph donors in $PhCOCH_2Me$ and $PhCOCH_2Ph$ ketones where electrostatic effects in the enolate ions are absent. Here the enolate ions no doubt have *Z* structures (**9** and **10**).



9 **10**

For $PhCOCH_2Me$, the ΔBDE is 105 − 88 = 17 kcal/mol and the sum of the individual RSEs is 12 + 7 = 19 kcal/mol; for $PhCOCH_2Ph$, the BDE is 105 − 82 = 23 kcal/mol compared to 12 + 17 = 29 kcal/mol for the sum of the individual effects. For $PhCOCH_2Ph$, therefore, the effects are not even additive, let alone synergistic. Steric effects in these systems are probably not large. In compounds of the type c-$C_5H_{10}NCH(Ph)CN$, if we focus on the c-$C_5H_{10}N$ donor (RSE ≃ 21) and CN acceptor (RSE = 12) and ignore the Ph donor (RSE = 17), the sum is 33. The ΔBDE of c-$C_5H_{10}NCH(Ph)CN$ is 28, relative to that of CH_3–H. The failure of additivity, or synergism, to occur is probably due in part to steric effects, as we suggested earlier,[5] but we now see that weakness of electrostatic attraction, as compared to that in **2**(*Z*), is no doubt a more important factor. Note that, in the radical derived from the enolate of c-$C_5H_{10}NCH(Ph)COPh$, the RSE is still large.

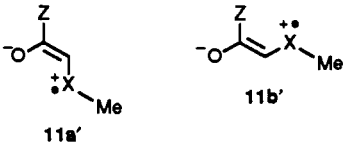
Our postulate of stabilizing electrostatic effect providing radical stabilization is consistent with the conclusion of Beckwith and Brumby, based on ESR spectra, that the α-methoxyacetonyl radical exists in conformation **11a** (Z = Me; X = O) rather than conformation **11b**.[7] Similar effects were observed in the α-



11a **11b**

(methylthio)acetonyl radical (Z = Me; X = S) and in the corresponding methyl esters (Z = MeO; X = O or S).

When **11a** and **11b** are represented in their resonance hybrid zwitterion forms **11a′** and **11b′**, it is apparent that it is electrostatic attractions that cause **11a** ↔ **11a′** to be favored over **11b** ↔ **11b′**.



11a′ **11b′**

Radical Cation Acidities. The estimates for the acidities of the radical cations, derived from the parent ketones by eq 4,[8] place the $pK_{HA^{\bullet+}}$ values in the range of −24 to −28. They reflect primarily the difficulty of removing an electron from the C=O π-bond. The consequent strongly positive $E_{OX}(HA)$ values

$$pK_{HA^{\bullet+}} = pK_{HA} + [E_{OX}(A^-) - E_{OX}(HA)]23/1.37 \quad (4)$$

dominate the other terms in eq 4 (i.e., pK_{HA} and $E_{OX}(A^-)$).[8] The $E_{OX}(HA)$ values for the α-dialkylamino ketones are for the most part much more negative because the nitrogen atom now serves as the source of the electron.

Summary and Conclusions

The radical-stabilizing abilities of acceptor (C=O) and donor (NR_2) groups in α-dialkylamino ketones are the following: (a) greater than additive, i.e., synergistic, for radicals derived from the *Z*-$PhC(O^-)=CHNMe_2$ enolate ion, (b) additive or less than additive for radicals derived from the $CH_3C(O^-)=CHNMe_2$ enolate ion, and (c) less than additive for heterocyclic analogues where the cyclic structure requires the enolate ions to have an *E* geometry. We conclude that donor–acceptor stabilizations of radicals may be synergistic (captodative), but only under special circumstances.

Experimental Section

1,2,2-Trimethylpyrrolidin-3-one[9] and 1,4,4-trimethylpyrrolidin-3-one[10] were prepared via established literature procedures. 1-Benzyl-4,4-dimethylpyrrolidin-3-one was prepared as described by Gosbee, and reaction of this derivative with methyl chloroformate gave 1-carbomethoxy-4,4-dimethylpyrrolidin-3-one.[11a,b]

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for support of this work. The pK_{HA} of 1,2,2-trimethylpyrrolidin-3-one was measured by T.-Y. Lynch.

Registry No. CH_3COCH_3, 67-64-1; CH_3COCH_3 radical cation, 34484-11-2; $CH_3COCH_2NMe_2$, 15364-56-4; $CH_3COCH_2NMe_2$ radical cation, 132751-42-9; $CH_3COCH_2NEt_2$, 1620-14-0; $CH_3COCH_2NEt_2$ radical cation, 132751-43-0; $PhCOCH_3$, 98-86-2; $PhCOCH_3$ radical cation, 34484-12-3; $PhCOCH_2NMe_2$, 3319-03-7; PhCOCH(Ph)-c-$C_5H_{10}N$, 794-05-8; PhCOCH(Ph)-c-$C_5H_{10}N$ radical cation, 132831-31-3; $PhCOCH(CHPh_2)NMe_2$, 132751-41-8; $PhCOCH(CHPh_2)NMe_2$ radical cation, 132751-44-1; cyclopentanone, 120-92-3; 1,2,2-trimethyl-3-pyrrolidinone, 53874-84-3; 1,2,2-trimethyl-3-pyrrolidinone radical cation, 132751-45-2; 2,2-dimethylcyclopentanone, 4541-32-6; 2,2-dimethylcyclopentanone radical cation, 132751-46-3; 1,4,4-trimethyl-3-pyrrolidinone, 36873-12-8; 1,4,4-trimethyl-3-pyrrolidinone radical cation, 132751-47-4; 1-benzyl-4,4-dimethyl-3-pyrrolidinone, 78599-34-5; 1-benzyl-4,4-dimethyl-3-pyrrolidinone radical cation, 132751-48-5; methyl 3,3-dimethyl-4-oxo-1-pyrrolidinecarboxylate, 78599-35-6; methyl 3,3-dimethyl-4-oxo-1-pyrrolidinecarboxylate radical cation, 132751-49-6.

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