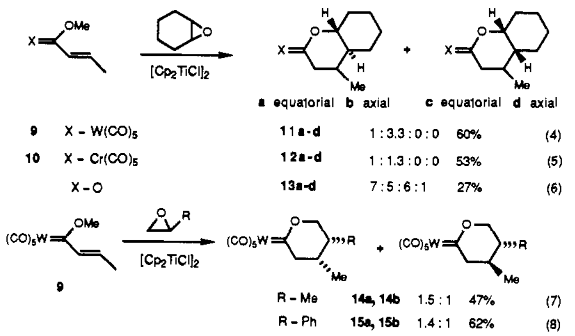
low yield of a 7:5:6:1 mixture of epimeric trans- and cis-fused products (eq 6). Thus, the carbene complexes **9** and **10** are superior radical traps compared to methyl crotonate in terms of reactivity, stereoselectivity, and yield.[13,14]



Central to this comparison is the β-substituent, which is known to inhibit intermolecular radical coupling reactions of unsaturated esters.[15] The principle organic radical acceptors containing substituents at the reacting center that readily participate in intermolecular radical coupling reactions are vinyl nitro compounds and unsaturated diesters.[16,17] The reactivity of unsaturated carbene complexes overcomes the steric inhibition induced by the β-substituent, allowing reaction at lower temperatures and in a nearly 1:1 ratio of substrate and radical, whereas the organic analogues generally require ratios of 10:1.[1,4,8] Therefore, these reactions can serve to construct functionalized carbene complexes and, potentially, serve as synthons for β-substituted esters.[13,17b,18]

The reaction mechanism involves generation of a β-alkoxy radical, addition to the unsaturated carbene complex, and trapping of a novel metal carbene α-radical by a second equivalent of titanocene monochloride. In terms of regioselectivity, the β-position of an α,β-unsaturated carbene complex proves to be more reactive toward alkyl radicals than the carbene carbon; no products arising from addition to the carbene carbon have been isolated. This contrasts with nucleophilic addition reactions where competing addition to both the carbene carbon and β-carbons has been observed.[19,20] Thus, the softer nature of alkyl radicals provides a regioselective reaction to functionalize the β-position. The exclusive formation of trans-fused bicyclic systems is in stark contrast with organic esters, which produce 1:1 or 2:1 mixtures of isomers.[4] This reflects selective equatorial reaction of the cyclohexyl radical with the carbene complexes due to the greater steric demands of the complexes as compared to esters.[21] The origins of the modest β-diastereoselectivity are under study and are possibly related to the nature of the radical acceptor as evidenced by the lower stereoselectivity of the less electrophilic, but equally effective, chromium carbene complexes. Note that at least 90% of the titanium can be recovered from these reactions by filtration of the bright red microcrystalline Cp_2TiCl_2 formed upon quenching with ethereal HCl.

In summary, we have demonstrated the first intermolecular couplings of organic radicals and unsaturated Fischer carbene complexes which proceed in good yields with excellent diastereoselectivity for trans ring junctions when cyclic epoxides are used, provide modest diastereoselectivity at the position β to the carbene, and serve as synthons for β-substituted esters. Current experiments will address the nature of the intermediate metal carbene α-radicals, enhance the diastereoselectivity of the reactions, test the potential for intramolecular reactions, and explore other metal-templated radical reactions.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the UCLA Academic Senate, Committee on Research, for support of this research.

Supplementary Material Available: General experimental procedure and spectral and analytical data for compounds **2**, **3**, **5a**,**b**, **7a**,**b**, **8**, **11a**,**b**, **12a**,**b**, **13a–d**, **14a**,**b**, and **15a**,**b** (4 pages). Ordering information is given on any current masthead page.

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[13] It should be noted that the product carbene complexes can be oxidized with ceric ammonium nitrate to provide esters and lactones, thus demonstrating the equivalence of the metal carbene complexes and the organic carbonyl compounds. (a) Casey, C. P.; Boggs, R. A.; Anderson, R. L. *J. Am. Chem. Soc.* **1972**, *94*, 8947. (b) Dötz, K. H.; Fügen-Köster, B.; Neugebauer, D. *J. Organomet. Chem.* **1979**, *182*, 489.

[14] An analogous test reaction employing methyl cinnamate failed to provide any coupled product.

[15] (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 771. (b) Giese, B.; Lachhein, S. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 967.

[16] For example, see: (a) Barton, D. H. R.; Togo, H.; Zard, S. Z. *Tetrahedron* **1985**, *41*, 5507. (b) Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, *31*, 1679.

[17] For β-substituted unsaturated nitrile acceptors, see: (a) Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1989**, *30*, 681. (b) Giese, B.; Harnisch, H.; Lachhein, S. *Synthesis* **1983**, 733.

[18] However, β-unsubstituted vinyl carbene complexes are so reactive that extensive polymerization occurs in the reaction.

[19] (a) Casey, C. P.; Brunsvold, W. R. *J. Organomet. Chem.* **1974**, *77*, 345. (b) Casey, C. P.; Brunsvold, W. R. *Inorg. Chem.* **1977**, *16*, 391. (c) Fischer, E. O.; Kalder, H. J. *J. Organomet. Chem.* **1977**, *131*, 57.

[20] For recent examples of selective reaction, see: (a) Macomber, D. W.; Hung, M.-H.; Madhukar, P.; Liang, M.; Rogers, R. D. *Organometallics* **1991**, *10*, 737. (b) Wulff, W. D.; Wang, S. L. B. *J. Am. Chem. Soc.* **1990**, *112*, 4550.

[21] Interestingly, reaction of **9** with cyclopentene oxide also only produces trans-substituted products.

Stereoelectronic Effects on the Stabilities of Anions and Radicals Derived from 2-Benzoylperhydropyrimidines

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Received August 14, 1991

The rate of removal of either a proton or a hydrogen atom from a C–H bond adjacent to a nitrogen or oxygen atom has been shown by theory and experiment to be subject to stereoelectronic control because of interactions of the lone pairs on these atoms with the carbanion or carbon-centered radical being formed. The size of the destabilizing interactions in carbanion formation will depend on the dihedral angle between the p (or sp^3) orbital of the carbanion and the lone-pair orbital on nitrogen or oxygen, being maximal when the angle is 0° and minimal when it is 90°.[1] In radical formation these interactions are stabilizing because of the formation of a three-electron bond.[2] The stereoelectronic theory has been supported by the observation of rate retardations in the removal of a proton[1] and rate accelerations in the removal of a hydrogen atom.[3] But these effects are small, and there is a paucity of thermodynamic information concerning their size.[4] In this paper we present quantitative thermodynamic information on these questions.

The α-dimethylamino group in $PhCOCH_2NMe_2$ increases the acidity of acetophenone in DMSO by 1.8 kcal/mol because of

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[1] Hine and Dalsin (Hine, J.; Dalsin, P. D. *J. Am. Chem. Soc.* **1972**, *94*, 6998–7002) observed a 5-fold rate retardation for α-deprotonation by MeO^- in MeOH of methyl 1,3-dioxolane-2-carboxylate relative to methyl cyclopentanecarboxylate.

[2] (a) Wolfe, S.; Schlegel, H. B.; Whangbo, M. H.; Bernardi, F. *Can. J. Chem.* **1974**, *52*, 3787–3792. (b) Baird, N. C. *J. Chem. Educ.* **1977**, *54*, 291–293. (c) Pasto, D. J.; Krananslcy, R.; Zercher, C. *J. Org. Chem.* **1987**, *52*, 3062–3072.

[3] (a) Hayday, K.; McKelvey, R. D. *J. Org. Chem.* **1976**, *41*, 2222–2223. (b) Malatesta and Ingold (Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609–614) observed an 8.8-fold rate acceleration for abstraction of the C-2 α-hydrogen atom from 1,3-dioxolane by the t-BuO$^•$ radical, relative to abstraction of the α-hydrogen atom in tetrahydrofuran. (c) Beckwith and Easton (Beckwith, A. I. J.; Easton, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 615–619) observed that the C-2 axial hydrogen atom in *cis*-2-methoxy-4,6-dimethyl-1,3-dioxane was abstracted by the t-BuO$^•$ radical 8.7 times more readily than the equatorial C-2 hydrogen atom in the trans isomer.

[4] It has been shown, however, that destabilization of the pyrazolide ion by four-electron repulsions between the electrons on the adjacent nitrogen atoms causes pyrazole to be 3.6 kcal/mol less acidic in the gas phase and 1.8 kcal/mol less acidic in DMSO than imidazole.[5]

[5] Taft, R. W.; Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 463–469.

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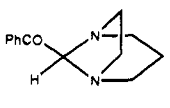
Table I. Relative ΔpK_{HA} and ΔBDE Values for 2-Benzoylperhydropyrimidines as Guides to Relative Anion and Radical Stabilization Energies

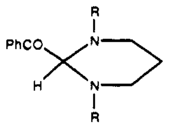
compound[a]	pK_{HA}[b]	ΔpK_{HA}[c]	$E_{ox}(A^-)$[d]	BDE[f]	ΔBDE (RSE)
$PhCOCH_2H$	24.7	(0.0)	−0.607	93.1	(0.0)
$PhCOCH_2NMe_2$	23.55	1.8	−1.447	72.1[g]	21
1	26.0 ± 0.05	−1.1	−0.874	88.7	4
2 (R = Me)	27.92 ± 0.04	−3.8	−1.678[e]	72.8	20
2 (R = Et)	27.0 ± 0.05	−2.5	−1.675[e]	71.6	21
3	28.90 ± 0.02	−5.1			

[a] The synthesis of **1**, **2**, and **3** are described in the 1976 Northwestern University Ph.D. Dissertation of N. R. Vanier. [b] In DMSO measured against two or more indicators. [c] In kcal/mol statistically corrected. [d] Irreversible potentials (unless otherwise noted) measured by cyclic voltammetry against the ferrocene–ferrocenium couple (F_c/F_c^+) using the Ag/AgI reference electrode and the method described in earlier publications.[6,9] [e] Reversible potential, $E_{1/2}(A^-)$ reported. [f] Calculated from eq 1; believed to be accurate to ±2 kcal/mol or better.[9] [g] Reference 6; the $E_{ox}(A^-)$ value reported here is 0.750 V more negative than that given in ref 6 because the F_c/F_c^+ couple is used as the reference point. (The constant C has been adjusted accordingly; see ref 9 for a discussion.)

the electron-withdrawing field/inductive effects of the nitrogen atom that stabilizes the anion.[6] The stabilizing effect of the α-dimethylamino group on the radical formed by oxidation of this anion is much larger, i.e., about 21 kcal/mol.[6] This effect, which is as large as that of a dimethylamino group on a methyl radical, is believed to be caused, at least in part, by the stabilizing three-electron bond formed by overlap of the orbital bearing the nitrogen lone pair and the odd electron in the adjacent carbon p orbital. This type of orbital overlap would lead to four-electron *destabilization* in the corresponding anion, so the radical and anion evidently adopt different conformations. This study has now been extended to the 2-benzoylperhydropyrimidines, **1**–**3**, each of which has two ring dialkylamino groups α to a proton acidified by a carbonyl group. These compounds were all found to be less acidic than acetophenone, indicating that destabilization of the carbanions by steric inhibition of solvation and/or interaction with the lone pairs on the adjacent nitrogen atoms overshadows the stabilizing field/inductive effects of the two nitrogen atoms. The preferred conformations likely for the carbanions derived from **1**–**3** are shown as **1a**, **2a**, and **3a**.[7]

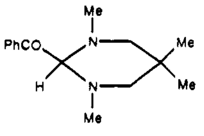


1

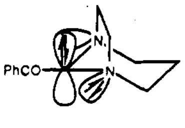


2

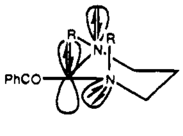
(R = Me or Et)



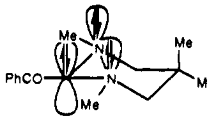
3



1a



2a

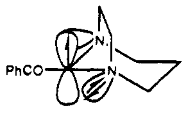


3a

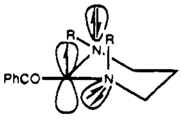
Examination of these conformations shows that (a) in **1a** the lone-pair orbitals are nearly orthogonal to the carbanion orbital, (b) in **2a** there is a destabilizing interaction of the carbanion with one of the lone pairs, and (c) in **3a** there are destabilizing interactions of the carbanion with both lone pairs. The order of acidities expected on the basis of the relative stabilities of the anions is, therefore, **1** > **2** > **3**, and this is the order found, the pK_{HA} values being 26.1, 27.9 (R = Me), and 28.9, respectively (Table I). Table I also presents data on the effects of structural changes in **1** and **2** on the $E_{ox}(A^-)$ values of their anions and the BDEs estimated from eq 1.[9]

$$\mathrm{BDE} = 1.37\, pK_{HA} + 23.06 E_{ox}(A^-) + 73.3 \qquad (1)$$

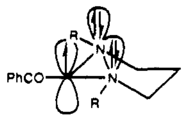
The effects of structural changes on radical stabilization energies (RSEs), as measured by ΔBDEs (Table I), will differ from their effects on anion stabilizations because orbital overlap can be radical stabilizing rather than destabilizing. The bridge in the **1a•** radical prevents conformational change, however. The result is a small radical stabilization (ΔBDE = RSE = 4 kcal/mol). In **2a•** good overlap is possible between the carbon orbital holding the odd electron and one of the orbitals on nitrogen holding a lone pair. A conformational change to radical **2b•** is also possible, which would allow overlap with both nitrogen lone-pair orbitals. Additional stabilization, if any, will be opposed, however, by four-electron repulsions, and the data indicate that the second dialkylamino group does not enhance radical stability. In fact, its effect, if any, is to decrease radical stability slightly, which is consistent with ESR data on α,α-dimethoxybenzyl radicals, where the effect of the second MeO group appears to be "antagonistic",[10] and with the calculations of Pasto.[2c]



1a•



2a•



2b•

The small degree of stabilization observed with radical **1a•**, where the effect of orbital overlap is essentially cut off, is somewhat similar to, but smaller than, the effect of *N,N*-dimethylation of the amino group in the 9-aminofluorenyl radical. Here the RSE of the radical decreases from 15 kcal/mol for the 9-aminofluorenyl radical (relative to the fluorenyl radical) to 8 kcal/mol for the 9-(dimethylamino)fluorenyl radical because of inhibition of overlap between the carbon p orbital and the nitrogen lone-pair orbital caused by steric repulsions between the *N*-methyl groups and the H–C bonds at C-1 or C-8 of the fluorene ring.[11] Steric inhibition of resonance together with saturation effects also may be responsible for the considerably less than additive effect of the R_2N and COPh groups on the stability of the $R_2NC^\bullet(Ph)COPh$ radicals, i.e., (21 + 12) = 33 kcal/mol calculated vs 6.9 kcal/mol observed.[12]

Acknowledgment. We are grateful to the National Science Foundation and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. 1, 137233-37-5; **1a**, 137233-41-1; **1a•**, 137233-45-5; **2** (R = Me), 137233-38-6; **2a** (R = Me), 137233-42-2; **2a•** (R = Me), 137233-46-6; **2** (R = Et), 137233-39-7; **2a** (R = Et), 137233-43-3; **2a•** (R = Et), 137233-47-7; **3**, 137233-40-0; **3a**, 137233-44-4; **3a•**, 137233-48-8.

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(7) *N,N'*-Dimethyl- and *N,N'*-diethylhexahydropyridimines have been shown to have a slight preference for both alkyl groups being equatorial,[8] but in the anion this would place both lone pairs on the nitrogen atoms in axial positions, leading to strong repulsive interactions with the carbanion.

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