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Accurate Calculations of Reactivities and Diastereoselectivities in Complex Molecules: An AM1 Study of 1,3-Dioxolan-4-ones and Related Oxygen Heterocycles

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Abstract: The AM1 semiempirical method has been used to calculate the heats of formation and preferred conformations of a variety of dioxolanes and related compounds, and of the radicals derived from them. The heats of formation and conformations of the transition structures for hydrogen-atom transfer from trialkylstannane to some of these radicals have also been determined. Among the major conclusions of this study are the following: the results of the calculations are highly consistent with experimental data; the regiochemistry of hydrogen-atom abstraction from dioxolanes is controlled mainly by thermochemical factors; the Sn- - -H- - -C bond angle in the transition structure for hydrogen-atom transfer is close to 180°; the calculated activation energies for reactions of dioxolanonyl radicals with trialkylstannane agree with observed diastereoselectivities; and the bond lengths and charge distribution in radicals bearing an α-ether and an α-carbonyl substituent are consistent with captodative stabilization.

Introduction

High-order *ab initio* MO calculations have been used with considerable success to determine the transition structure (TS) energies for a variety of organic free-radical reactions.[2,3] The results of such calculations can be used to examine the validity of hypothetical mechanistic pathways, to determine the relative importance of various structural factors on reactivity, and to predict the outcomes of reactions. However, because *ab initio* calculations are costly in computer time, alternative procedures involving the combination of *ab initio* and molecular mechanics methods have been developed.[4] They have been shown to provide reliable predictions of the relative rates, regiochemistry, and stereochemistry of a variety of *intramolecular* radical reactions, sometimes with substrates of considerable complexity. However, for *intermolecular* processes with moderately complex reactants, *ab initio* calculations are not practicable, while molecular mechanics methods cannot cope with the subtle interplay of the electronic and steric factors that affect diastereoselectivity. The most practicable approach, therefore, appears to be by means of a semiempirical method. AM1 calculations have been successfully used to describe radical reactions,[5] including one reaction exhibiting diastereoselectivity.[6] We have now examined the applicability of the semiempirical AM1 method[7] to some regio- and diastereoselective reactions of dioxolanones and related compounds.

The interaction of the SOMO orbital with the adjacent π system in allylic radicals or with the lone pair in radicals containing an adjacent hetero atom is expected to give rise to significant stereoelectronic effects in reactions of such species.[8] There have been a number of experimental studies of stereoelectronic effects of this type.[9,10] The influence of the anomeric effect in radical reactions of cyclic ethers, such as dioxolanes and dioxanes, has also been examined.[10] There have been reports[8,11−14] of significant diastereoselectivities in the reactions of dioxolanones (**1**) and oxazolidinones (**2**), which can be readily prepared from α-hydroxy acids and α-amino acids.[8,15] Such compounds appear to be promising substrates for pursuing selectivity in radical reactions. They are also interesting because of their potential use in synthesis, especially the oxazolidinones, which can be used for the preparation of nonproteinaceous α-amino acids with a wide range of biological activity.[16]

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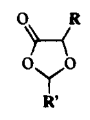
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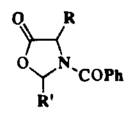
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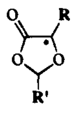
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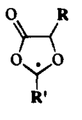
B

a, R = H, R′ = H
b, R = CH_3, R′ = H
c, R = H, R′ = CH_3
d, R = CH_3, R′ = CH_3
e, R = H, R′ = $C(CH_3)_3$
f, R = CH_3, R′ = $C(CH_3)_3$

Hydrogen atom abstraction by radicals from 1,3-dioxolan-4-ones, **1**, may generate a radical at C(5) adjacent to the carbonyl (here designated type **A**) or at C(2) between the two oxygens (type **B**). The relative reactivities at the two positions toward *tert*-butoxyl radicals have been determined experimentally for various substituents R and R′.[17] The stereochemistry of the products resulting from type **A** radicals has also been determined experimentally for reactions with tributylstannane, with tributyldeuteriostannane, and with bromine.[12] The stereochemistry of radical additions to the double bond of methylene groups at the 5-position also has been studied.[11,12] Hydrolysis of the products leads to α-hydroxy acids with new substituents at the α-position. The reactivity patterns observed[11,18] are not easily ascribable to a single major factor, such as exothermicity, steric, polar, or captodative effects, conformational preferences in the starting or transition structure (TS), or the energy barriers involved. Therefore, some of these systems were examined by modeling the reactions in the hope that, if the model were successful, some insight might be gained into the factors that determine the observed reactivity patterns.

We have applied the AM1 semiempirical MO calculation[7] to radical reactions involving species related to **1a–f** and **2e**. The results of the calculations are remarkably consistent with experiment and indicate that modeling such reactions can be helpful in selecting the most promising combination of reactants for the preparation of particular products with the desired stereochemistry.

Results and Discussion

Photolysis of di-*tert*-butyl peroxide in the presence of **1a–f** in the cavity of an ESR spectrometer at −31 °C gives type **A** and type **B** radicals by hydrogen-atom abstraction by *tert*-butoxyl radicals from C(5) and C(2). The relative stationary concentrations of **A** and **B** radicals can be determined by integration of the relevant ESR signals; the relative rates of their formation are directly related to their relative concentrations.[17] The experimentally determined ratios of the concentrations of **A** and **B** radicals are shown in Table 1, normalized on a per hydrogen basis. The normalization is justified by the fact that both molecular mechanics[19] and AM1 calculations show small puckering of the ring of the substrates and a small barrier to flipping of the ring (see below). The heats of formation calculated by AM1 with the CI = 2 option for the various radicals are consistent with the observed relative rates of hydrogen abstraction from the two positions, and there is a linear correlation, eq 1, between observed ln(**A**/**B**) and calculated Δ(BDE), with a correlation coefficient of 0.98, as shown in Figure 1. Equation 1[20] is essentially an Evans–Polanyi–Semenov relationship; in a series of closely related reactions, differences in activation energy, being directly proportional to the logarithm of the relative rates, are linearly related to differences in the heats of reaction.

Table 1. Experimental Ratios[a] of Radicals **A** and **B** and Calculated Heats of Formation of Substituted 1,3-Dioxolan-4-ones and Their Corresponding Radicals

substrate			exptl[b]	calcd heat of formation[c]			
1	R	R′	A/B	substrate	A	B	Δ(BDE)[d]
a	H	H	1.42	−123.15	−91.49	−90.24	−1.23
b	CH_3	H	13.98	−127.55	−99.13	−94.85	−4.28
c	H	CH_3	0.87	−127.55	−96.04	−96.27	0.23
d	CH_3	CH_3	6.57	−131.86[e]	−103.17	−100.77	−2.40
e	H	$C(CH_3)_3$	1.10	−140.03	−108.52	−108.12	−0.41
f	CH_3	$C(CH_3)_3$	11.25	−144.31[f]	−116.09	−112.41	−3.68

[a] Hydrogen abstraction by *tert*-butoxyl radicals at −31 °C, by ESR.[18] [b] Normalized on a per hydrogen basis. [c] Values in kcal/mol; AM1 with the PRECISE option was used for the substrates and with the C.I. = 2 option for the radicals. [d] Δ(BDE) = $\Delta H_f(\mathbf{A}) - \Delta H_f(\mathbf{B})$. [e] Value for the trans isomer; the cis isomer is calculated to have a more puckered ring, but the value of the heat of formation is almost identical (−132.01 kcal/mol). [f] The calculated heats of formation for the trans and cis isomers were the same within the energy convergence criterion of the PRECISE option, 0.03 kcal/mol.

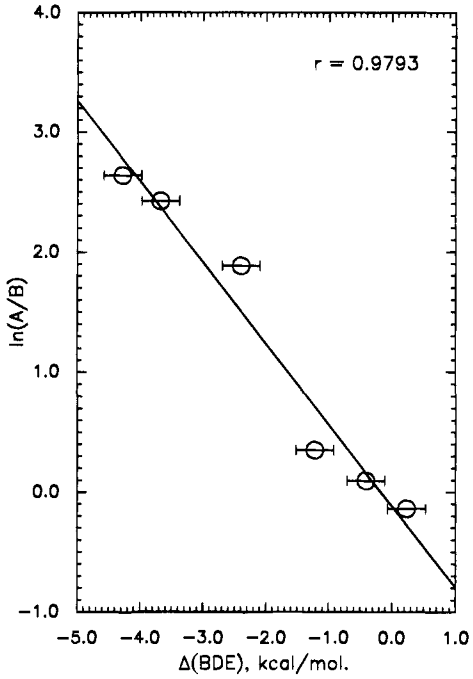

Figure 1. Plot of the logarithm of the experimentally determined relative reactivities for hydrogen abstraction from either C(5) or C(2) (per hydrogen) vs the difference in the calculated heats of formation of type **A** and type **B** radicals formed from compounds **1a–f**. The linear regression line is ln(**A**:**B**) = −0.676 Δ(Δ*H*) − 0.119 (data from Table 1).

$$\ln(\mathbf{A}/\mathbf{B}) = -0.6763[\Delta(\Delta H_f)] - 0.1187 \qquad (1)$$

In this case, 68% of the difference in exothermicity is reflected in the energies of activation. In view of the convergence criterion of ±0.3 kcal/mol for the AM1 CI = 2 calculation,[21] this linear relationship is adequate for attributing primarily to thermodynamic effects the observed relative reactivities of hydrogen abstraction.[22]

The calculated geometry (AM1 PRECISE) of the substituted 1,3-dioxolan-4-ones shows the ring as fairly planar with

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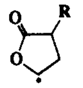
puckering up to 10° for the various R and R′ groups examined. Consistent with X-ray results,[15] it is the ether type of oxygen that is most out of plane with the other four atoms of the ring. The AM1 calculation shows the ring to be flexible; fixing the dihedral angle of the ether oxygen to pucker the ring by 10° more than the AM1 optimum geometry results in a loss of only 0.4 kcal/mol of stability for 2-*tert*-butyl-1,3-dioxolan-4-one, **1e**. Type **A** radicals show similar ring geometry and planar trigonal geometry at the radical center at C(5). Type **B** radicals also show small ring puckering, but the calculated geometry around the radical center at C(2) deviates considerably from planarity in all cases by as much as 31°, depending on the substituent. Such radical geometry would be expected to lead to detectable inversion. Inversion at the radical center at C(2), presumably with concomitant inversion of ring puckering, has been observed by ESR; with a *tert*-butyl substituent at C(2), the energy of activation for the inversion is 7.9 ± 0.5 kcal/mol.[17]

AM1 calculations also predict correctly the preferred position of hydrogen atom abstraction by *tert*-butoxyl radicals from similar substrates. For abstraction from γ-butyrolactone, the only radical detected by ESR is **3**, not **4**;[17] the AM1 CI = 2 calculation shows that the heat of formation of **3** is 4.05 kcal/mol more negative than that of **4**. The weaker C−H bond is attacked, and the more stable radical is formed. Abstraction from α-methyl-γ-butyrolactone occurs preferentially to give **5**, not **6**;[17] the AM1 CI = 2 calculation shows **5** to be more stable than **6** by 1.80 kcal/mol. The radical detected by ESR on hydrogen-atom abstraction from tetrahydrofuran is the 2-yl, **7**; the calculation shows it to be more stable than the 3-yl by 3.87 kcal/mol. Hydrogen abstraction by the bromine atom from dioxolane gives **8**, not **9**. The AM1 CI = 2 calculation shows **8** to be more stable than **9** by 0.64 kcal/mol.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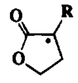
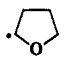

4, R = H
6, R = CH_3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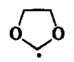
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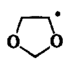
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Since AM1 calculations are successful in simulating many aspects of the radical reactions of the heterocyclic five-membered-ring compounds treated above, we pursued additional calculations of the behavior of C−H bonds adjacent to ether and carbonyl functions and the stabilities of the carbon radicals resulting from hydrogen abstraction.

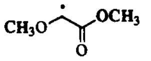
AM1 calculations do not give significant resonance stabilization for a carbon radical α to a carbonyl. When the heats of formation given by AM1 are used in eq 2, equal bond dissociation energies are obtained for C−H in acetone and for primary C−H in propane [Δ(BDE) = 0.05 kcal/mol].

$$\Delta(\mathrm{BDE}) = \Delta H_f(\mathrm{R}) - \Delta H_f(\mathrm{RH}) - \Delta H_f(\mathrm{R'}) + \Delta H_f(\mathrm{R'H}) \quad (2)$$

For the acetonyl radical, the calculated geometry does show the C=O and C−H bonds to be on the same plane, making the π-orbitals parallel to the SOMO p orbital of the radical. When the geometry is constrained to orthogonality, only 1.03 kcal/mol is lost in radical stability. This minor effect is not consistent with theoretical calculations[2] nor with recent work based on pK_a and oxidation potential correlations, which indicates that the BDE of the C−H in acetone is 5−6 kcal/mol weaker than the primary C−H.[23] Older results, based on halogenation equilibria, had resulted in values 1−2 kcal/mol weaker in acetone.[24] Hydrogen abstraction by *tert*-butoxyl radicals from methyl α-methoxyacetate gave **10** (86%) and **11** (14%).[18] The results of AM1 CI = 2 calculations show **10** to be more stable than **11** by 2.60 kcal/mol; substitution into eq 1 leads to a calculated distribution of 88% of **10** and 12% of **11**, in good agreement with experiment. Similarly, methoxyacetone gave **12** as the only radical detected by ESR.[18] AM1 CI = 2 calculations show **12** to be more stable than **13** by 5.85 kcal/mol. The use of eq 1 leads to a calculated 98% yield of **12**. Tetrahydrofuran-3-one has been found to be attacked by *tert*-butoxyl radicals to form **14**, as detected by ESR,[17] and AM1 CI = 2 calculations show **14** to be more stable than **15** by 1.34 kcal/mol and more stable than **16** by 7.03 kcal/mol. Recent work has led to the conclusion that the α-C−H bond in tetrahydrofuran is weaker than that in cyclopentanone by about 1.1 kcal/mol;[25] AM1 CI = 2 calculations show the same effect, but it is more pronounced at 4.6 kcal/mol.

Table 2. C−H Bond Dissocation Energies in kcal/mol Given by AM1 CI = 2, Relative to the Primary C−H Bond Dissociation Energy in Propane

bond	Δ(BDE)	radical formed
$CH_3CH_2CH_2$−H	(0.00)	*n*-propyl
$(CH_3)_2CH$−H	−5.59	isopropyl
CH_3COCH_2−H	0.05	acetonyl
cyclohexane	−4.74	cyclohexyl
cyclopentane	−5.18	cyclopentyl
$CH_3OCOCH_2OCH_2$−H	−3.62	**11**
$CH_3OCOCH(OCH_3)$−H	−6.22	**10**
$CH_3COCH(OCH_3)$−H	−10.33	**12**
$CH_3COCH_2OCH_2$−H	−4.48	**13**
γ-butyrolactone, α-C−H	−0.33	α-yl
γ-butyrolactone, γ-C−H	−4.37	γ-yl
α-methyl-γ-butyrolactone, α-C−H	−6.28	α-yl
tetrahydrofuran, C(2)−H	−7.41	2-yl
tetrahydrofuran, C(3)−H	−3.54	3-yl
cyclopentanone, C(2)−H	−2.80	2-yl
cyclopentanone, C(3)−H	−4.67	3-yl
tetrahydrofuran-3-one, C(2)−H	−8.00	**14**
tetrahydrofuran-3-one, C(4)−H	−0.97	**16**
tetrahydrofuran-3-one, C(5)−H	−6.66	**15**
1,3-dioxolane, C(2)−H	−6.27	2-yl
1,3-dioxolane, C(4)−H	−5.63	4-yl
1,3-dioxolan-4-one, C(5)−H	−4.99	**A**, R = R′ = H
1,3-dioxolan-4-one, C(2)−H	−3.75	**B**, R = R′ = H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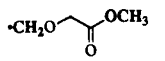
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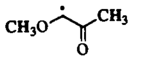
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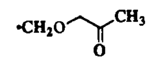
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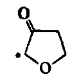
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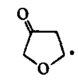
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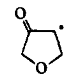
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Values of relative bond dissociation energies given by AM1 CI = 2 calculations and eq 2 for a series of C−H bonds in compounds containing ether and carbonyl functions are given in Table 2. When eq 1 was used, the heats of formation obtained were uniformly successful in quantitatively simulating experimental relative reactivities of C−H bonds in the same molecule.

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(22) When the AM1 UHF PRECISE options are used, the relative stabilities of radicals **A** and **B** for R = CH_3 and R′ = $C(CH_3)_3$ are calculated to be opposite the entries in Table 1, with **B** more stable than **A** by 0.29 kcal/mol. We find that, in this case also, the CI = 2 option (Dewar's half-electron correction) leads to more reliable results for radicals than the UHF option. However, the CI 2 option requires considerably longer CPU times.

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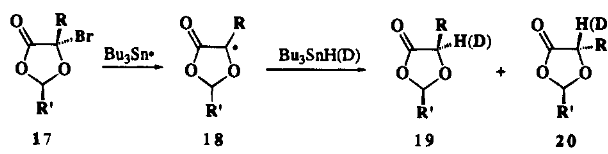
Scheme 1



a, R = H, R′ = C(CH₃)₃ **c**, R = CH₂CO₂H, R′ = C(CH₃)₃
b, R = CH₃, R′ = CH₃ **d**, R = H, R′ = CH₃

The method is generally successful in simulating the direction of relative reactivities reported for C−H bonds in different molecules, but it does not do so quantitatively. In one instance, the direction is also reversed. Indirect competitive experiments have shown that tetrahydrofuran is more reactive than tetrahydrofuran-3-one by 1.8:1.0[17] per reactive hydrogen, implying a somewhat weaker bond in the former (eq 1). As seen in Table 2, AM1 calculations show the attacked bond in the latter (tetrahydrofuran-3-one) to be weaker by 0.56 kcal/mol. A study of the entries in Table 2 shows that increased strain is introduced in a five-membered-ring ketone when a second sp^2 carbon is introduced by the formation of a radical. The amount of strain depends both on the position of the radical center and on the number of oxygen atoms forming part of the ring. The C−H bond in cyclopentane is 0.7 kcal/mol weaker than in cyclohexane;[26] the calculations give a difference of 0.44 kcal/mol.

Experiments on the reduction of 5-bromodioxolanones **17** (Scheme 1) with tributylstannane have shown that, in all cases where R′ is alkyl, hydrogen-atom transfer from the tin to the radicals **18** occurs preferentially from the face of the ring opposite to the alkyl substituent at C(2), with diastereoselectivity depending on the substituents at the C(2) and C(5) positions.[12]

By performing extensive calculations for a series of substituted 1,3-dioxolan-4-ones, the C(5) carbon radicals derived from them, and the transition structures of products obtained from the reaction of the radicals with trialkylstannane, we have examined the ability of the AM1 method to mimic the observed results. As the experimental results could not be rationalized by the thermodynamic stabilities of the products formed, TS calculations were pursued. First we simulated the reaction between ethyl radical and trimethylstannane to give ethane and trialkyltin radical. The heat of reaction was calculated as $\Delta H = -26.3 \pm 2$ kcal/mol from the known values of BDE(Bu_3Sn-H) = 73.7 ± 2[26] and BDE(CH_3CH_2-H) = 100 ± 1 kcal/mol.[27] The AM1 PRECISE option, with trimethylstannane as a model for Bu_3SnH,[28] gave the heats of formation shown in Table 3 for the relevant species from which a calculated value of $\Delta H = -28.84 \pm 0.3$ was obtained, in good agreement with the experimental value. The calculated geometry for the TS has a C- - -H- - -Sn angle of 173°, consistent with the widely held but infrequently verified view that such transition structures are approximately collinear at or near 180°. In agreement with previous theoretical[29] and experimental[30] studies, the calculated geometry of the trimethyltin radical was pyramidal, possibly because the bond dipoles of this species are similar to $X_3C^\bullet$ where X is electron withdrawing.

Table 3. Calculated (AM1 UHF PRECISE) Heats of Formation and Heats of Reaction or Enthalpies of Activation, in kcal/mol

species	heat of formation	reaction	heat of reaction
$(CH_3)_3SnBr$	−26.706		
$(CH_3)_3Sn^\bullet$	12.741		
$(CH_3)_3SnH$	8.656		
CH_3CH_2Br	−13.121		
$CH_3CH_2^\bullet$	15.506	$C_2H_5Br \rightarrow C_2H_5$	−10.82[a]
CH_3CH_3	−17.414	$C_2H_5 \rightarrow C_2H_6$	−28.83[b]
TS (CH_3CH_3)	29.381	$C_2H_5 \rightarrow C_2H_6$	5.219[c]
17a	−126.970		
18a	−110.699	**17a** → **18a**	−23.18[a]
19a	−140.029	**18a** → **19a**	−25.25[b]
20a	−140.029	**18a** → **20a**	−25.25[b]
TS (**19a**)	−94.878	**18a** → **19a**	7.173[c]
TS (**20a**)	−93.828	**18a** → **20a**	8.215[c]
17b	−128.434		
18b	−118.689	**17b** → **18b**	−29.70[a]
19b	−144.286	**18b** → **19b**	−21.51[b]
20b	−144.306	**18b** → **20b**	−21.53[b]
TS (**19b**)	−100.128	**18b** → **19b**	9.905[c]
TS (**20b**)	−98.756	**18b** → **20b**	11.277[c]
17c	−210.461		
18c	−205.649	**17c** → **18c**	−34.64[a]
19c	−232.807[d,e]	**18c** → **19c**	−23.07[b,d]
20c	−232.428[d,f]	**18c** → **20c**	−22.54[b,d]
TS (**19c**)	−187.209[g]	**18c** → **19c**	9.785[c,d]
TS (**20c**)	−186.451[h]	**18c** → **20c**	10.543[c,d]
17d	−113.628		
18d	−98.215	**17d** → **18d**	−24.04[a]
19d	−127.553	**18d** → **19d**	−25.25[b]
20d	−127.553	**18d** → **20d**	−25.25[b]
TS (**19d**)	−82.442	**18d** → **19d**	7.117[c]
TS (**20d**)	−82.241	**18d** → **20d**	7.319[c]

[a] Heat of reaction leading to the indicated species by reaction with $Bu_3Sn^\bullet$. [b] Heat of reaction leading to the indicated species by reaction with Bu_3SnH. [c] Enthalpy of activation for reaction with Bu_3SnH leading to the indicated species. [d] Not PRECISE. [e] Other minima obtained: −232.46, −229.10. [f] Other minima: −231.597, −230.586. [g] Other minima: −186.018, −185.861, −185.788, −184.934, −184.859. [h] Other minima: −186.447, −186.433.

The energy of activation for hydrogen transfer from Bu_3SnH to ethyl radical has been measured as 3.8 ± 0.6[31] and 3.7 ± 0.3 kcal/mol.[32] We used the semiempirical "equibonding" method[33] to calculate the energy of activation and obtained $E_a = 3.9 \pm 1.5$ kcal/mol; this method has been found to give accurate energies of activation for over 100 hydrogen abstraction reactions and provides additional confidence in the experimental values.[33] The transition structure for this reaction was simulated with AM1 UHF PRECISE as follows. The CH_3CH_2-H and $H-Sn(CH_3)_3$ bond lengths were fixed at various combinations of stretched distances, and all other parameters were optimized. The heats of formation obtained with 25 combinations of various C−H and H−Sn bond lengths allowed us to construct a potential energy surface useful for approximating the location of the TS. Subsequently, only the C−H bond length was fixed at distances

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(26) *Handbook of Chemistry and Physics*, 72nd ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 1991−1992.

(27) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493−532.

(28) The flexible *n*-butyl groups would have added inordinate amounts of time to the calculation and would have produced many possible local minima.

(29) Glidewell, C. *J. Organomet. Chem.* **1993**, *461*, 15−19.

(30) Fieldhouse, S. A.; Lyons, A. R.; Starkie, H. C.; Symons, M. C. R. *J. Chem. Soc., Dalton Trans.* **1974**, 1966.

(31) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739−7742.

(32) Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594−4596.

(33) Zavitsas, A. A.; Melikian, A. A. *J. Am. Chem. Soc.* **1975**, *97*, 2757−2763. The input parameters used are (in the order BDE, r_e, stretching frequency) as follows: Bu_3Sn-H (73.7 ± 2,[27] 1.711, 1815.5), $H-CH_2-CH_3$ (100 ± 1,[26] 1.096, 2955), and n-$Bu_3Sn-CH_2CH_3$ (63 ± 4,[27] 2.14, 510). Physical constants are as follows: r_e(Sn−H) is the value for H_3Sn-H from Kattenberg and Oskam (Kattenberg, H. W.; Oskam, A. *J. Mol. Spectrosc.* **1974**, *51*, 377). The stretching frequency for Bu_3Sn-H was obtained from *The Aldrich Library of FT-IR Spectra* (Pouchert, C. J., Ed.; Aldrich Chemical Co.: Milwaukee, WI, 1989; Vol. 3). The frequency used for R_3Sn-Et is the observed Sn−C frequency in Bu_3SnH given in *The Aldrich Library of FT-IR Spectra*, and r_e(Sn−C) is the value for H_3Sn-CH_3 from Kimmel and Dillard (Kimmel, H.; Dillard, C. R. *Spectrochim. Acta* **1968**, *24A*, 909).

between 1.68 and 1.78 Å (at 0.01 Å intervals), and all other geometries were optimized. In this way, the minimum energy reaction path was established in the vicinity of the TS, and the least stable species, the TS, was located at C−H = 1.720 Å; the corresponding H−Sn bond length was 1.699 Å, and the heat of formation was 29.388 kcal/mol. This was confirmed to be the transition state by running the AM1 FORCE option which showed a single imaginary frequency, listed at -928.5 cm^{-1}. From the heats of formation of the TS and the reactants (Table 3) the enthalpy of activation was calculated to be $\Delta H^{\ddagger} = 5.22$ kcal/mol,[34] somewhat higher than the experimental values but in sufficiently satisfactory agreement to indicate that AM1 calculations might give reasonable results in calculations of $\Delta H^{\ddagger}$ for the more complex reactions of the radical **18**. Nevertheless, we find that AM1 is not always successful in predicting energies of activation for simple hydrogen abstractions. Thus for $H_2 + D^{\bullet}$, it predicts a negative energy of activation, while for the identity reaction $CH_3OH + CH_3O^{\bullet}$, it predicts too high a value (28 kcal/mol) compared to about 3 kcal/mol from experimental work on similar hydrogen abstractions.[35]

Since experimental measurements of the diastereoselectivity of the reaction of **18** with $Bu_3SnH(D)$ indicate that differences in the energies of activation are of the order of 0.85 ± 0.65 kcal/mol (see below), AM1 calculations were performed with the PRECISE option (energy convergence criterion of ±0.03 kcal/mol, instead of ±0.3 kcal/mol without this option); the combination of PRECISE with CI = 2 resulted in long CPU times for TS structures, and we opted for the combination UHF PRECISE.

The heats of formation of the substituted 1,3-dioxolan-4-ones and the tin species involved in the reactions of **17** and **18** were calculated and are shown in Table 3, as are the heats of formation of the TS for the reactions of **18a**−**d**. With compounds **18c** and **19c** the PRECISE option failed to coverge in over 10 h of CPU time, and the values given in Table 3 were obtained without this option and, therefore, are less accurate. In addition, convergence occurred at several local minima, depending on the input geometry. This is not surprising in view of the rotational flexibility of the C−C and O−H bonds in the CH_2COOH group, and care was exercised not only to input many different conformations but also to enter those likely to lead to the minimum energy conformer. The values listed in Table 3 are for the most stable conformer found, while other values obtained are given as footnotes. In addition to the conformational flexibility of the CH_2COOH group, internal hydrogen bonding is possible with both the cis and trans isomers, and some of the local minima found have the C−O bond rotated inward toward the ring. The most stable conformers for both isomers have the elements of the CH_2COOH group directed away from the ring. It should be noted that, in this case, the method could have appeared to produce reactivities in the wrong direction if a thorough search for the most stable conformers had not been made and the input geometries for the TS had not been constructed to lead to these conformers (see footnotes *e*−*h* in Table 3).

For TS calculations, we followed the procedure described above for hydrogen transfer to the ethyl radical. The most unstable structure in the minimum energy path was confirmed to be the TS, with the AM1 FORCE option showing only one imaginary frequency, usually listed around -980 cm^{-1}. In the case of the TS leading to the cis and the trans isomers of 2-*tert*-butyl-5-(carboxymethyl)-1,3-dioxolan-4-ones, **19c** and **20c**, respectively, the input geometry was chosen such as to lead to the most stable conformer, and the UHF PRECISE option was successful after about 10 CPU h. The type of energy diagram produced by AM1 calculations is shown in Figure 2 for formation of *trans*-2-*tert*-butyl-5-deuterio-1,3-dioxolan-4-one, **19a**, from **18a**; an early TS is clearly indicated.

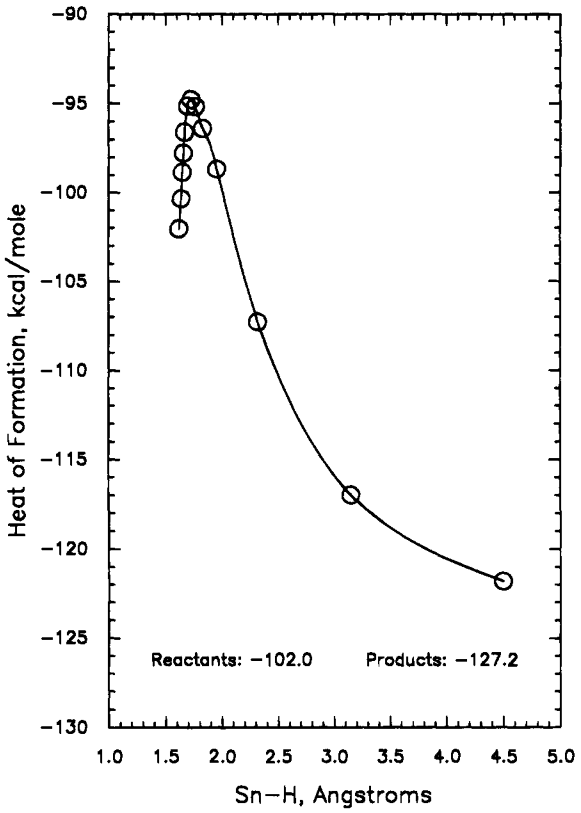

Figure 2. Minimum energy path showing the reaction coordinate for radical **18a** reacting with $(CH_3)_3SnD$ to give **19a**. Calculated enthalpy of formation vs the breaking Sn- - -H bond length. The tin is approaching from the face of the ring opposite to the *tert*-butyl substituent at C(2).

Table 4. Experimental Product Distribution, **19** and **20**, from the Reduction of Substituted 5-Bromo-1,3-dioxolan-4-ones **17** with $Bu_3SnH(D)$, Calculated Distributions, and Energies of Activation[a]

		exptl[7]			calcd	
substrate	*t*, °C	**19**:**20**	% **19**	ΔE_a[**20**−**19**][b]	% **19**[c]	$\Delta(\Delta H^{\ddagger})$[**20**−**19**][b]
17a	10	6:1	86	1.01	86	1.04
17a	80	3:1	75	0.77	82	1.04
17b	10	11:1	92	1.35	92	1.37
17b	80	7:1	88	1.37	87	1.37
17c	80	8:1	89	1.46	75	0.76
17d	10	2:1	67	0.39	59	0.20
17d	80	1.3:1	57	0.18	57	0.20

[a] In kcal/mol. [b] $\Delta E_a = RT \ln(\mathbf{19}:\mathbf{20})$, based on the assumption that the pre-exponential terms are equal. [c] From the difference in the calculated enthalpies of formation of the two TS in Table 3: % **19** = $\exp\{\Delta(\Delta H^{\ddagger})[\mathbf{20}-\mathbf{19}]/RT\}/\{1 + \exp\{\Delta(\Delta H^{\ddagger})[\mathbf{20}-\mathbf{19}]/RT\}$.

The calculated heats of formation in Table 3 indicate that the relative stabilities of the cis and trans products from reactions of **18a** and **18b** are not sufficiently different to justify attributing the observed preference for approach of the tin from the face opposite the alkyl substituent at C(2) to differences in exothermicity. We proceeded, therefore, to calculate the diastereoselectivity on the assumption that the entire effect is due to the difference in the calculated enthalpy of activation for formation of **19** vs **20**. The results are shown in Table 4, where they are compared to the experimentally determined product distribution. The overall agreement between the observed and calculated

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(34) AM1 gives heats of formation at 298 K, including ZPE.

(35) Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 630−632.

percent distribution is remarkably good. The worst case occurs with **19c**:**20c**, where the PRECISE option was not used. Whereas poor selectivity is not of interest synthetically, cases where the selectivity is poor are more challenging calculationally than those where one product is present in large excess. It is the former case that requires accurate calculation of small differences in enthalpies of activation.

The experimental distribution of products allows the calculation of ΔE_a for formation of **19** vs **20** at 10 °C and at 80 °C, on the assumption that the observed selectivities are due only to differences in E_a [$\Delta E_a = RT \ln(\mathbf{19}{:}\mathbf{20})$]. Table 4 shows that the values of ΔE_a obtained at each of the two temperatures are essentially the same for each species within the expected experimental error. This would not have been the case were the pre-exponential factor of significant importance in controlling product distribution. Table 4 also shows that the differences in the enthalpy of activation calculated by the AM1 method are in good agreement with those derived from the experimental results, again the poorest case being with **19c**:**20c**.

The TS geometries obtained for approach of the tin from the same face of the ring as an alkyl substituent at C(2) or the preferred opposite face show that the C- - -H- - -Sn angles deviate somewhat from 180°, in all cases. These deviations are small, and the angles found are between 166° and 175°. Drawings of the structures produced by AM1[36] indicate that the deviations from collinearity are caused by 1,3 interactions across the ring between the bulky trialkylstannane approaching C(5) and either hydrogen or alkyl at C(2). While small deviations from collinear transition structures for hydrogen abstraction would have little effect on the energy, the difference in the enthalpy of activation for formation of the isomers **19** or **20** is correlated well with the difference in the C- - -H- - -Sn angle for each. In other words, the difference between the strain energy of the two diastereoisomeric transition structures arises from nonbonded interactions between the trialkylstannane and the substituent at C(2) and is reflected in the C- - -H- - -Sn angle. The greater the difference in angle, the greater the selectivity. For the small range of angles found here, the correlation is linear, as is shown in Figure 3. The distortion of the C- - -H- - -Sn angle from collinearity at the TS for formation of **20c** is shown in Figure 4.

Table 3 also lists the calculated heats of the reaction of bromo compounds with $Bu_3Sn^\bullet$. This reaction is exothermic in all cases, with values of ΔH ranging from −10.8 to −34.6 kcal/mol. Least exothermic is the reaction of ethyl bromide. Its calculated exothermicity allows an estimate to be made for the BDE of R_3Sn-Br of 79 ± 4 kcal/mol. The reaction of carbon-centered radicals with Bu_3SnH shows a much narrower range of exothermicities, from −22.5 to −25.3 kcal/mol; there is no correlation between calculated exothermicity and observed selectivity. This is not surprising in view of the very early TS for this process; e.g., in the activated complex for hydrogen transfer to ethyl radical, the Sn−H bond has been stretched by only 5% of the calculated bond length of 1.618 Å in R_3Sn-H, and the C−H bond length of 1.72 Å is very far from its calculated equilibrium value of 1.11 Å.

The good diastereoselectivities observed with 5-substituted 2-*tert*-butyl-4-oxo-1,3-dioxolan-5-yl radicals led to the expectation that similar results would be obtained with appropriately substituted oxazolidinones. However, the reaction of Bu_3SnH with **21** (Scheme 2) having various R protecting groups on the nitrogen or having phenylthio instead of bromine showed no selectivity at 80 °C.[37] This is a challenging case for reaction modeling, since the TS energies for the formation of the two isomers should be nearly identical.

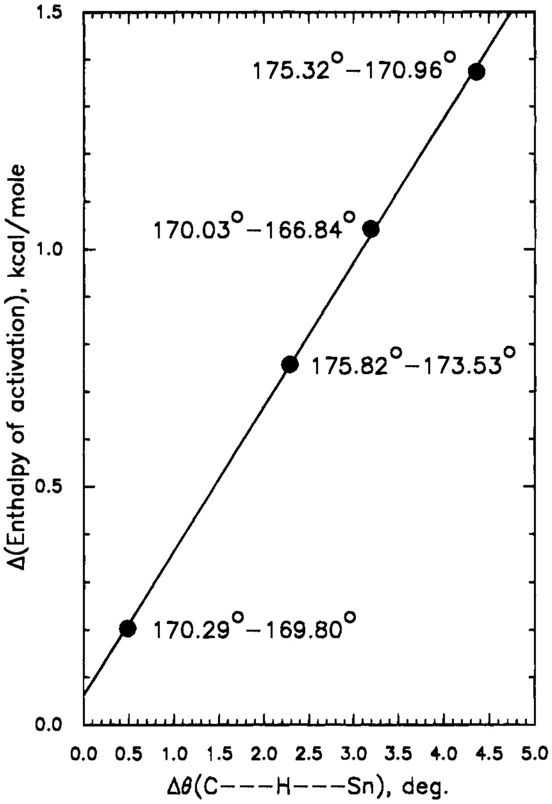


Figure 3. Plot of the difference in the enthalpy of activation calculated for reaction of **18** to form either **19** or **20** vs the difference in the C- - -H- - -Sn angles for the TS leading to each. From left to right, reactions of **18d**, **18c**, **18a**, and **18b**.

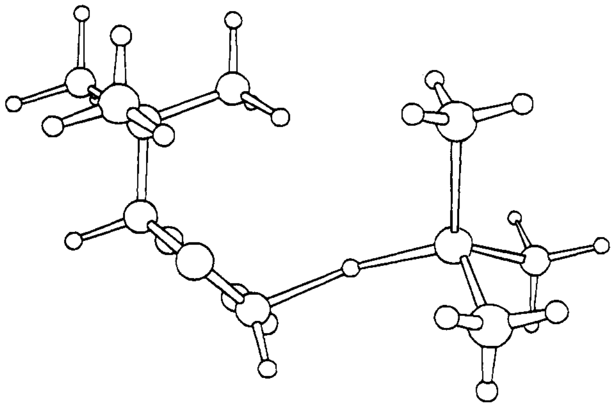
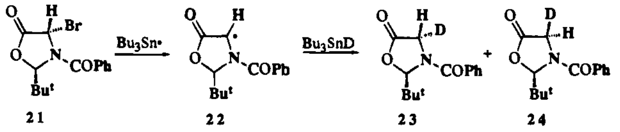


Figure 4. AM1 UHF structure for reaction of **18c** with trimethyltin hydride to form **20c**. $(CH_3)_3SnH$ is on the right, and the ring is seen edge-on. The tin is approaching from the same face of the ring as the *tert*-butyl substituent at C(2).

Scheme 2



We applied the AM1 procedure to the calculation of the enthalpies of activation for reaction of **22** with $(CH_3)_3SnD$

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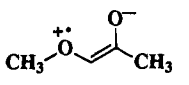
[36] We thank Dr. S. Brumby of the Research School of Chemistry at the Australian National University for providing us with his MOLPLOT-A program.

[37] Chai, C. L. L. Ph.D. Thesis, The Australian National University, Canberra, 1992.

approaching from the same face of the ring as the *tert*-butyl substituent and from the opposite face (as preferred with dioxolanones) to give **23** and **24**, the structures of which as given by AM1 are quite similar to those measured by X-ray crystallography.[15] As expected for amides there are two energy minima (conformers) each for **23** and **24** arising from restricted rotation about the C−N bond; one has the aromatic ring rotated toward the *tert*-butyl group, and the other has the aromatic ring rotated away from the *tert*-butyl group. Consistent with X-ray crystallographic studies,[15] the latter is the more stable by 2.3 kcal/mol. The input geometry chosen for the TS calculations was such as to lead to the formation of the more stable conformer. The heat of formation of **22** was calculated[38] (AM1 UHF PRECISE) to be −60.19 kcal/mol, while the highest points on the minimum energy paths to **23** and to **24** were −39.830 and −39.868 kcal/mol, respectively. Assuming equal pre-exponential terms and assigning the product distribution to differences in TS energies, we calculate the ratio of **23** to **24** as 0.95:1.0 at 80 °C, which is in excellent agreement with the reported ratio of 1:1.[37]

We searched for evidence of an expression of the "captodative" effect in the AM1 results because of the success of the method in simulating the reactions of carbon radicals flanked by electron-donating and electron-withdrawing groups, e.g., **10**, **12**, **14**, and **18**. If "captodative" structures such as **25** and **26** are contributing to the character of radicals **12** and **18** (R = R′ = H), respectively, then in going from the parent compound to the radical the following should be found in the calculated geometries and atomic charges listed. (1) The shortening of the C−CO bond length should be greater in **12** than in the acetonyl radical and greater in **18** (R = R′ = H) and in **14** than in **4**. (2) The increase in charge on the carbonyl oxygen should be greater in **12** than in acetonyl radical and greater in **18** (R = R′ = H) and **14** than in **4**. (3) The decrease in charge on the ether oxygen should be greater in **18** (R = R′ = H) and **4** than in **9**. The AM1 CI = 2 results show all of the above behavior in the direction consistent with captodative structures such as **25** and **26**. However, this result must be interpreted in the context of the relative values of BDE (C−H) given in Table 2 for other five-membered-ring compounds which show C−H bonds at several noncaptodative positions in cyclopentane, tetrahydrofuran, and dioxolane to be weaker than those at the captodative position of **1a**. The weakest C−H bond in a five-membered-ring is calculated to be at the captodative position of tetrahydrofuran-3-one, the precursor of **14**. Furthermore, comparison of the data for **1a** with the data for tetrahydrofuran-3-one shows that the introduction of one more oxygen into the ring of the latter decreases the calculated influence of the captodative effect by 3 kcal/mol. Evidently relative ring strain effects are not the same when a second sp^2 center is introduced upon radical formation.



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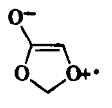

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Our finding that the AM1 calculation accurately describes radical reactions of dioxolanones and related compounds contrasts with a recent report based *inter alia* on an examination of the tetrahydropyran-2-yl and hydroxymethyl radicals that "AM1 and PM3 poorly model anomeric stabilization in radicals and are not useful for predicting radical conformations".[39] With the aim of resolving this discordance we have now used AM1 with the CI = 2 option to re-examine the stabilities of both of these species and also the configuration of the tetrahydropyran-2-yl radical. Calculation of the heats of formation of tetrahydropyran and tetrahydropyran-2-yl radical gave the BDE of the α-C−H bond in tetrahydropyran as −6.98 kcal/mol relative to that for primary C−H in propane. Comparison with the data in Table 2 shows that the α-C−H bond in tetrahydropyran is weaker than C−H in cyclohexane by 2.24 kcal/mol, consistent with modest stabilization of the radical by the adjacent oxygen. When the UHF option was used, a smaller value of 1.28 kcal/mol was obtained.

Product studies of the reactions of the tetrahydropyran-2-yl radical have been interpreted to indicate that the SOMO is oriented axial to the plane of the chair ring.[39] The AM1 calculation with CI = 2 shows the SOMO to be axial to a chair ring, consistent with the experimental results. The ESR spectrum has been interpreted as being due to a slightly pyramidal radical.[40] The calculated lowest energy conformation deviates from planarity by about 10°, with deviations of 5−15° causing energy changes of less than 0.1 kcal/mol. High-level theoretical calculations (UMP2/6-31G*//6-31G*) show a much more pyramidal radical,[39] deviating from planarity by about 40°, a value apparently inconsistent with the ESR interpretations. The UMP2/6-31G*//6-31G* calculation also indicates that there is no metastable conformation for tetrahydropyran-2-yl with the SOMO equatorial to the ring. The AM1 CI = 2 calculation shows the same result.

We have also used the AM1 method to evaluate the relative BDE for the C−H bonds in ethane and methanol. From the calculated heats of formation for ethane, methanol, ethyl radical, and hydroxymethyl radical, the difference when the CI = 2 is used is 5.0 kcal/mol, in good agreement with experiments which show the C−H bond in methanol to be 4[26] to 6[27] kcal/mol weaker than the C−H bond in ethane. The AM1 calculation with the UHF option gives 8.6 kcal/mol.

On the basis of these results we conclude that the AM1 CI = 2 method is capable of modeling the stabilization of radicals such as tetrahydropyran-2-yl and methoxymethyl equally as well as it does the anomeric radicals shown in Table 2. In summary, we believe that AM1 provides a practicable and economical method for predicting the behavior of a variety of carbon-centered radicals, provided that the CI = 2 option is employed. In the light of this conclusion, the claim that AM1 poorly models anomeric stabilization[39] appears to have arisen from the fact that the earlier work employed the UHF option from the MOPAC 6.0 package of programs.[41] For AM1 with the CI = 2 option, this claim appears to be unjustified.

Computational Methodology

In most cases, including the estimation of relative radical stabilities and the entries of Tables 1 and 2, the AM1 method from the MOPAC and AMPAC 2.1 package of programs was used with the CI = 2 option. This option includes both the HOMO and the LUMO in the calculation of odd-electron systems, while it has no effect on closed-shell systems. The CI = 2 option is considerably more time consuming than the UHF

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(38) By use of a VP 2200 machine from Fujitsu Corp. at the Australian National University. In this installation, the AMPAC program was dimensioned for 50 atoms, comprising 25 hydrogens and 25 heavy atoms.

(39) Rychnovsky, S. D.; Powers, J. P.; LePage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375−8384.

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option,[42] but is more successful with radicals. For example, AM1 calculations with the CI = 2 option give the difference of the calculated heats of formation of toluene and of $PhCH_2$- - -H, with the C- - -H bond "fixed" at a stretched distance of 6.0 Å (when the C−H bond is more than 99.9% broken), as 89.5 kcal/mol, in good agreement with the currently accepted experimental value for the BDE of $PhCH_2$−H in toluene of 88 ± 2 kcal/mol.[26] The calculated BDE with the UHF option of 76.3 kcal/mol is in much poorer agreement. Similarly, with AM1 CI = 2 the calculated BDE(PhO−H) for phenol is 90.8 kcal/mol, in good agreement with the experimental value for of 91 ± 2 kcal/mol,[43] while with AM1 UHF it is 79.1 kcal/mol. For transition state calculations the PRECISE option was necessary. For as many as 40−50 atoms, as is the case here, the AM1 calculation with the CI = 2 and PRECISE options resulted in long CPU times, often well over 10 h on the VAX 6210 machine. Therefore, we opted for the faster UHF and PRECISE combination.

Conclusions

The results discussed above indicate that relative values of BDE(C−H) obtained from heats of formation calculated by the AM1 method with the CI = 2 option allow the successful prediction of the relative reactivities toward hydrogen-atom abstraction of various C−H bonds in cyclic and acyclic ethers and ketones, lactones, dioxolanes, and dioxolanones. The method also gives correct estimates of the additional ring strain introduced by the formation of a radical sp^2 center. The calculations afford geometries and atomic charges that are consistent with resonance structures describing the captodative effect for carbon radicals flanked by electron-accepting and electron-donating groups. Calculated molecular geometries for five-membered oxygen heterocycles and radicals derived from them agree well with X-ray and ESR data.

Application of the method to the heats of formation of transition structures gives relative energies of activation for the formation of diastereoisomers that are consistent with observed diastereoselectivities. The results suggest that the selectivity of hydrogen-atom transfer from Bu_3SnH is controlled by steric effects arising primarily from nonbonded interactions between the substituent at C(2) and the approaching trialkylstannane. In qualitative terms this observation is in accord with the experimental observation that diastereoselectivity increases with increasing bulk of the C(2) substituent. Such steric interactions are reflected in small deviations from collinearity in the Sn- - -H- - -C array.

In summary, this study suggests that the AM1 method of calculation with the CI = 2 option will prove to be a useful practicable tool for predicting the relative rates, regioselectivity, and diastereoselectivity of radical reactions of relatively complex substrates.

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