

evaluate the relative importance of these factors.

The above arguments are predicated on the assumption that intercalation is an essential feature of the molecular mechanism of PAH-DNA interaction. While this seems reasonably probable in most of the cases examined to date, an alternative mechanistic pathway involving external binding without prior intercalation appears to be operative in the case of 3-MC<sup>59,65</sup> and cannot be entirely ruled out in other cases.

### Future Directions

Recent advances have expanded our knowledge of the molecular mechanism of PAH carcinogenesis to include detailed information on the interaction of the active PAH metabolites with DNA. The experimental methods utilized in these studies can be extended in principle to a wider range of PAH derivatives to elucidate further the molecular basis of observed structure-activity relationships. One of the practical limitations of this approach is the multiplicity of adducts formed on various base sites by the direct alkylation of DNA. As a consequence, the findings represent an average of the structures present. An important direction for future research lies in the preparation of DNA sequences alkylated on specific base sites to gain more specific information on the molecular structures of the individual adducts formed.

Complete understanding of the mechanism of induction of tumors by PAHs and other chemical carcinogens requires the solution of many additional problems. Among the most important is determination of

the specific sites on DNA which are essential for tumor induction. Alkylation of native double-stranded DNA in vitro takes place at numerous sites along the nucleic acid chain, with preferential binding in G-C-rich regions.<sup>74</sup> The sites of alkylation in vivo are restricted by the secondary structure of DNA and its association with chromatin. However, it is likely that alkylation at only a few sites is relevant to carcinogenesis. While there is evidence to suggest that oncogenes, such as the ras gene,<sup>75</sup> may be important regions of alkylation damage, the critical targets for tumor induction are unknown. Other important questions concern the nature of the specific mutations involved<sup>76</sup> and the role of repair processes in the mechanism of tumor induction.

While many problems remain, it appears that complete elucidation of the molecular mechanism of PAH carcinogenesis is now an attainable goal.

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(74) Boles, T. C.; Hogan, M. E. *Biochemistry* 1986, 25, 3039.

(75) Zarbl, H.; Sukumar, S.; Arthur, A. V.; Martin-Zanca, D.; Barbacid, M. *Nature (London)* 1985, 315, 382. Vousden, K. H.; Bos, J. L.; Marshall, C. J.; Phillips, D. H. *Proc. Natl. Acad. Sci. U.S.A.* 1986, 83, 1222.

(76) Eisenstadt, E. In *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symp. Ser. 283; American Chemical Society: Washington, DC, 1985; pp 327-340.

## Probing Radicals with Alcohol Thermolysis and Molecular Mechanics

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The difference between the layman and the synthetic organic chemist is that the former is often unwittingly engaged in the indiscriminate scission of C-C bonds in the form of fossil fuels, whereas the latter is more actively concerned with the selective formation of the same. What they have in common is that neither is directly interested in the energies of these vital bonds, this topic lying in the realm of the thermodynamicist and the physical organic chemist.

In fact, the homopolar dissociation energy of the C-C bond varies very considerably, 11 kcal mol<sup>-1</sup> being enough to break it in the Gomberg dimer<sup>1,2</sup> and 88 kcal mol<sup>-1</sup> being required to cleave ethane.<sup>3</sup> From Ziegler's early work<sup>4</sup> it is known that C-C bond dissociation is

facilitated by bulky substituents to the bonded atoms and by groups that can stabilize the incipient radicals. Rüchardt and Beckhaus, more recently, have established quantitative relationships between thermal stability, strain, and resonance effects of substituents.<sup>5</sup> Despite surveys and compilations<sup>3,6,7</sup> going back almost 40 years, however, there is still much debate about the C-C and C-H bond energies of small alkanes and about the corresponding heats of formation of the derived alkyl radicals: for the *tert*-butyl radical, for example, in recent years  $\Delta H_f^\circ_{298}$  has been ascribed values in the

(1) Ziegler, K.; Ewald, L. *Justus Liebigs Ann. Chem.* 1929, 473, 163.

(2) McBride, J. M. *Tetrahedron* 1974, 30, 2009.

(3) Kerr, J. A. *Chem. Rev.* 1966, 66, 465.

(4) Ziegler, K. *Angew. Chem.* 1949, 61, 168.

(5) Rüchardt, C.; Beckhaus, H. D. *Top. Curr. Chem.* 1985, 130, 1.

(6) A short list: Szwarc, M. *Chem. Rev.* 1950, 47, 75. Benson, S. W. *J. Chem. Educ.* 1965, 42, 502. Golden, D. M.; Benson, S. W. *Chem. Rev.* 1969, 69, 125. Egger, K. W.; Cocks, A. T. *Helv. Chim. Acta* 1973, 56, 1516.

Canosa, C. E.; Marshall, R. M. *Int. J. Chem. Kinet.* 1981, 13, 303. McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* 1982, 33, 493.

(7) Tsang, W. J. *Am. Chem. Soc.* 1985, 107, 2872.

John Lomas was born in the U.K., took his B.Sc. at University College, London, and obtained his Ph.D. with P. B. D. de la Mare in 1965. After postdoctoral work with V. M. Clark at the University of Warwick, in 1967 he came to work with J. E. Dubois in Paris. He is now a C.N.R.S. Research Director and his main research interests relate to the physical organic chemistry of highly strained organic molecules.

range 6.7–12.9 kcal mol<sup>-1</sup>, rising in the latest analysis<sup>7</sup> to 11.0 or 12.4 kcal mol<sup>-1</sup>, depending on the barrier assumed for CH<sub>3</sub> rotors. For bridgehead alkyl radicals the situation is even worse, comparable data being virtually nonexistent.<sup>8,9</sup>

Perhaps to circumvent thermodynamic problems, there have been many rather naive attempts to determine the relative “stabilities” of bridgehead radicals by measuring the rates of reactions in which they are implicated in order to gain insights into the effects of enforced nonplanarity at the trivalent carbon. Rates of azoalkane and perester thermolysis and of other reactions involving radical formation or capture yielded a mass of incoherent results,<sup>10</sup> and it was some time before anybody realized that the mechanisms of these reactions were not simple nor necessarily constant and that the thermodynamic stability of the radical, sometimes well removed from the transition state, was only one of the factors controlling the rate.<sup>11</sup> One of the major errors was the failure to distinguish between I (internal) and F (front) strain effects, to use Brown's terminology,<sup>12</sup> the latter being completely ignored. In the past it was difficult to allow for the interaction between the residuum<sup>13</sup> and the leaving group (F strain) but, with the development of molecular mechanics (MM),<sup>14</sup> it has become possible to calculate strain energies of molecules (preferably hydrocarbons) and, with somewhat less certitude, of transition states or surrogates thereof.

The work described here represents an attempt to put a “naive” approach onto a more quantitative footing by choosing a reaction, the thermolysis of tertiary alcohols, whose mechanism is simple and constant and for which, by means of MM calculations, the problems of steric effects and transition-state position can be addressed.

## History

“Tri-*tert*-butylcarbinol is especially worthy of careful study and we look forward to further work on it at the earliest opportunity”.<sup>16</sup> Contrary to expectation, Bartlett's enthusiastic announcement in 1945 was not followed by any noticeable activity in this area. It was not until 10 years later that the yield of the alcohol was raised from 5% to 80% by the use of *tert*-butyllithium and that the *p*-nitrobenzoate was synthesized and solvolysed.<sup>17</sup> A further 13 years later, with Tidwell, Bartlett showed that the solvolysis products had been wrongly identified.<sup>18</sup> By this time the interest in hy-

(8) 1-Norbornyl: O'Neal, H. E.; Bagg, J. W.; Richardson, W. H. *Int. J. Chem. Kinet.* **1970**, *2*, 493.

(9) 1-Adamantyl: Kruppa, G. H.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 2162.

(10) For references to earlier work, see: Lomas, J. S. *J. Org. Chem.* **1985**, *50*, 4291.

(11) Bartlett, P. D.; Fickes, G. N.; Haupt, F. C.; Helgeson, R. *Acc. Chem. Res.* **1970**, *3*, 177. Tabushi, I.; Aoyama, Y.; Kojo, S.; Hamuro, J.; Yoshida, Z. *J. Am. Chem. Soc.* **1972**, *94*, 1177. Beckwith, A. L. J.; Cross, R. T.; Gream, G. E. *Aust. J. Chem.* **1974**, *27*, 1673.

(12) Brown, H. C.; Bartolomay, H.; Taylor, M. D. *J. Am. Chem. Soc.* **1944**, *66*, 431.

(13) Alborz, M.; Douglas, F. T. *J. Chem. Soc., Chem. Commun.* **1980**, 728.

(14) By “molecular mechanics” we mean the method of calculating strain energies based on classical energy functions akin to those used in vibrational analysis; many more-or-less comprehensive reviews are available.<sup>15</sup>

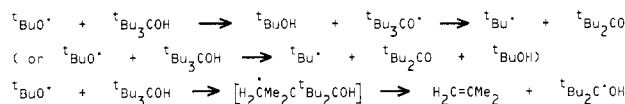
(15) The most complete: Burkert, U.; Allinger, N. L. *Molecular Mechanics*, American Chemical Society: Washington, DC, 1982.

(16) Bartlett, P. D.; Schneider, A. *J. Am. Chem. Soc.* **1945**, *67*, 141.

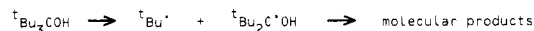
(17) Bartlett, P. D.; Lefferts, E. B. *J. Am. Chem. Soc.* **1955**, *77*, 2804. Bartlett, P. D.; Stiles, M. *J. Am. Chem. Soc.* **1955**, *77*, 2806.

## Scheme I

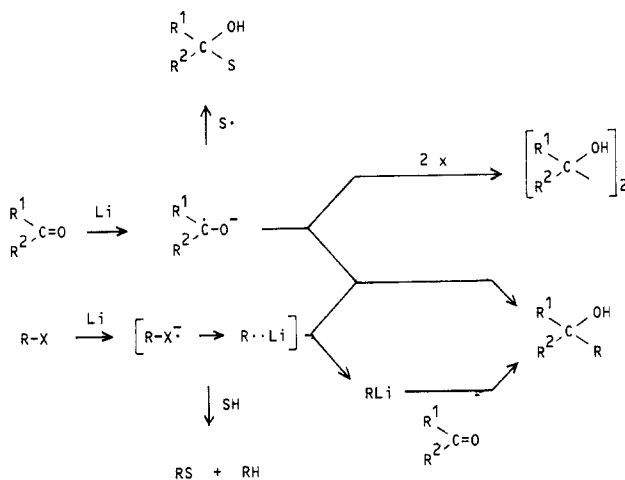
O-H or C-H SCISSION OF ALKOXY RADICALS



C-C SCISSION OF ALCOHOL



## Scheme II



perconjugation that had inspired the 1945 remark had given way to questions about  $\sigma$ -bond participation in solvolysis. Tertiary alkyl substrates were unlikely candidates for such assistance, and Tidwell's work gave no support for its occurrence in this and related systems where the *tert*-butyls were progressively replaced by neopentyls. Since this time work on tri-*tert*-butylmethyl derivatives has accelerated significantly. Lee reduced the *p*-nitrobenzoate to tri-*tert*-butylmethane,<sup>19</sup> whose structure was determined by electron diffraction spectroscopy<sup>20</sup> and calculated by MM.<sup>21,22</sup> This alkane decomposes when treated with a superacid<sup>23</sup> or when heated.<sup>24</sup>

From the viewpoint of this Account, the critical events occurred in 1974, which saw three studies on the radical reactions of the parent alcohol. Hydrogen atom transfer from the alcohol to *tert*-butoxyl radical<sup>25</sup> leads either to *t*-Bu<sup>•</sup> and ketone or to isobutene and *t*-Bu<sub>2</sub>C<sup>•</sup>OH, while a C–C bond homolyzes directly when the alcohol is heated in hexamethylphosphoramide or alone; products of both carbenium ion and radical reactions are formed in DMSO<sup>26</sup> (Scheme I).

## Synthesis

Until 1978 tri-*tert*-butylmethanol (**1a**) was unique in its class. Attempts to extend thermolysis studies to related structures had resulted only in the synthesis of

(18) Bartlett, P. D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1968**, *90*, 4421.

(19) Lee, H. H. Thesis, University of Michigan, 1970.

(20) Bürgi, H. B.; Bartlett, L. S. *J. Am. Chem. Soc.* **1972**, *94*, 5236.

(21) Bartlett, L. S.; Bürgi, H. B. *J. Am. Chem. Soc.* **1972**, *94*, 5239. Hagler, A. T.; Stern, P. S.; Lifson, S.; Ariel, S. *J. Am. Chem. Soc.* **1979**, *101*, 813.

(22) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005.

(23) Olah, G.; Halpern, Y.; Shen, J.; Mo, Y. K. *J. Am. Chem. Soc.* **1973**, *95*, 4960.

(24) Rüchardt, C.; Weiner, S. *Tetrahedron Lett.* **1979**, 1311.

(25) Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 630. Elson, I. H.; Kochi, J. K. *J. Org. Chem.* **1974**, *39*, 2091.

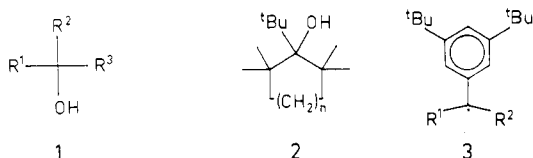
(26) Lomas, J. S.; Dubois, J. E. *J. Org. Chem.* **1974**, *39*, 1776.

Table I  
Overall Yields from the Thermolysis of R<sup>1</sup>R<sup>2</sup>R<sup>3</sup>COH in Degassed Toluene (%)

R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	ketones	secondary alcohols	solvent adducts	total	dibenzyl	
							found	calcd
<i>t</i> -Bu	Nor	Nor	30	50	12	92		
Ad	Ad	Ad	61	26	10	97	30	28
Ad	Ad	Oc	53	36	6	95	33	38
Ad	Ad	Nor	39, 7 <sup>a</sup>	52		98	57	60
Ad	Oc	Oc	49	41	12	102	37	40
Oc	Oc	Oc	42	46	6	94	49	49

<sup>a</sup> Ring-opened products.

*tert*-amyl-di-*tert*-butylmethanol (**1b**) and of two tied-back analogues,<sup>27</sup> **2a** and **2b**. The introduction of bi-



**1a:** R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = *t*-Bu  
**1b:** R<sup>1</sup> = R<sup>2</sup> = *t*-Bu, R<sup>3</sup> = *t*-Am  
**1c:** R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = 1-Ad  
**2a:** n = 2  
**2b:** n = 3

and tricyclic *tert*-alkyl groups, starting with 1-adamantyl (Ad), was then envisaged. Reaction of (1-adamantyl)lithium with di-*tert*-butyl ketone in ether according to the normal procedure did not afford (1-adamantyl)di-*tert*-butylmethanol but adoption of the Barbier technique,<sup>28</sup> whereby reaction between the ketyl radical anion and the alkyl radical/lithium atom pair occurs on the metal surface (Scheme II), gave 40–50% of the desired product.<sup>27,29</sup> Application of this procedure and, in a few cases, of the conventional two-step Grignard method,<sup>30,31</sup> made it possible to synthesize 19 of the 20 alcohols that can be obtained by permuting *t*-Bu, Ad, 1-bicyclo[2.2.2]octyl (Oc), and 1-norbornyl (Nor) groups. Yields are high except when the alcohol is very congested. The most congested of all, tri(1-adamantyl)methanol (**1c**), cannot be obtained by this method but is accessible (27% yield) by reaction of excess 1-AdBr with 1-AdCO<sub>2</sub>Me in freshly distilled THF.<sup>31,32</sup>

No direct structural determinations have been performed on any of these alcohols yet but MM calculations indicate that the C–C bond lengths increase in the order Nor–C, *t*-Bu–C, Oc–C, Ad–C, alcohol **1c** having probably the longest pure C–C bonds yet known (1.657 Å). So far, however, the fragility of this compound has thwarted efforts to determine these bond lengths by X-ray crystallography.<sup>33</sup>

### Thermolysis Products

The C–C bonds being so long, it is not surprising that they show such a pronounced proclivity to fission. The formation of the *tert*-alkyl and the dialkylhydroxymethyl radicals is followed by a series of hydrogen atom transfers involving the radicals and solvent, SH, or the solvent-derived radical. Molecular products are formed

(27) Lomas, J. S.; Luong, P. K.; Dubois, J. E. *J. Org. Chem.* **1979**, *44*, 1647.

(28) Barbier, P. L. *C. R. Hebd. Seances Acad. Sci.* **1898**, *128*, 110.

(29) Bauer, P.; Molle, G. *Tetrahedron Lett.* **1978**, 4853. Molle, G.; Bauer, P. *J. Am. Chem. Soc.* **1982**, *104*, 3481.

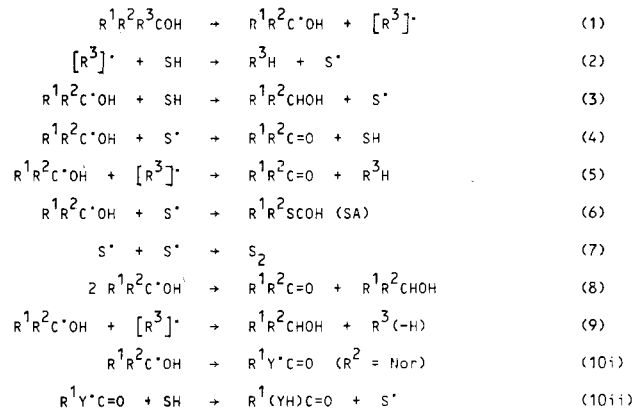
(30) Lomas, J. S.; Dubois, J. E. *J. Org. Chem.* **1982**, *47*, 4505.

(31) Lomas, J. S. *Nouv. J. Chim.* **1984**, *8*, 365.

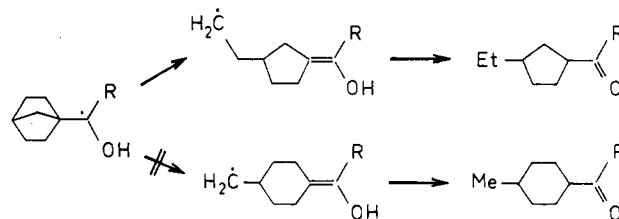
(32) Since this alcohol is virtually insoluble in ether, it can be obtained almost pure simply by quenching the reaction mixture in ether and water.

(33) Ermer, O., personal communication.

### Scheme III



### Scheme IV



by dismutation or addition.<sup>10</sup> Since product ratios are constant, independent of the extent of reaction, it would appear that the molecular products, once formed, do not participate in further reactions with radicals. In Scheme III are listed only those reactions that correspond to observed products; some, such as (8), may be superfluous but cannot be excluded. Provided that reaction 9 can be eliminated by using only bi- and tricyclic alkyl groups,<sup>34</sup> the “disolvent” (dibenzyl, if SH is toluene) yield can be calculated from the alcohol-oxygen-containing products. The similarity of the calculated and experimental yields (Table I) strongly supports the proposed scheme and, taken with the high overall yields, suggests that other reactions, if any, must be of very minor importance.

An unusual feature arises when norbornyl groups are present: at sufficiently high temperatures anomalous cyclopentane derivatives are formed by stereoelectronically controlled opening of the norbornylalkylhydroxymethyl radical (Scheme IV). Calculations in this laboratory, based on Spellmeyer and Houk’s parameters for radical–ene additions,<sup>35</sup> show that the preferred conformations of 1-(*tert*-alkyl)-1-(1-norbornyl)ethyl radicals are those that would open in this

(34) Hydrogen atom abstraction from bi- and tricyclic bridgehead radicals is precluded by Bredt’s rule, which prohibits the formation of a double bond at a bridgehead. For a recent statement of this rule, see: Maier, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 1891.

(35) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

**Table II**  
Relative Yields from the Thermolysis of OcNor<sub>2</sub>COH in Degassed Toluene (%)

<i>T</i> , °C	ring-opened ketones	Nor <sub>2</sub> C=O	Nor <sub>2</sub> CHOH	<i>R</i> <sup>a</sup>
286	20	50	30	1.67
305	32	40	28	1.42
325	46	33	21	1.54
345	5	28	17	1.64

<sup>a</sup>*R* = Nor<sub>2</sub>C=O/Nor<sub>2</sub>CHOH.

way and that the corresponding transition state is 7 kcal mol<sup>-1</sup> lower than that leading to cyclohexanes. The relative importance of this reaction, (10i), increases with temperature (Table II): clearly, it is a first-order process with little or no activation entropy, while all the processes leading to the other products involve two species and, therefore, have more negative activation entropies.

### Thermolysis Kinetics

**Aliphatics: The *tert*-Butyl Radical.** All alcohols investigated show first-order thermolysis kinetics; the rate constants are not significantly affected by change of solvent (dodecane, mesitylene, toluene, etc.), by degassing, or by the addition of more effective radical scavengers, such as styrenes.<sup>36</sup> Rates can be determined by following alcohol disappearance, ketone formation, or, in toluene, dibenzyl formation. The activation entropies all lie in the range 17 ± 5 cal mol<sup>-1</sup> K<sup>-1</sup>; when two different radicals are formed competitively from a common alcohol precursor (vide infra), the activation entropies differ by no more than 1 cal mol<sup>-1</sup> K<sup>-1</sup>. But for one datum,<sup>37</sup> for **1b**, the activation energies for *t*-Bu<sup>•</sup> formation from a series of alcohols, *t*-BuR<sup>1</sup>R<sup>2</sup>COH, correlate well with the sum of the steric parameters, *E*<sub>s</sub><sup>'</sup>, of R<sup>1</sup> and R<sup>2</sup> with a high gradient (δ = -5.8), indicative of the importance of steric effects upon this reaction.<sup>10,30</sup> However, more quantitative information about the reaction can only be obtained by MM calculations. Before 1980, since there was no force field<sup>38</sup> for alcohols, it was customary to approximate to the OH group by replacing it for calculational purposes by H<sup>27</sup> or by Me.<sup>39</sup> This same practice has been adopted for the treatment of leaving groups in solvolysis reactions.<sup>40,41</sup> Since the response of the trivalent carbon in radicals to steric constraints is considered to lie somewhere between that of the positively charged carbon in a carbenium ion and that of carbon in an alkane,<sup>42</sup> both approximations have been used in calculations on radical reactions.<sup>40,43</sup> The possibilities for modeling the alcohol thermolysis reaction are therefore manifold.

(36) Lomas, J. S.; Adenier, A., unpublished results.

(37) The large deviation of the *tert*-amyl group must indicate that the effective size of this group in alcohol thermolysis is much greater than in the defining reaction; note that it lacks the approximate trigonal symmetry of most of the other groups studied.

(38) The expression "force field" denotes the set of energy functions and parameters employed in the MM method.

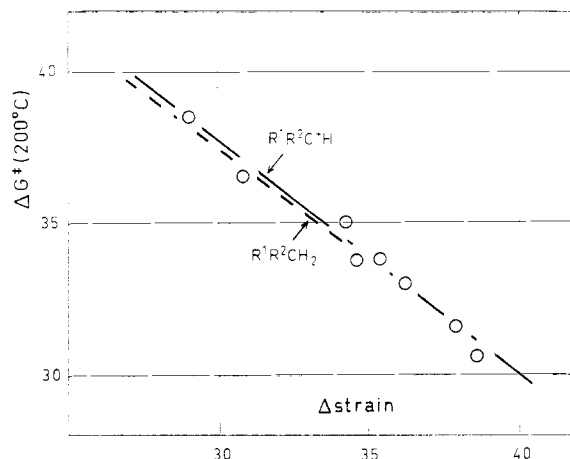
(39) Müller, P.; Perlberger, J. C. *J. Am. Chem. Soc.* **1975**, *97*, 6862. Müller, P.; Blanc, J. *Tetrahedron Lett.* **1981**, 715.

(40) Bingham, R. C.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 3189.

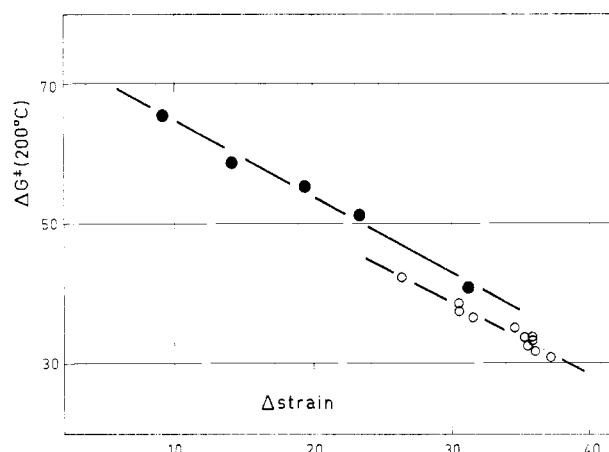
(41) Farcasiu, D.; Jähme, J.; Rüdhardt, C. *J. Am. Chem. Soc.* **1985**, *107*, 5717.

(42) Fort, R. C.; Schleyer, P. v. R. *Adv. Alicycl. Chem.* **1966**, *1*, 284. Fort, R. C. *Adamantane—The Chemistry of Diamond Molecules*; Marcel Dekker: New York, 1976; p 233.

(43) Hellmann, S.; Beckhaus, H. D.; Rüdhardt, C. *Chem. Ber.* **1983**, *116*, 2238.



**Figure 1.** Testing carbenium ion and alkane models for MM correlation of alcohol thermolysis activation energies (EAS force field; points relate to the solid line; all values in kcal mol<sup>-1</sup>).



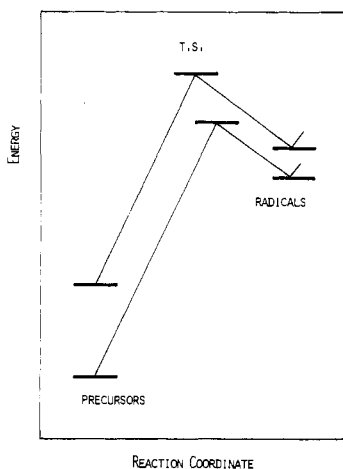
**Figure 2.** Comparison of MM2 correlations for thermolysis of alcohols (O) and analogous alkanes (●) (all values in kcal mol<sup>-1</sup>).

Hydrocarbon models (OH replaced by H or Me) were first tested, carbenium ions and the corresponding alkanes being taken as the extremes (EAS force field<sup>22</sup>) and the strain energy of *t*-Bu<sup>•</sup> being neglected.<sup>30</sup> Alkane, R<sup>1</sup>R<sup>2</sup>CH<sub>2</sub>, and carbenium ion, R<sup>1</sup>R<sup>2</sup>C<sup>+</sup>H (or R<sup>1</sup>R<sup>2</sup>CHMe and R<sup>1</sup>R<sup>2</sup>C<sup>+</sup>Me), have such similar strain energies that the correlation of activation energy against strain energy change (Δstrain) is virtually unaffected by the choice of the radical surrogate (Figure 1). Either extreme is therefore a valid approximation to the radical itself. Since OH lies between H and Me in terms of size, the same must be true for the radical R<sup>1</sup>R<sup>2</sup>C<sup>•</sup>OH. However, heteroatoms and carbenium ions are infrequently parametrized in MM and never together, so the choice is more restricted than for alkyl radicals. Nevertheless, the strain energy of R<sup>1</sup>R<sup>2</sup>C<sup>•</sup>OH can be accurately calculated by representing it as R<sup>1</sup>R<sup>2</sup>CHOH, which is possible with the MM2 force field.<sup>44</sup> We obtain thus a linear correlation (*r* = 0.983) between the activation energy and the difference between the tertiary and secondary alcohol strain energies, SE<sub>tert</sub> and SE<sub>sec</sub>, respectively, with a slope close to unity:

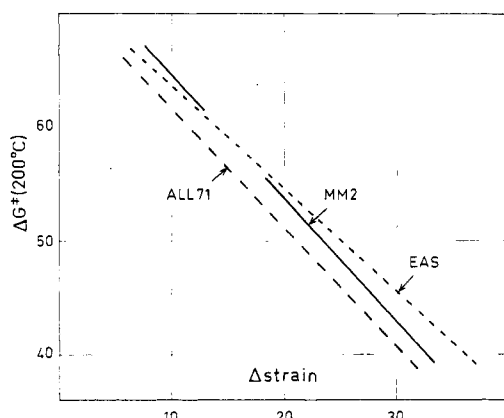
$$\Delta\text{strain} = \text{SE}_{\text{tert}} - \text{SE}_{\text{sec}} \quad (11)$$

$$\Delta G^{\ddagger} = 69.1 - 1.02\Delta\text{strain} \quad (12)$$

(44) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Allinger, N. L.; Chang, S. H. M.; Glaser, D. H.; Hönig, H. *Isr. J. Chem.* **1980**, *20*, 51.



**Figure 3.** The nearer the transition state is to the radicals, the closer the activation energy change matches the strain energy change.



**Figure 4.** Modeling alkane thermolysis with various force fields (all values in kcal mol<sup>-1</sup>).

This value indicates that the activation energy data, which relate to the transition state preceding the radical intermediates, also relate to the radicals themselves; i.e., the transition state and the radicals are very close energetically (Figure 3). This conclusion is consistent with the fact that the recombination of *tert*-alkyl radicals is entropy controlled.<sup>45</sup> To test this point further, MM calculations were run on selected data for the thermolysis of *t*-BuR<sup>1</sup>R<sup>2</sup>CH hydrocarbons, using various force fields.<sup>30</sup> Results show that the slope, although slightly force field dependent, is always close to unity (0.90, 0.99, and 1.08 for EAS, Allinger 1971, and MM2, respectively) (Figure 4).

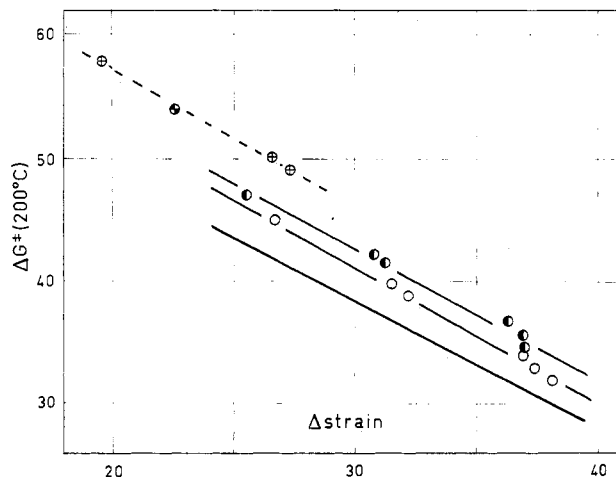
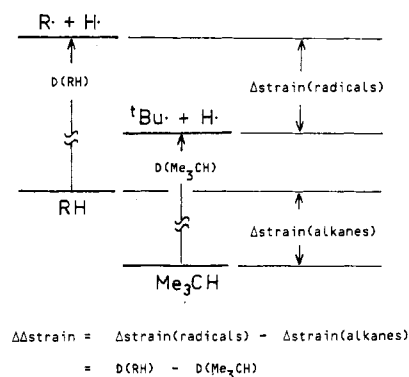
When the MM2 set for hydrocarbons is compared with the alcohol series, it is seen that there is a separation of 3–4 kcal mol<sup>-1</sup>, the hydroxy-substituted radicals being easier to form.<sup>30</sup> This difference corresponds to the effect of the OH group on the C–C bond dissociation energy and is very similar to effects on C–H bond dissociation energies found in earlier studies.<sup>6,46</sup> The combination of thermolysis and MM does therefore give results compatible with prior knowledge based on more conventional techniques.

**Aliphatics: Other *tert*-Alkyl Radicals.** It was noticed early on<sup>30</sup> that radicals other than *t*-Bu<sup>•</sup> could be generated, Ad<sup>•</sup> in particular. In order to interpret

(45) Parke, D. A.; Quinn, C. P. *J. Chem. Soc., Faraday Trans. 1* 1976, 72, 1952.

(46) Alfassi, Z. B.; Golden, D. M. *J. Phys. Chem.* 1972, 76, 3314.

**Scheme V**



**Figure 5.** Activation energy:  $\Delta\text{strain}$  correlations for *tert*-butyl (solid line), Ad (○), Oc (●), and Nor (⊙), experimental; ⊕, extrapolated) (all values in kcal mol<sup>-1</sup>).

activation energies for the formation of these other radicals, it is necessary to modify the computational model very slightly so as to include their strain energy contribution, it being assumed that the strain energy of the radical R<sup>•</sup> is the same as that of the alkane RH:

$$\Delta\text{strain}_{\text{calcd}} = \text{SE}_{\text{tert}} - \text{SE}_{\text{sec}} - \text{SE}_{\text{RH}} \quad (13)$$

By working back from the experimental activation energies for R<sup>•</sup> formation and taking eq 12 as applicable, one can determine the “experimental”  $\Delta\text{strain}$  value and compare it with the value above.<sup>47</sup> If the alkane approximation were correct for the radical R<sup>•</sup>, the two would be the same. In fact,  $\Delta\text{strain}_{\text{exptl}}$  is always smaller than  $\Delta\text{strain}_{\text{calcd}}$  by an amount denoted  $\Delta\Delta\text{strain}$ :

$$\Delta\Delta\text{strain} = \Delta\text{strain}_{\text{calcd}} - \Delta\text{strain}_{\text{exptl}} \quad (14)$$

This can be seen from Scheme V to correspond to the difference in the bond dissociation energies of the alkane RH and isobutane.<sup>48</sup> It is therefore a direct measure of the strain energy increase involved in forming the radical R<sup>•</sup> from RH, that for  $\text{Me}_3\text{CH} \rightarrow t\text{-Bu}^{\bullet}$  being taken as zero. Generalization of this procedure<sup>10</sup> gives linear correlations for Ad<sup>•</sup> and Oc<sup>•</sup>, nearly parallel to the original correlation (eq 12) but separated from

(47) Lomas, J. S.; Dubois, J. E. *Tetrahedron Lett.* 1983, 24, 1161.

(48) Insofar as the activation energy deviations are translated into strain energy double differences (by eq 12–14) and that strain energies are by definition differences in heats of formation at 25 °C, the  $\Delta\Delta\text{strain}$  values can be converted into radical heats of formation, provided that the reference value,  $\Delta H_f^\circ_{298}(t\text{-Bu}^{\bullet})$  is known:

$$\Delta\Delta\text{strain}(\text{R}^{\bullet}) = \Delta H_f^\circ_{298}(\text{R}^{\bullet}) - \Delta H_f^\circ_{298}(\text{RH}) - \Delta H_f^\circ_{298}(t\text{-Bu}^{\bullet}) + \Delta H_f^\circ_{298}(\text{Me}_3\text{CH})$$

**Table III**  
Relative Activation Energies for Reactions via *tert*-Butyl and Bridgehead Radical Intermediates and Gradients for Correlations vs  $\Delta\Delta$ Strain

reaction	T, °C	$\Delta\Delta G^\ddagger$ , kcal mol <sup>-1</sup>				gradient
		<i>t</i> -Bu	Ad	Oc	Nor	
iodine abstraction from RI by Ph <sup>•</sup>	60	0.0	0.33	0.45	1.22	0.157
chlorination of RH by nitrogen cation radicals	15		0.0	-0.11	1.61	0.332
Bu <sub>3</sub> SnH reduction of RCl	80		0.0	0.48	2.23	0.430
Bu <sub>3</sub> SnH reduction of RBr	80		0.0	0.19	2.17	0.431
thermolysis of <i>t</i> -BuN=N-R	300	0.0	3.56	4.40	6.10	0.476 <sup>a</sup>
photolysis of PhCOR	22	0.0	0.64	1.04	3.41	0.543 <sup>a</sup>
perester thermolysis	80	0.0	-0.26	1.30	4.38	0.868 <sup>a</sup>
perester thermolysis	65	0.0	0.60	2.01	5.26	0.879 <sup>a</sup>
perester thermolysis	80	0.0	-0.24	1.62	4.61	0.896 <sup>a</sup>
aldehyde decarbonylation	135	0.0	-0.74	-0.17	4.05	0.945 <sup>a</sup>
halogen abstraction by [Co(CN) <sub>6</sub> ] <sup>3-</sup>	25	0.0	3.50	4.22	8.96	1.132

<sup>a</sup> *t*-Bu not included in the correlation.

**Table IV**  
Radical Strain Energies: Experimentally Determined, Estimated from Solvolysis Data, or Calculated from Molecular Mechanics Force Fields for Radicals<sup>a</sup>

radical	$\Delta G^\ddagger$ (solvolysis)	$\Delta\Delta$ strain	$\Delta$ BDE <sup>b</sup>	$\Delta$ BDE <sup>c</sup>
1-norbornyl	37.5	7.7	4.2	3.8
1-bicyclo[2.2.2]octyl	26.5	4.0	1.8	2.6
1-adamantyl	20.8	2.4	2.5	0.9
1-bicyclo[3.3.1]nonyl	19.4	1.4, <sup>d</sup> 1.7 <sup>e</sup>	0.3	-1.4
<i>tert</i> -butyl	16.4	0.0	0.0	0.0
1-homoadamantyl	19.8	1.6, <sup>d</sup> 1.4 <sup>e</sup>	0.8	-0.8
1-bicyclo[3.2.2]nonyl	20.4	1.8, <sup>d</sup> 0.7 <sup>e</sup>	-1.2	-2.7
3-homoadamantyl	17.1	0.6 <sup>d</sup>	-2.6	-4.3
1-bicyclo[3.3.2]decyl	15.4	-0.1 <sup>d</sup>	-4.7	-6.3

<sup>a</sup> All values in kcal mol<sup>-1</sup>. <sup>b</sup> BDE difference (*t*-Bu = 0.0) calculated from the force field of ref 51. <sup>c</sup> BDE difference (*t*-Bu = 0.0) calculated from the force field of ref 52. <sup>d</sup> Estimated from solvolysis correlation. <sup>e</sup> Product-only intramolecular competition estimate (ref 53).

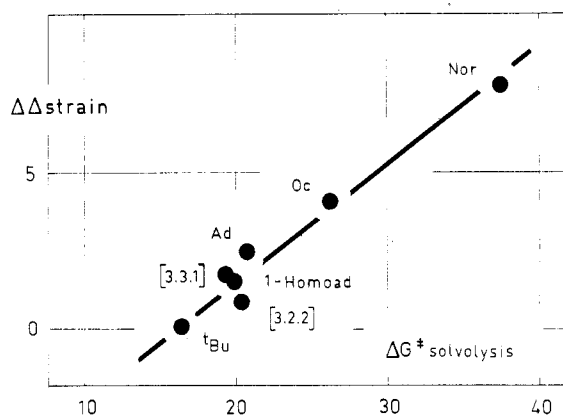
it by 2.4 and 4.0 kcal mol<sup>-1</sup>, respectively (Figure 5). For 1-norbornyl, data on one compound give a value of 7.7 kcal mol<sup>-1</sup>.

Other estimates of the strain energy of the Ad<sup>•</sup> radical range from approximately zero<sup>49</sup> to the most recent EPS value<sup>9</sup> of 3.7 ± 1.2 kcal mol<sup>-1</sup>. Earlier data<sup>10</sup> on relative radical "stabilities" based on a variety of reactions give almost random values (Table III). Occasionally, the data for *t*-Bu, Ad, Oc, and Nor correlate reasonably well with our values, though the gradients are generally small; almost always the correlation is improved by omitting the *t*-Bu datum. This suggests that the *tert*-butyl derivatives are behaving anomalously in some way, but further interpretation is impossible because of ignorance about the reaction mechanisms, the position of the transition state relative to the radical, and the magnitude of direct steric and polar effects upon the reactivity.

The  $\Delta\Delta$ strain values correlate quite well with the activation energies for solvolysis of the corresponding tosylates in 80% aqueous ethanol,<sup>40,41,50</sup> with a slope of 0.36. This result confirms the long-held but essentially qualitative view that steric effects upon radicals are similar in nature to those on carbenium ions but smaller in magnitude.<sup>42</sup> For other bi- and tricyclic systems  $\Delta\Delta$ strain values can be interpreted from available solvolysis data: generally they prove to be rather higher

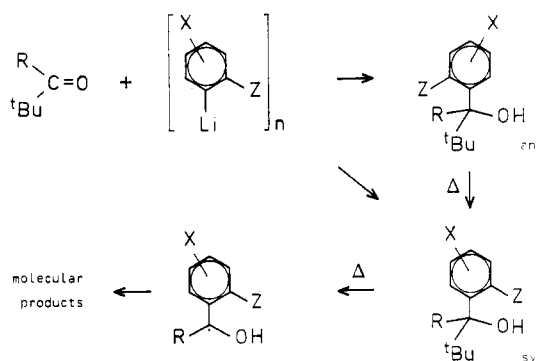
(49) Beckhaus, H. D.; Flamm, M. A.; Rüdhardt, C. *Tetrahedron Lett.* 1982, 23, 1805.

(50) Bentley, T. W.; Roberts, K. *J. Org. Chem.* 1985, 50, 5852.



**Figure 6.** Correlation of  $\Delta\Delta$ strain against activation energies for tosylate solvolysis in 80% aqueous ethanol at 70 °C (all values in kcal mol<sup>-1</sup>).

**Scheme VI**



than those predicted by extensions of the MM2 force field to radicals<sup>51,52</sup> (Table IV). One of these<sup>52</sup> indicates negative values, i.e., the radical less strained than the alkane, for 1-homoadamantyl, 1-bicyclo[3.2.2]nonyl, and other, flatter systems, while interpolation and preliminary product-only competition experiments<sup>53</sup> suggest small positive values for the first two of these at least (Figure 6; Table IV).

**Aryl Systems: Substituent Effects.** The first mention of alcohol thermolysis after 1974 concerns the synthesis of *o*-tolyl *tert*-butyl ketone by thermolysis of *syn*-*o*-tolyl-di-*tert*-butylmethanol<sup>54</sup> but this reaction has only recently been investigated on any detail. Reaction of (*o*-tolyl)lithium with di-*tert*-butyl ketone gives the

(51) Imam, M. R.; Allinger, N. L. *J. Mol. Struct.* 1985, 126, 345.

(52) Peyman, A.; Hickl, E.; Beckhaus, H. D. *Chem. Ber.* 1987, 120, 713.

(53) Lomas, J. S. *J. Org. Chem.* 1987, 52, 2627.

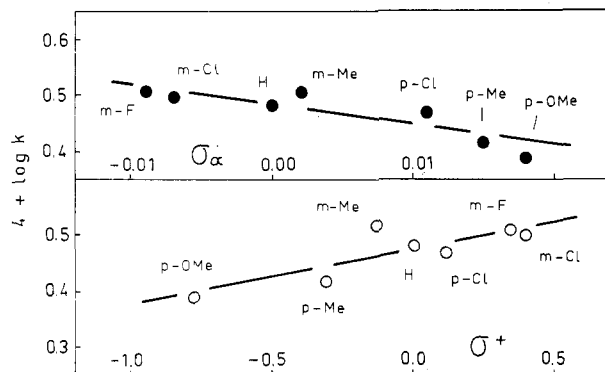


Figure 7. Linear free energy relationships for 4- and 5-substituted *o*-tolyl-di-*tert*-butylmethanol thermolysis (at 263 °C;  $k$  in  $s^{-1}$ ).

anti isomer with about 10% of the stabler syn isomer<sup>54</sup> (Scheme VI). The anti rotamer is converted to syn at a temperature about 100 °C below that required for the radical reaction.

Substituent effects in the 4- and 5-X-substituted *o*-tolyl-di-*tert*-butylmethanols<sup>55</sup> are remarkably small,<sup>56</sup> the rate ratio from fastest (5-F or 5-Me) to slowest (4-OMe or 5-*t*-Bu) being only 1.3 at 263 °C. Correlations with  $\sigma_\alpha$ <sup>57</sup> or  $\sigma^+$ <sup>58</sup> are equally good statistically but neither is chemically satisfactory: the  $\rho_\alpha^*$  is negative (-3.9), contrary to what is expected for a reaction in which spin density should be delocalized by substituents with positive  $\sigma_\alpha^*$ ; on the other hand,  $\rho^+$  is positive (0.1) (Figure 7), whereas correlations with conjugatively electron-donating substituents are normally associated with negative  $\rho^+$  values. The only reasonable hypothesis is that there is substituent effect on the initial state which is *lost* in the thermolysis transition state. The fact that anti  $\rightarrow$  syn rotation correlates with  $\sigma^+$  ( $\rho^+ = -0.24$ )<sup>54</sup> suggests that electron donors stabilize  $sp^2$ - $sp^3$  bond elongation in the transition state of this reaction. If thermolysis proceeds with monotonic bond shortening, it is conceivable that a similar stabilization of the elongated  $sp^2$ - $sp^3$  bond decreases from the initial state to the transition state and that this factor is more important than spin delocalization.

**Aryl Systems: Structure Effects.** In the same way that Rüchardt et al.<sup>59,60</sup> have determined benzyl stabilization by the thermolytic cleavage of diaryl-ethanes, we thought it possible to use structural modifications of aryl-substituted alcohols together with MM calculations to reach the same information. Replacing the *o*-methyl of the set used in the previous study by hydrogen or ethyl and one of the *tert*-butyl groups by a variety of other *tert*-alkyl groups provides a larger number of suitable structures.<sup>36,55</sup> Use of the same calculational model as before (eq 11) (with Beckhaus's extension of the MM2 force field<sup>61</sup> and our own incre-

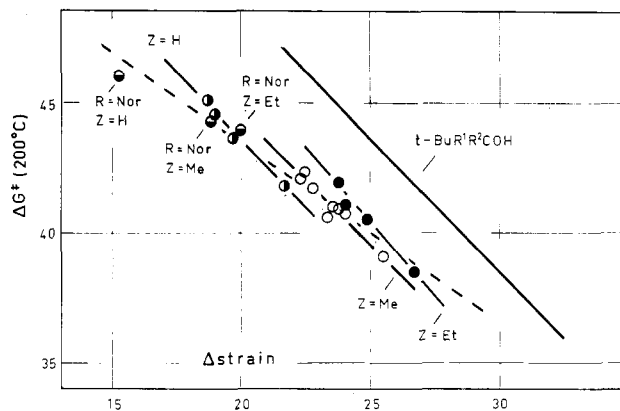
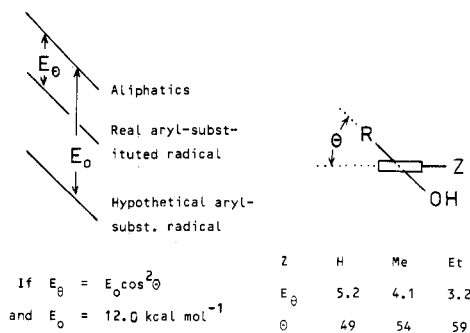


Figure 8. Structural effects on aryl-*tert*-alkyl-*tert*-butylmethanol,  $ArR'BuCOH$ , thermolysis: the dashed line is the general correlation (eq 15); the short lines pertain to  $Z = H$  (●), Me (○), and Et (●) with gradients of 1.04, 0.98, and 1.13, respectively; the solid line on the right is for  $t-BuR'2COH$ ; ● indicates  $R = Nor$ .

Scheme VII



ments for converting steric energies to strain energies<sup>55</sup>) gives a linear correlation (eq 15;  $r = 0.970$ ) whose intercept on the  $\Delta G^*$  axis is approximately 11.8 kcal mol<sup>-1</sup> below that for the aliphatic series (Figure 8):

$$\Delta G^* = 57.3 - 0.68\Delta\text{strain} \quad (15)$$

This *apparent* value of the stabilization induced by replacing a *tert*-alkyl group by an aryl group is *fortuitously* close to estimates obtained by comparing BDE's for benzyl radical formation with those for similarly substituted alkyl radicals<sup>62</sup> (mean value: 11.9 kcal mol<sup>-1</sup>). Extrapolation of eq 15 leads to the unacceptable prediction that for  $\Delta\text{strain}$  greater than about 35 kcal mol<sup>-1</sup> the stabilization would be zero or less. A second approach is to group the data according to the identity of the ortho substituent, neglecting those for  $R = Nor$ .<sup>64</sup> Approximately parallel lines of near-unit slope emerge, implying that for  $Z = H$ , Me, and Et the interplanar angle  $\theta$  takes values of 49, 54, and 59°, respectively, a  $\cos^2 \theta$  relationship being assumed for the stabilization energy<sup>66</sup> (Scheme VII). This interpretation, however,

(61) Beckhaus, H. D. *Chem. Ber.* 1983, 116, 86.

(62) Benzyl stabilization has been attributed values from 7.1 to about 14 kcal mol<sup>-1</sup> in the recent literature.<sup>60,63</sup> Comparison of the C-H bond dissociation energies for alkanes<sup>7</sup> and alkylbenzenes<sup>63</sup> suggests values of 12.1, 13.1, and 10.6 kcal mol<sup>-1</sup> for benzyl,  $\alpha$ -methylbenzyl, and  $\alpha,\alpha$ -dimethylbenzyl radicals, respectively.

(63) Meot-Ner, M. *J. Am. Chem. Soc.* 1982, 104, 5.

(64) Calculations suggest that the 1-norbornyl derivatives should be excluded from this correlation, their conformations being different from those of all others where  $R$  is greater than *t*-Bu. In agreement with the known structures of such alcohols,<sup>65</sup> it is found that the two *tert*-alkyl groups are not disposed symmetrically with respect to the aryl plane. Whereas the norbornyl group lies close to the plane, with the *tert*-butyl group more remote, for all other  $R$  the *tert*-butyl group is closest to the plane.

(65) van Meurs, F.; van Koningveld, H. *Tetrahedron* 1977, 33, 2699. Hough, E.; Lomas, J. S. *Acta Crystallogr., Sect. C* 1984, C40, 1938.

(54) Lomas, J. S.; Luong, P. K.; Dubois, J. E. *J. Org. Chem.* 1977 42, 3394.

(55) Lomas, J. S.; Adenier, A.; Boussad, N. *Bull. Soc. Chim. Fr.*, in press.

(56) This is no doubt aggravated by the rather short range of substituents available for this series.

(57) Arnold, D. R. *Substituent Effects in Radical Chemistry*; Viehe, H. G., Janousek, Z., Merényi, R., Eds.; De Reidel: The Netherlands, 1986; p 171.

(58) Okamoto, Y.; Brown, H. C. *J. Am. Chem. Soc.* 1958, 80, 4972.

(59) Eichin, K. H.; Beckhaus, H. D.; Hellmann, S.; Fritz, H.; Peters, E. M.; Peters, K.; Schnering, H. G. v.; Rüchardt, C. *Chem. Ber.* 1983, 116, 1787.

(60) Kratt, G.; Beckhaus, H. D.; Rüchardt, C. *Chem. Ber.* 1984, 117, 1748.

conflicts with ESR data<sup>67</sup> on sterically hindered benzyl radicals, **3**, which show substantially smaller twist angles, values of 0–10° and of 25° being estimated for R<sup>1</sup> = *t*-Bu, R<sup>2</sup> = H and for R<sup>1</sup> = *t*-Bu, R<sup>2</sup> = Me, respectively. Moreover, the model is self-contradictory: while the R–C–C–Ar angle is typically 85–90° in the secondary alcohol, our conclusion is that in the radical it is 49–59°. The secondary alcohol is therefore manifestly inadequate as a transition-state surrogate for the thermolysis of aryl-substituted alcohols. We are currently working on a force field for the hydroxy-substituted benzyl radicals, this being the only means of rationalizing our data.

Rüchardt and Beckhaus<sup>5,59,60</sup> have constructed an ad hoc force field for the aryl-substituted alkyl radicals formed in the thermolysis of 1,2-diarylethanes. When these latter are compared with ethanes in which the aryl groups have been replaced by alkyls the correlations against  $D_{sp}$  (analogous to  $\Delta$ strain) have similar gradients but intercepts that indicate resonance energies of 7.8 and 8.4 kcal mol<sup>-1</sup> for secondary and tertiary benzyl radicals, respectively. Though the MM calculations on the radicals show that benzyl resonance is not sterically hindered,<sup>60</sup> both these values lie somewhat below the most plausible current estimates.<sup>62</sup> It is not clear whether this should be attributed to differences in the degree of advancement of the reaction at the transition state, to radical pairing,<sup>68</sup> or to eventual defects in the radical force field. The problem of representing the interplay of steric and resonance effects has been handled by setting the C–C–C–Ar and H–C–C–Ar torsional energy parameters so as to impart a certain degree of planarity to the radical.<sup>69</sup> However, this would seem to be tantamount to *assuming* a value for the resonance

(66) de la Mare, P. B. D.; Johnson, E. A.; Lomas, J. S. *J. Chem. Soc.* 1964, 5317.

(67) Schreiner, K.; Berndt, A. *Angew. Chem., Int. Ed. Engl.* 1975, 14, 366.

(68) It should be noted that in the aryl series there are large  $\Delta S^\ddagger$  variations, due in part to tight pairing of the radicals in the bond dissociation transition state.<sup>60,61</sup> This could well affect the apparent stabilization energy.

(69) Beckhaus, H. D., personal communication.

energy. It is to be hoped that by reference to a larger body of structural, thermodynamic, and kinetic data it will be possible to devise a fully compatible force field with predictive capacity.

### Concluding Remarks

Thermolytic homolysis of C–C bonds in tertiary alcohols gives two unequal fragments. If appropriate sets of compounds are chosen, the reaction can be used as a means of investigating either radical. Alcohol thermolysis has several advantages over other reactions that have been used to study radical energies: the reaction is clean and mechanistically simple; MM calculations suggest that the transition state is energetically close to the radicals formed; polar effects, even if difficult to understand, are small enough to be neglected; direct steric effects, i.e., those not related to strain at the trivalent carbon, can be calculated; and finally, tertiary alcohols are relatively easy to synthesize.

Further work in this field will be directed toward the study of alkyl radicals at the extremes of the strain energy range, leading, we hope, to a reliable force field for these species. As MM is further extended toward the description of heteroatomic and unsaturated molecules, it should become possible to apply the techniques described above to a greater variety of structural types. It must always be borne in mind, however, that a linear correlation of rate data is not enough; several criteria must be satisfied before significant, quantitative numerical information is forthcoming. Above all, care must be taken to ensure that the transition-state surrogate is appropriate, that the structural implications of the model are internally and externally consistent, and that its mathematical construction does not beg the question.

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