The Mechanism for Nucleophilic Substitution of α-Carbonyl Derivatives. Application of the Valence-bond Configuration Mixing Model

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The valence-bond configuration mixing model (VBCM) is applied to the nucleophilic substitution reactions of α-carbonyl derivatives. The model appears to resolve satisfactorily a number of features of these reactions that current mechanisms have not dealt with. These include: (i) the dependence of the rate-enhancing effect of the carbonyl upon the nucleophilic strength of the entering group, (ii) the unusually large Hammett ρ value for the reaction of $PhCOCH_2Br$ with substituted pyridines, and (iii) the mechanism by which the rate-enhancing effect of the carbonyl group is transmitted to the reaction centre.

Despite the fact that the nucleophilic substitution reactions of α-halogenocarbonyl compounds, *e.g.* $PhCOCH_2Br$, have attracted considerable attention over several decades,[1–11] many aspects of the reaction mechanism remain poorly understood, and conflicting and contradictory opinions abound. For example, the longstanding view that the α-carbonyl group invariably enhances S_N2 reactivity was recently demonstrated to be false.[2] The rate ratio k_{PhCOCH_2Br}/k_{MeI} was measured for a series of nucleophiles, and while some large values (ranging up to 110) were found, small and even inverse rate ratios were observed for weaker (generally neutral) nucleophiles.[2] Such an observation is not in accord with those rationalizations that focus attention upon the activating effect of the α-carbonyl group, and a reassessment is thus necessary. It can scarcely be claimed that the carbonyl activation phenomenon is an obscure effect of little practical significance and therefore of academic interest only. Accelerations of the order of 10^5 over alkyl halide S_N2 rates have been recorded.[1,4]

In this article we draw together the major experimental patterns that have emerged from studies of S_N2 reactions of α-halogenocarbonyl compounds and show how these may be qualitatively understood using the valence-bond configuration mixing (VBCM) model.[12] The model has recently been successfully applied towards the rationalization of a wide range of reactivity phenomena concerned with nucleophilic substitution,[12b,d–g] elimination,[12c] and proton transfer [12d] reactions. The treatments in these papers show that the VBCM model, based on sound quantum mechanical principles, provides a simple yet useful approach to questions concerning reactivity and mechanism in organic processes.

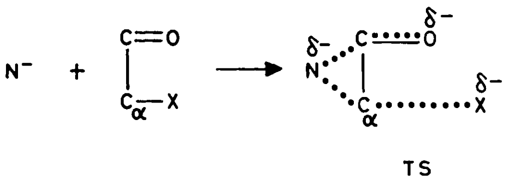
Discussion

Experimental Patterns.—Any reasonable mechanistic model for the S_N2 reactions of α-halogenocarbonyl compounds must answer the following questions.

(i) Is the mechanism a concerted process or are intermediate(s) involved?

(ii) Why is the rate-enhancing effect of the α-carbonyl group dependent on the nucleophilic strength, being most pronounced for strong, anionic nucleophiles while being apparently absent for weaker neutral nucleophiles?[2] In this context, as elsewhere,[13] we invoke the dipolar character of thiourea to count it in the anionic nucleophile class.

(iii) Is the rate-enhancing effect with substituted nucleophiles the result of bridging of the nucleophile between the α-carbon and the carbonyl carbon in the transition state [3,4] [equation (1)]? Or, is resonance delocalization into the carbonyl group of the electrons in the $N\cdots C_\alpha\cdots X$ partial bonds the factor responsible?[4,5] Or, do favourable electrostatic interactions between the incoming group and the polarized carbonyl group comprise the dominant effect?[6]



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(iv) Why do σ-acceptor substituents generally depress S_N2 reactivity, even when strong nucleophiles are involved [10,14] whilst π acceptors such as carbonyl usually accelerate rates?

(v) Why is the ρ value for reaction of substituted pyridines with phenacyl bromide (—1.87)[9] significantly more negative than the corresponding value (−0.85) for an alkyl bromide such as dodecyl bromide?[15]

Let us now consider these questions.

The possible formation of intermediates has been ruled out by Thorpe and Warkentin[8] and others.[9,16] In view of the instability of α-acyl carbenium ions,[17] rate-limiting attack of nucleophiles on ion pairs of the type $RCOCH_2^+X^-$ is also unlikely. This conclusion is reinforced by the observation of low solvolytic reactivity of α-halogenoketones in alcoholic solvents.[9] We therefore examine the reactions on the basis of a simple S_N2 mechanism.

In earlier papers Pross and Shaik [12b,d–g,j,k] have proposed that the wave function describing the S_N2 reaction profile be built up from a linear combination of four valence bond (VB) configurations (1)—(4). Configuration (1) is termed the reactant configuration since it represents the major contributor to the wave function describing the reactants N + RX. Similarly, (2) is the product configuration, whilst (3) and (4) are termed the carbenium ion and carbanion configurations respectively. For an S_N2 reaction on a methyl compound it was suggested that only the reactant and product configurations, (1) and (2) are needed to understand most aspects of reactivity behaviour.[12d,g] This is because intermediate configurations (3) and (4) are high in energy for R = Me, so that their contribution to the overall wave function will be either negligible [for (4)] or constant [for (3)].[12g]

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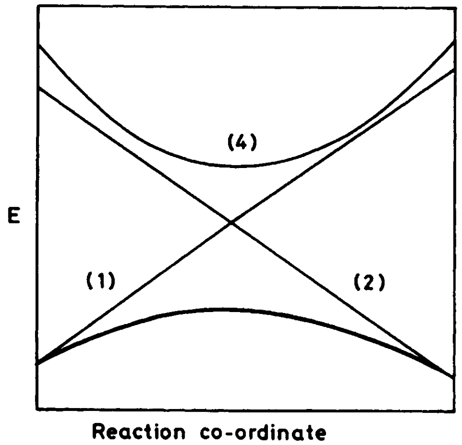
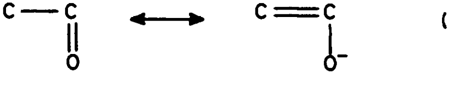
$N\colon\ \ R\cdot\ \ \cdot X$ (1) $N^{\dot{+}}\ \ R\cdot\ \ \colon X^{-}$ (2)

$N\colon\ \ R^{+}\ \ \colon X^{-}$ (3) $N^{\dot{+}}\ \ R^{\dot{-}}\ \ \cdot X$ (4)



Schematic energy profile for the S_N2 reaction of an α-halogenoketone. Configuration (1) is the reactant configuration, (2) is the product configuration, and (4) is the carbanion (enolate) configuration. The solid line represents the resultant profile

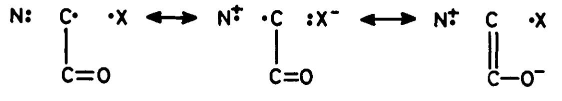
For α-carbonyl derivatives this argument no longer holds. While configuration (3) is likely to be even more destabilized by an α-carbonyl group,[17] the carbanion configuration (4) is likely to be stabilized to a considerable extent. In simple resonance terms this may be depicted in equation (2), which



$$\bar{C}—\underset{\underset{O}{\|}}{C} \longleftrightarrow C{=}\underset{\underset{O^{-}}{|}}{C} \qquad (2)$$

describes the well known resonance stabilization of an enolate ion. It is therefore our contention that the wave function describing the reaction profile for the S_N2 reactions of α-halogenocarbonyl compounds may be satisfactorily built up using three configurations: reactant (1), product (2), and carbanion (4).

A schematic diagram illustrating the general behaviour of these three configurations along an S_N2 reaction co-ordinate, together with the resultant reaction profile (solid line) is shown in the Figure. The bases for the behaviour of the individual configurations are detailed elsewhere.[12c,e] We can now see that the transition state, being the point along the reaction co-ordinate where all three configurations make a significant contribution, may be simply represented by the resonance forms corresponding to these configurations [equation (3)]. We now attempt to explain some basic characteristics of the S_N2 reactions of α-carbonyl derivatives in terms of this simple and novel representation. If the stability of (4) is, as we suggest, important in determining reactivity then one would expect that the S_N2 reactivity sequence of a family of derivatives bearing π-acceptor groups on the α-carbon atom would parallel the relative stabilities of the corresponding carbanions R^-. This obvious comparison has not to our knowledge been applied to this particular problem. The predicted behaviour is indeed observed, and is illustrated by data in the Table. Included is S_N2 rate data for an S_N2 series of RCH_2X compounds, and relevant solution and gas phase acidity data for RCH_3 derivatives. If the acidity order is accepted as the order of stability of carbanions RCH_2^-, our expectation is realised. Rate data for other nucleophilic systems are available,[4] and generate the same reactivity sequence. It is noteworthy that the sequence of acidities of the comparison compounds is not altered on transfer from solution to the gas phase; solvent effects can therefore be eliminated as a contributing factor.



$$N\colon\ \underset{\underset{C=O}{|}}{C\cdot}\ \ \cdot X \longleftrightarrow N^{\dot{+}}\ \underset{\underset{C=O}{|}}{\cdot C}\ \ \colon X^{-} \longleftrightarrow N^{\dot{+}}\ \underset{\underset{C—O^{-}}{\|}}{C}\ \ \cdot X \qquad (3)$$

Relative reactivity of RCH_2Cl with KI in acetone, solution acidities of RCH_3 in DMSO, and relative gas phase acidities of RCH_3

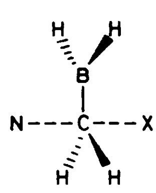
R	Relative substitution rate with KI in acetone at 50 °C [a]	pK_a of RCH_3 (DMSO)	$\delta\Delta G°_{acid}$/ kcal mol^{-1} [f]
CH_3CH_2	1		
Ph	250 [b]	40.9 [c]	36.3
EtOCO	1 600		44.3
NC	2 800	31.3 [d]	44.2
CH_3CO	33 000	26.5 [d]	47.0
PhCO	97 000	24.7 [e]	52.2

[a] Data from Table 15, ref. 4. [b] Calculated from data in Table 4 of ref. 4. [c] Obtained using the CsCHA–CHA system; unlikely to be more than 1 pK unit discrepancy between this and DMSO system. [d] Data from W. S. Matthews, J. E. Bares, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.*, 1975, **97**, 7006. [e] From F. G. Bordwell and F. J. Cornforth, *J. Org. Chem.*, 1978, **43**, 1763. [f] $\delta\Delta G°_{acid} = \Delta G°_{acid}(CH_4) - \Delta G°_{acid}(RCH_3)$. Data from J. E. Bartness, J. A. Scott, and R. T. McIver, *J. Am. Chem. Soc.*, 1979, **101**, 6056.

Supporting theoretical evidence for the importance of the carbanion configuration has recently appeared.[18] Kost and Aviram studied the energies of S_N2 transition states with various substituents on the α-carbon.[18] Of particular relevance to our study are the results observed for reaction (4).

$$N^{-} + CH_2BH_2{-}X \longrightarrow NCH_2BH_2 + X^{-} \qquad (4)$$

The BH_2 group is a powerful π-acceptor and when the transition state of the reaction was studied with the BH_2 aligned with the π-interaction ' turned on ' as indicated in (5) it was found to be 28.7 kcal mol^{-1} *more* stable than in that conformation where this π-interaction is ' turned off ', (6). In this system the BH_2 substituent models the effect of a strong π-acceptor group, suggesting that an α-CO group may stabilize the transition state through a conjugative interaction between the developing carbanionic 2*p* orbital on the central carbon and the adjacent π^*_{CO} orbital. In fact, theoretical calculations conducted on the S_N2 transition state $[FCH_2(CHO)F]^-$ by Wolfe *et al.*[19] confirm this idea. In the ' on ' configuration [equivalent to (5)], the CHO substituent was found to be



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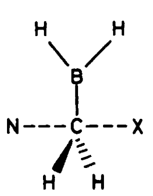


(6)

14.1 kcal mol^{-1} more stabilizing than H. Thus the above observations provide the crucial evidence that the carbanion (enolate) configuration is of importance in understanding the S_N2 reactivities of α-halogenocarbonyl compounds.

We can now address ourselves to the experimental observation of Halvorsen and Songstad [2] to the effect that the accelerative influence of the carbonyl group is most pronounced when powerful anionic nucleophiles are involved. Of the important configurations contributing to the transition state, two contain the nucleophile in its N^+ form [equation (3)]. In particular, the stability of (4) as a whole will be governed not only by the stability of $R:^-$ but also by the stability of N^+ relative to the reactant form N : ; in other words, by the strength of the nucleophile. Thus the carbanion configuration will play a greater role in stabilizing the transition state if *both* $R:^-$ and N^+ are stable. But if a weak nucleophile is considered the energy of (4) is increased and its contribution to the transition state is reduced. The result will be a lowering of the reactivity of the α-carbonyl derivative relative to a simple alkyl analogue, and this is exactly what is observed.[2] The same effect is discovered in S_N2 reactivities of benzyl compounds. It has been observed that in reactions with strong nucleophiles, *p*-nitrobenzyl derivatives are more reactive than *p*-methoxybenzyl compounds (positive Hammett ρ), while with weaker nucleophiles the reverse is the case, insofar as *p*-methoxybenzyl is more reactive than benzyl itself.[12,20,21]

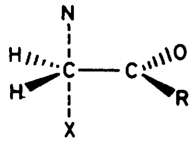
Our model also allows us to readily explain why the ρ value for reaction of $PhCOCH_2Br$ with a series of substituted pyridines in methanol (−1.87) [9] is significantly more negative than that observed when a straight-chain alkyl bromide is the substrate in the solvent (−0.85).[15] In the case of a simple alkyl halide the transition state may be simply described by a hybrid of (1) and (2) [12d,g,j,k] (*i.e.* the reactant and product configurations) in view of the disenchantment of primary alkyl groups with positive or negative charge.[22] Within this framework, any substituent effect stabilizing N^+ with respect to N : will lead to an increase in rate as a simple two-configuration energy diagram illustrates.[12d,g,j,k] A negative value of ρ will therefore result. For α-carbonyl derivatives however the transition state is described by equation (3) which contains within it an extra resonance form, (4). Now *two* of the three forms contain the N^+ species, so stabilization of N^+ is expected to lead to an even larger rate enhancement than with the simple two-configuration situation. Thus ρ should be even more negative, in accord with the experimental result. A more rigorous argument based on configuration curves has recently been presented.[12g]

Two important points need to be made here. First, the indiscriminate use of ρ values for model reactions without regard to identical solvent conditions could at first sight have led to a contrary conclusion. The Hammett ρ values for the reactions of substituted pyridines with methyl iodide and ethyl iodide in 2-nitropropane [23] are respectively −2.8 and −2.7, and are in fact more negative than that for phenacyl bromide in methanol. This does not disturb our argument, for although ρ is numerically large it still only reflects partial charge transfer from nitrogen to the alkyl halide, since the equilibrium ρ value for the pyridines reacting with methyl iodide (charge transfer complete) is −8.9 in acetonitrile.[23] Second, the large negative ρ value observed for $PhCOCH_2Br$ in comparison with the smaller value obtained for a saturated analogue should not be construed as a relative measure of the ' earliness ' or ' lateness ' of N ⋯ C bond formation in these two reactions, at least not in the geometric sense. They do convey information regarding extents of charge transfer but, contrary to common usage, do not in our current view provide any geometric information about the transition state. We would add that in certain systems not even the degree of charge transfer is reliably reflected by ρ (or α) values.[12g,j,k]

If carbanion stabilizing substituents form the basis of the α-rate-enhancing effect one might expect σ-acceptors on the α-carbon to bring about a rate enhancement as well. However, this is not the case. Indeed, a rate-retarding effect is observed. The inability of certain σ-acceptors (*e.g.* halogens) resident on the α-carbon atom, to enhance S_N2 reactivity appears to have its origin in the weak carbanion-stabilizing effect of σ-acceptors. *Ab initio* calculations on HXC_2^- anions reveal that π-acceptors, *e.g.* CHO, CN, or NO_2, are considerably more effective in stabilization than are σ-acceptors. For example, XCH_2^- is stabilized by 50.1 kcal mol^{-1} for X = CHO over X = F (at the MP2/6-31G* level).[24] The rate-retarding effect of α-bound σ-acceptors on S_N2 reactivity has in fact been ascribed to separate effects altogether. Shaik and Pross have attributed the effect to the delocalization of the odd electron in the C−X three-electron bond into each of the two available C−X bonds,[12e,h] while Kost has attributed the effect to four-electron repulsion between the carbanionic charge on carbon and the lone pair on the substituent.[18] So, while some σ-stabilisation of the carbanion may take place, the predominant effect does seem to be in the π-system.

In the light of the above discussion, the various mechanisms which have been proposed to explain the α-CO substituent effect may be reviewed. Dewar first suggested that the α-CO group stabilizes the TS through resonance delocalisation.[5] Dewar postulated that the partial N ⋯ C and C ⋯ X bonds (collinear) must necessarily be aligned with the π-plane of the carbonyl group so that excess negative charge can be delocalized into the π* molecular orbital. In VB terms this is equivalent to the resonance forms of equation (2). In a variation of this idea, Winstein and his co-workers [3] suggested that delocalization could be assisted by partial N ⋯ C=O bridging [equation (1)]. In contrast, Pearson invoked an electrostatic effect to explain the α-carbonyl enhancement.[6] The carbonyl group dipole was held to induce favourable charge–dipole or dipole–dipole interactions which would stabilize the transition state. We now consider evidence for and against these proposals in the light of the valence bond configuration mixing (VBCM) model.

Evidence indicating a definite geometric requirement in the transition state was furnished by Bartlett and Trachtenberg,[7] but it transpires that their result is consistent with all three major proposals: conjugation, bridging, and electrostatic effects. Experiments conducted by Thorpe and Warkentin [8] do suggest however that electrostatic effects are not the major reason for rate enhancement. These workers investigated the relative S_N2 reactivities of fixed conformation *cis*- and *trans*-4-t-butylcyclohexyl chlorides and 2-chloro-4-t-butylcyclohexanones. They observed a major rate enhancement (*ca.* 200) only in the *trans*-2-chloro-4-t-butylcyclohexanone but not in the corresponding *cis*-isomer. Examination of models suggests that electrostatic effects might be similar in these two compounds. In fact, a plausible case might be made for more favourable interactions of this kind in the *cis*-isomer. These results, therefore, provide support for either the Dewar or the Winstein models, both of which require a perpendicular geometry, (7), and is fully borne out by the calculations con-



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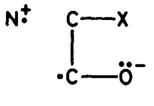

(8)

ducted by Kost [18] and Wolfe.[19] It is only in such a geometry that the developing carbanionic charge on C_α can effectively delocalise into the π^*_{CO} orbital as is required to stabilize the carbanionic configuration (4) (consistent with the Dewar mechanism), or the nucleophile may undergo partial interaction with the carbonyl group leading to bridging (as in the Winstein scheme) [equation (1)]. The configuration which would encourage bridging is indicated in (8).

The VBCM model does not answer the question whether configuration (8) is involved in building up the reaction coordinate. Such a configuration is certainly not ruled out on theoretical grounds. In fact, it is quite analogous to the *E*2C configuration, which has recently been proposed to rationalize aspects of elimination mechanisms.[12c] We would point out however that for benzyl systems, where the same basic pattern emerges, no bridging mechanism can occur, since the substituent is too remote. Thus the fact that the S_N2 reactivity of benzyl derivatives is enhanced by the substitution of a *p*-nitro-group suggests that the carbanionic configuration (4) plays a significant role in defining the transition state for the *p*-nitrobenzyl case, this without any bridging being possible. Also the absence of any significant steric effect in acyclic compounds, $RCOCH_2X$, studied by Thorpe and Warkentin, suggests that any bridging that may take place in α-carbonyl derivatives is sufficiently small so as to not respond to steric variations in R. On this basis we prefer to assume (8) is not an important contributor to the transition state, and that the stabilizing effect of (4) is responsible for the special effects associated with α-carbonyl derivatives.

The analogy between the carbanion configuration (4) and actual enolate ions can be pursued. In the case of substituted phenacyl bromides, $ArCOCH_2Br$, the transition state carbanion configurations resemble the enolate ions of substituted acetophenones $[ArCOCH_2]^-$. The ρ values for the pyridine–$ArCOCH_2Br$ reaction series in methanol is 0.26,[9] and it is significant that this is less than ρ for the rate of the hydroxide-promoted deprotonation of substituted acetophenones in water (0.90).[25] In the former case the carbanion configuration is but one of three major contributors to the transition state wavefunction whereas in acetophenone ionization it is one of two key (reactant and product) configurations. We again caution against overenthusiastic comparison of ρ values,[26] and this time cite the apparently anomalous ρ value for S_N2 substitution of $ArCH_2CH_2Cl$ by iodide ions in acetone (0.59 ± 0.15).[27] However, the change in nucleophile, leaving group, and solvent render a comparison invalid.

The VBCM model enables us to make a prediction about an aspect of reactivity that has not yet been tested. If we regard configuration (1), (2), and (4) as being roughly equal contributors to the transition state wavefunction we see that only one of them (2) contains the leaving group X in its anionic form. The S_N2 transition state for a simple alkyl derivative is dominated by configurations (1) and (2), thus one out of two have X in its anionic form. We predict that if a series of substrates with suitably substituted leaving groups (*e.g.* arenesulphonates) are studied ρ (or β_{LG}) would be numerically larger for the alkyl series than for the α-carbonyl series.

Acknowledgements

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References

1 J. B. Conant, W. R. Kirner, *J. Am. Chem. Soc.*, 1924, **46**, 233, J. B. Conant and R. E. Hussey, *ibid.*, 1925, **47**, 476; J. B. Conant W. R. Kirner, and R. E. Hussey, *ibid.*, p. 488.
2 A. Halvorsen and J. Songstad, *J. Chem. Soc., Chem. Commun.*, 1978, 327.
3 S. Winstein, E. Grunwald, and H. W. Jones, *J. Am. Chem. Soc.*, 1951, **73**, 2700.
4 A. Streitwieser, ' Solvolytic Displacement Reactions,' McGraw-Hill, New York, 1962, p. 28.
5 M. J. S. Dewar, ' The Electronic Theory of Organic Chemistry,' Oxford University Press, Oxford, 1949, p. 73.
6 R. G. Pearson, S. H. Langer, F. V. Williams, and W. J. McGuire, *J. Am. Chem. Soc.*, 1952, **74**, 5130.
7 P. D. Bartlett and E. N. Trachtenberg, *J. Am. Chem. Soc.*, 1958, **80**, 5808.
8 J. W. Thorpe and J. Warkentin, *Can. J. Chem.*, 1973, **51**, 927.
9 W. Forster and R. M. Laird, *J. Chem. Soc., Perkin Trans. 2*, 1982, 135.
10 F. G. Bordwell and W. T. Brannen, *J. Am. Chem. Soc.*, 1964, **86**, 4645.
11 A. J. Sisti and S. Lowell, *Can. J. Chem.*, 1964, **42**, 1896.
12 (*a*) S. S. Shaik, *J. Am. Chem. Soc.*, 1981, **103**, 3692; A. Pross and S. S. Shaik, *ibid.*, (*b*) p. 3702; (*c*) *ibid.*, 1982, **104**, 187; (*d*) *ibid.*, p. 1129; (*e*) *ibid.*, p. 2708; (*f*) S. S. Shaik, *Nouv. J. Chim.*, 1982, **6**, 159; (*g*) A. Pross, *J. Org. Chem.*, in the press; (*h*) S. S. Shaik, *J. Am. Chem Soc.*, 1983, **105** 4359; (*i*) for an alternative application of the CM model to π-acceptor substituents see ref. 12*h* (*j*) A. Pross, *Adv. Phys. Org. Chem.*, in the press; (*k*) A. Pross and S. S. Shaik, *Acc. Chem. Res.*, 1983, **16**, 363.
13 D. J. McLennan, *J. Chem. Soc., Perkin Trans. 2*, 1977, 298.
14 Ref. 4, p. 25.
15 K. Murai, S. Takeuchi, and C. Kimura, *Nippon Kagaku Zasshi*, 1973, 95.
16 D. J. McLennan, *Acc. Chem. Res.*, 1976, 9, 281.
17 J.-P. Bégué and M. Charpentier-Morize, *Acc. Chem. Res.*, 1980, **13**, 207.
18 D. Kost and K. Aviram, *Tetrahedron Lett.*, 1982, 4157.
19 S. Wolfe, D. J. Mitchell, and H. B. Schlegel, *Can. J. Chem.*, 1982, **60**, 1291.
20 P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, 1979, **101**, 3288.
21 R. F. Hudson and G. Klopman, *J. Chem. Soc.*, 1962, 1062.
22 D. N. Kevill, *J. Chem. Soc., Chem. Commun.*, 1981, 421.
23 E. M. Arnett and R. Reich, *J. Am. Chem. Soc.*, 1980, **102**, 5892,
24 A. Pross, D. J. De Frees, B. A. Levi, S. K. Pollack, L. Radom, and W. J. Hehre, *J. Org. Chem.*, 1981, **46**, 1693.
25 J. R. Jones, R. E. Marks, and S. C. Subba Rao, *Trans. Faraday Soc.*, 1967, **63**, 111.
26 D. J. McLennan, *Tetrahedron*, 1978, **34**, 2331.
27 G. Baddeley and G. M. Bennett, *J. Chem. Soc.*, 1935, 1819.

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