An MNDO SCF-MO Study of the Mechanism of the Benzilic Acid and Related Rearrangements

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Mechanisms for the benzilic acid and related rearrangements have been studied using the MNDO SCF-MO method. The barriers to concerted closed shell [1,2] migration of a substituent R in the initially formed intermediate (**2**) were found to display a much smaller range of values than is commonly found in rearrangements involving cations or radicals. Both the formation of (**2**) and its subsequent rearrangement are predicted to be enhanced if either R or the non-migrating group X bears electron-withdrawing substituents. The calculated hydrogen isotope effect and the Bell tunnelling correction for the rearrangement of glyoxal are both significantly larger than for the analogous hydride transfer in the Cannizzaro reaction of formaldehyde. Alternative open shell pathways involving intramolecular single-electron-transfers (SET) to the carbonyl group are relatively high in energy if the non-migrating substituent X is not capable of stabilising an adjacent radical centre (*i.e.* X = H), but are much more favourable for *e.g.* the case of X = phenyl. When R bears an electron-withdrawing substituent, electron-transfer to this group is favoured. We suggest on this basis that an SET mechanism may explain the migration of hydrogen rather phenyl in the reaction of phenylglyoxal. Electron-transfer is also favoured for the rearrangement of benzoin to benzilic acid itself, and is predicted to result in the formation of low-energy cyclic intermediates. Intervention of a counter-ion was modelled with $Li(H_2O)_2^+$ co-ordinating to two oxygen atoms during migration. The migratory barriers were actually increased as a result, and it is suggested that the role of the counter-ion in non-polar solvents is to alter the pre-equilibrium in favour of the intermediate (**2**).

The benzilic acid rearrangement is one of a general class of molecular rearrangements which involves the hydroxyl anion-catalysed conversion of a 1,2-diketone (**1**) into an α-hydroxy carboxylic acid (**4**). Such reactions are thought to proceed by reversible addition of a nucleophile such as OH^- to a carbonyl group to give the intermediate (**2**), followed by a rate-limiting intramolecular [1,2] migration of a formally nucleophilic R^- group to the second carbonyl group (Scheme, path a).[1,2] The kinetics of such a reaction can be expressed by equation (1).

$$(1) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (2) \xrightarrow{k_2} \quad (1)$$

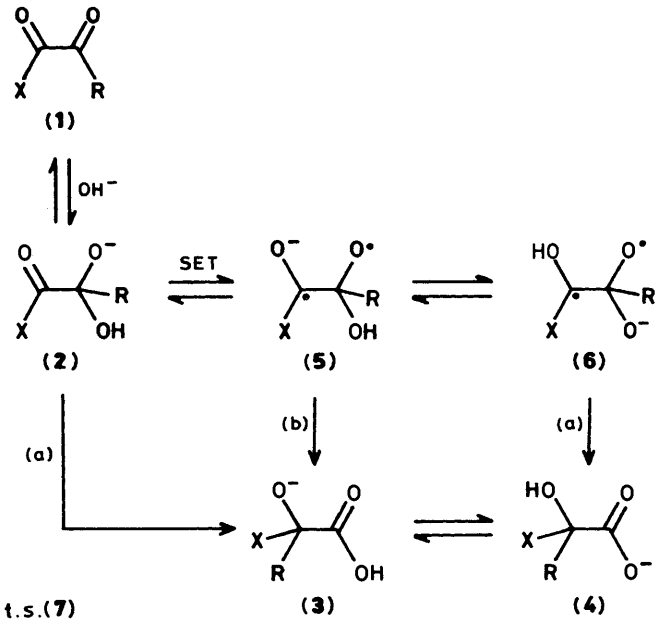
Under steady-state conditions, the observed second-order rate constant is given by the expression;

$$k_{obs.} = k_1/(1 + k_{-1}/k_2) \quad (2)$$

If $k_{-1}/k_2 \gg 1$, this reduces to;

$$k_{obs.} = K \cdot k_2 \quad (3)$$

where K represents the equilibrium constant for the formation of (**2**). The composite nature of the observable rate constant means that it is difficult to interpret substituent effects in this reaction in terms of a single constant. Nevertheless, a wide variety of substituent effects on the overall rate of reaction have been established, and also the identity of the migrating group R for pairs of substituents R and X by means of isotopic labelling. One of the most unusual features of this reaction is the wide variety of formally nucleophilic groups that have been observed to migrate, including R = H, alkyl, aryl, acyl, aroyl, ester, amide, and acid. In addition, a wide range of structural variation is tolerated.[1–8] It is also interesting to contrast these results with the migratory properties of the corresponding electrophilic R^+ groups, as known from the molecular rearrangements of carbocations and related species, and with a third category of migratory group formally intermediate to R^- and R^+, the neutral radical species R•.



Scheme.

We have previously studied the mechanism of such [1,2] migrations in radicals using the MNDO SCF-MO procedure, finding[9] surprisingly different mechanisms according to the nature of the migrating radical R•. This led us to speculate whether similar diversity might be found in the migration of formal R^- groups. It has also been recently reported that the mechanism of the closely related Cannizzaro reaction may involve an intermolecular single-electron-transfer (SET)[10] followed by hydrogen atom migration, as an alternative to the transfer of a formal H^- group. Mechanisms involving an SET process have hitherto not been suggested for the benzilic acid-

type rearrangement. We report in this paper a theoretical study of this type of rearrangement, using the MNDO SCF-MO procedure.[11] This method was previously used in our theoretical study of the Cannizzaro reaction[12] and has been recently shown[13] to predict transition-state structures for a wide variety of molecular systems in reasonable accord with results obtained from more time consuming *ab initio* calculations.

Computational Procedure

Calculations were carried out using the MNDO SCF-MO method[11] with a standard *s/p* valence basis set and the closed shell single determinantal restricted Hartree–Fock approach. In studying the migration of a group R from the sp^3 to the sp^2 carbon atom, two reaction co-ordinates were defined; R_1, the projected horizontal distance of the group R along the C–C bond, and R_2 corresponding to the vertical height of group R from the C–C bond (Figure 1). Such a co-ordinate system has

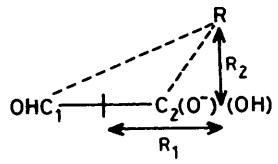


Figure 1. Reaction co-ordinate system for studying the migration of R

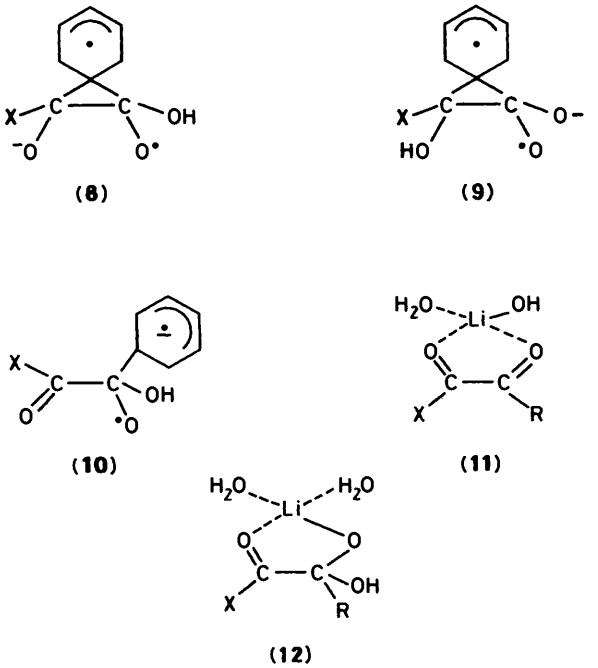
been previously employed by us in studying migrations in carbon radicals.[9] Within such a definition, R_1 corresponds to the direct [1,2] migration of the group R, and R_2 to dissociation/recombination of R^-. Enthalpies of formation were calculated at fixed values of R_1 and R_2, with full optimisation of the remaining $3N - 8$ geometrical variables, and used to construct a contour map. Approximate transition states were located as saddle points on these contour maps. These approximate geometries were then located exactly by minimising the sum of the squared scalar gradients[14] and characterised as transition states by calculating the cartesian force-constant matrix[15] and showing that this had only one negative eigenvalue with the correct form for the eigenvectors. Where transition states differed only in the nature of the group R or X, previously optimised structures could be used as a starting point in the refinement of the saddle point. For the mechanism where a single-electron-transfer occurs before migration of group R to give either (**5**) [Scheme, path (b)] or (**10**), the excited-state wavefunction was modelled using a triplet state, calculated using the spin-unrestricted HF(UHF) method.[16] Whilst clearly an approximation, such a procedure should give a qualitative indication of the characteristics of such species and the expected substituent effects. The UHF procedure however cannot be used to model quantitatively the conversion of biradicals such as (**5**) to (**3**), since a conversion from the triplet into singlet manifolds occurs. Pathway (c) (Scheme) involves intramolecular proton transfer in (**5**) resulting in the formation of a singlet biradical (**6**), followed by migration to form (**4**). Such a process can be studied within the UHF formalism, since it occurs entirely on the singlet manifold.

Thermodynamic quantities and kinetic and equilibrium isotope effects were calculated from the normal vibrational frequencies as previously described.[17]

Results and Discussion

The Rearrangement of Glyoxal to Glycolic Acid (R = X = H).—The simplest rearrangement involves the conversion of glyoxal (**1**; R = X = H) into glycolic acid (**4**; R = X = H) *via* a [1,2] intramolecular hydride shift.[1] Phenylglyoxal (**1**; R = H, X = Ph)[1] is also known to rearrange *via* a hydride shift rather than migration of the phenyl group. We chose to study the reaction of glyoxal for our initial studies in order to establish the general features of the MNDO potential surface for this type of reaction.

By analogy with the closely related Cannizzaro reaction[12] a mechanistic scheme can be postulated in which not only a classical hydride transfer route can be envisaged [Scheme, path (a)] but also alternative routes involving a single-electron-transfer to the carbonyl oxygen atom, either before [path (b)] or



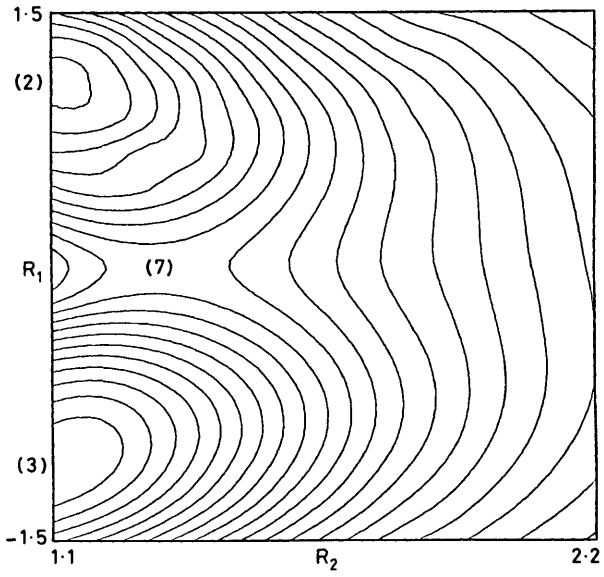


Figure 2. Energy contour map as a function of the two reaction co-ordinates R_1 and R_2 for the conversion of (**2**) into (**3**) (R = X = H). The separation between contour levels is 3.6 kcal mol^{-1}

Table 1. Calculated MNDO transition-state properties for the benzilic acid rearrangement

R	ΔH^a	ΔS^b	ΔG^a	$\Delta H_{3-2}{}^c$ $\Delta H_{4-2}{}^c$	q^d	Bond length[e]	Bond angle[f]
H	28.81	−5.96	30.55	−9.45 (−20.11)	−0.38	1.55 (1.50)	58.8
Me	36.17	−1.13	36.50	−10.27 (−24.23)	−0.41	2.08 (2.05)	42.3
$CH{=}CH_2$	30.34	−4.22	31.58	−12.09 (−23.69)	−0.45	2.00 (1.94)	44.7
CO_2H	20.94	−0.81	21.18	−7.00 (−14.64)	−0.69	2.26 (2.18)	39.7
$\overline{CH_2CH_2CH}$	31.84	−2.51	32.58	−14.99 (−28.95)	−0.59	2.19 (2.20)	39.9
$-CH_2CH_2-$	26.26	4.11	25.06	11.47 (2.69)		2.41 (2.51)	36.4
CN	26.34	−2.74	27.14	−13.15 (−21.01)	−0.65	1.98 (1.94)	45.4
CHO	28.46	−3.55	29.50	−12.39 (−25.07)	−0.50	2.09 (2.03)	42.7
$CONH_2$	21.55	−1.73	22.06	−8.45 (−20.02)	−0.68	2.26 (2.16)	39.9
OH[g]	48.57			−7.58 (−15.49)	−0.63	2.03 (1.91)	44.7
COSH	17.10	5.77	15.41	−9.56 (−15.46)	−0.85	2.66 (2.41)	34.4
CO_2Me[g]	18.05			−13.10 (−24.94)	−0.79	2.39 (2.29)	37.7
Ph	27.02	−2.71	27.81	−12.82 (−22.82)	−0.57	2.11 (2.06)	42.3
p-C_6H_4CN	24.28	−1.46	24.71	−12.13 (−24.30)	−0.63	2.16 (2.10)	41.5
p-C_6H_4OH	27.14	−1.79	27.66	−11.78 (−26.19)	−0.58	2.12 (2.06)	42.2

[a] In cal mol^{-1}. [b] In cal mol^{-1} K^{-1} at 293 K. [c] $\Delta H_{3-2} = \Delta H^f$ (**3**) − ΔH^f (**2**). Values in parenthesis correspond to ΔH^f (**4**) − ΔH^f (**2**). [d] Charge on the migrating group in the transition state. [e] Bond length C_1–R and (C_2–R) in the transition state, in Å. [f] Angle C_1–R–C_2 in the transition state. [g] Transition states for OH and CO_2Me transfer were not characterised by force constant calculation due to problems with hydroxy and methyl group rotations leading to the presence of extra negative eigenvalues.

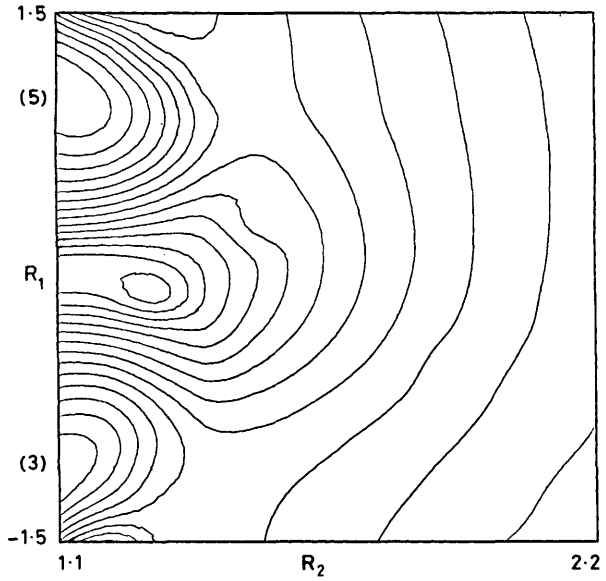


Figure 3. Energy contour map as a function of the two reaction co-ordinates R_1 and R_2 for the conversion of (**5**) into (**3**) (R = X = H) on the triplet UHF surface. The separation between contour levels is 2.4 kcal/mol

after [path (c)] a proton transfer between the oxygen atoms. A potential-energy contour map for path (a) reveals (Figure 2) that the rearrangement of (**2**; X = R = H) to (**3**; X = R = H) is a concerted process occurring *via* transition state (**7**), with a calculated barrier (Table 1) rather higher than that found for the Cannizzaro reaction itself.[12] This is to be expected for what is a highly non-linear hydride transfer, although the magnitude of the barrier is not inconsistent with the known rearrangement of glyoxal.[1] The contour map reveals no dissociative pathway corresponding to formation of isolated H^- ion, in contrast to the results obtained previously for the rearrangement of ethyl radical,[9] where *two* pathways corresponding to dissociative and concerted migration were apparent.

Since single-electron-transfer (SET) has been implicated[18] in a number of electron-rich reactions, we also investigated several routes for the glyoxal reaction which include such a process. The first of these [Scheme, path (b)] corresponds to intramolecular electron-transfer to the carbonyl group to give an excited singlet electronic state (**5**), followed by migration of R and then proton transfer. We modelled this route by calculating (**5**; X = R = H) as a triplet state using the spin-unrestricted UHF approximation,[16] finding this species to be 39.4 kcal mol^{-1} higher in energy than (**2**). Since MNDO is known to predict excitation energies to be too low,[19] this is likely to be a lower bound on the energy of the SET process, suggesting that an SET is improbable for the reaction of glyoxal itself. It is interesting to compare the triplet potential surface (Figure 3) for the conversion of (**5**) into (**3**) with the singlet surface previously calculated (Figure 2). A purely dissociative mechanism operates, with no corresponding concerted pathway available for rearrangement of (**5**).

A second route [Scheme, path (c)] corresponds to initial proton transfer to give the biradicaloid species (**6**), followed by

Table 2. Calculated hydrogen isotope effects for the rearrangement of (**1**; R = X = H)

Reaction	T/K	HRR[a]	TUN COR[b]	K_{eq}[c]	$KIE_{(obs.)}$[d]
Cannizzaro[12]	300.0000	3.868	2.350	0.90	8.2
	373.0000	2.980	1.450	0.94	4.1
	400.0000	2.770	1.354	0.98	3.7
(**1**) ⟶ (**4**) (R = X = H)	300.0000	4.700	—	0.84	
	373.0000	3.452	1.998	0.90	6.2
	400.0000	3.168	1.696	0.91	4.9

[a] HRR = Harmonic rate ratio as defined in ref. 17. [b] TUN COR = Tunnelling correction as defined in ref. 21. [c] $K_{eq} = K_H/K_D$ for the equilibrium (**1**) = (**2**) as defined in ref. 17. [d] $KIE_{(obs.)}$ = (HRR)*(TUN COR)*(K_{eq}).

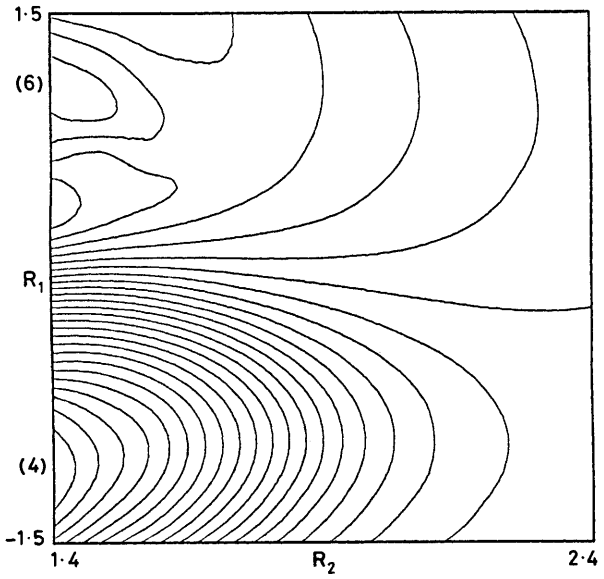


Figure 4. Energy contour map as a function of the two reaction co-ordinates R_1 and R_2 for the conversion of (**6**) into (**4**) (R = X = H) on the singlet UHF surface. The separation between contour levels is 4.0 kcal/mol

migration of group R = H. Species (**6**) was higher in energy than (**5**) by 22.3 kcal mol^{-1} and the potential surface for rearrangement to (**4**) is predicted to involve a concerted migration with an extremely early transition state (Figure 4) and a low barrier of 8.0 kcal mol^{-1}. A third possibility, of electron-transfer to the migrating group R itself, is excluded for the specific case of R = H. We conclude that the glyoxal rearrangement involves an intramolecular hydride transfer and occurs on the ground-state singlet surface, with a low probability of *e.g.* any single-electron-transfer process occurring.

Kinetic Isotope Effects for the Hydride Transfer in (**1**; R = X = H).—There has been much recent speculation on the degree of linearity of hydride transfers and whether tunnelling is important in such reactions.[20] The rearrangement of glyoxal is of some interest since it can be considered as an almost unique example of a highly non-linear hydride transfer. In order to be able to compare the reaction of glyoxal with other types of hydride transfers, we have focused on the intramolecular conversion of (**2**) into (**3**) *via* transition state (**7**). The calculated primary hydrogen isotope effect for this step and the tunnelling correction factors derived from the formula given by Bell[21] are shown in Table 2, together with the results previously obtained for the Cannizzaro reaction.[12] Both the hydrogen isotope effect, and the tunnelling correction are significantly larger than was previously predicted for the relatively linear intermolecular hydride transfer in the Cannizzaro reaction.[12] We have also calculated the equilibrium isotope effect on the pre-equilibrium step [*cf.* eqn. (3)].[17] A small *inverse* isotope effect was obtained (Table 2), which is probably due to the weakening of the C–H(D) bond in (**2**) as a result of the 'oxy-anion' effect.[22] Overall, the observable isotope effect *via* the classical hydride-transfer mechanism is predicted to be quite large by the MNDO procedure.[23]

Migration of Group R via *Transition State* (**7**) *and with* X = H.—There has been considerable discussion concerning the electronic factors which control the rate of the rearrangement (**1**)—(**4**).[1] The equilibrium between (**1**) and (**2**) is clearly controlled by the ability of R to enhance the electrophilic nature of the α-carbonyl group. On the other hand, the rearrangement of (**2**) to (**3**) entails the migration of a nucleophile *towards* an electrophilic centre, which it has been assumed will be enhanced if R is a good nucleophile. The observed enhancement by electron-withdrawing substituents on the migrating group R has been rationalised[1] by proposing an early transition state, such that the equilibrium constant K rather than the rate constant k_2 is the dominant term. However, such a simple Hammond-type model may be over simplified, particularly if other mechanistic pathways involving *e.g.* electron-transfer are possible, or if the transition state is a very 'tight' one in which the nucleophilic characteristics of the migrating group are less important.

The specific substituent effect on the rate constant k_2 can be studied theoretically by the expedient of calculating the barriers for the conversion of (**2**) into (**3**) and maintaining the second substituent constant (X = H, Table 1). We initially chose to study the route following path (a) in the Scheme *via* transition state (**7**). One general feature that emerges (Table 1) is that the migration is generally concerted and does not involve the type of cyclic intermediates that were found previously for the corresponding migrations of *e.g.* vinyl or phenyl groups at the radical or cation oxidation level. The other notable feature is that the range of activation energies is much smaller than was found for *e.g.* the migration of R· or R^+ groups (Table 1).[9]

The calculated entropies of activation for the migration step (Table 1) tend to be similar in value and generally negative (with the exception of the COSH group), suggesting a relatively tight and symmetrical transition state (Figure 5). This symmetry is also reflected in the similar values of the calculated bond lengths to the migrating group R (Table 1). The calculated overall charges on R range from −0.38 for R = H to −0.85 for R = COSH, with R = Ph having an intermediate value of *ca.* −0.6. In general the larger negative charge is found on the better electron-withdrawing groups.

Unactivated alkyl groups such as methyl are predicted to have relatively high barriers to migration, although if the alkyl group is contained within *e.g.* a four-membered ring the barrier is significantly reduced. It is indeed known that cyclobutane-1,2-dione rearranges in water *without* any added OH^- catalyst.[6]

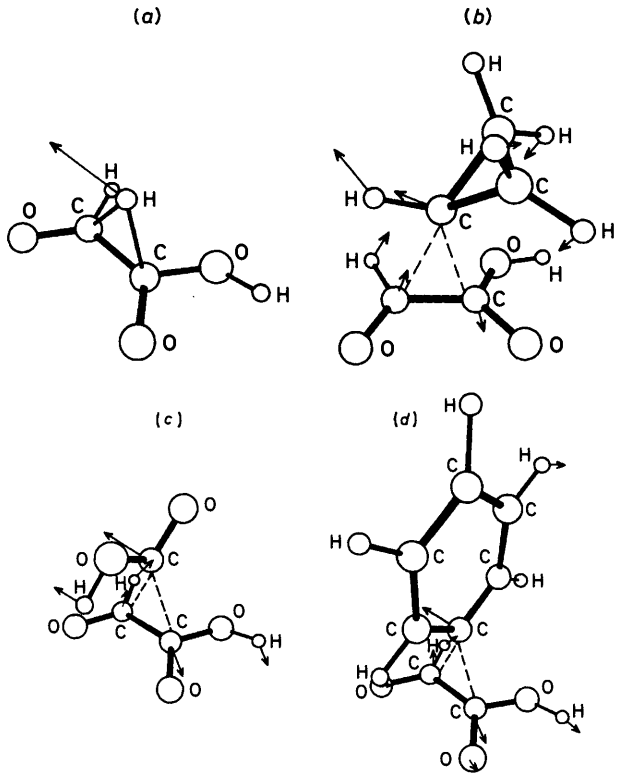


Figure 5. Transition states (**7**) on the reaction pathway between (**2**) and (**3**) for (*a*) R = H, (*b*) R = cyclopropyl, (*c*) R = CO_2H, and (*d*) R = phenyl. Arrows indicate the calculated MNDO displacement co-ordinates for the imaginary frequency

Cyclohexane-1,2-dione is also reported[1] to undergo ring contraction slowly, but in general methyl groups are not observed to readily migrate.[3,5,7] We note that such migration is predicted to occur with *retention* of configuration at the carbon centre (Figure 5). The other substituent where MNDO predicts a large barrier to migration is OH. In this case, the method may be partly in error, since the calculated energy of an isolated OH^- is too high[24] by 36 kcal mol^{-1}. Experimentally of course, it would be difficult to prove if OH migration ever occurs, since the product would be indistinguishable from the species formed in the reversible pre-equilibrium.

Groups such as ester, acid, and amide are predicted to have relatively small barriers. The best such group is thioacid (or ester) (Table 1), for which experimental results appear not to have been reported. We note that such groups were also predicted to migrate readily in radical reactions.[9] Other groups such as vinyl or phenyl are predicted to migrate less readily in the benzilic acid-type rearrangements with respect to *e.g.* ester than they are in radical rearrangements.

The most revealing trend is to be found for the three *para*-substituted aryl groups (Tables 1 and 3). It is known experimentally[14] that electron-withdrawing substituents (modelled here with *p*-CN) on the migrating group R significantly enhance the observed rate of rearrangement, although the assumption has been that this is due largely to the effect on the equilibrium constant K rather than on the rate constant k_2. The MNDO results indicate that, for phenylglyoxal at least (X = H), *both* K and k_2 are favoured by such substitution. For example a *p*-cyano substituent on the group R = Ph is predicted to promote the equilibrium in favour of (**2**) (by ΔH = 7 kcal mol^{-1}, Table 3), to decrease the barrier to migration (by 2.7 kcal mol^{-1}), and to increase the calculated overall negative charge on R, the entropy of activation, the bond lengths in the transition state, and the formal resemblance of the migrating group to R^- (Table 1). The change in entropy in particular is in such a direction as to favour ΔG for the electron-withdrawing group (Table 1). The calculated effect of an electron-donating substituent on R such as *p*-OH is more complex, increasing the barrier to migration *and* the bond lengths in the transition state. The above results illustrate the

Table 3. Calculated MNDO energies for different R and X substituents in kcal mol^{-1}

X	R	(**1**)	(**2**)	ΔH_{2-Rea} [a]	(**7**)	ΔH_{7-2} [b]	(**5**) (**10**)	ΔH_{5-2} [c] (ΔH_{10-2} [c])
H	H	−62.64	−135.45	−31.04	−106.63	28.81	−96.06	39.39
H	Ph	−38.94	−104.45	−23.74	−77.43	27.02	−68.52	35.93
							(−72.95)	(31.50)
Ph	H	−38.94	−112.02	−31.31	−70.96	41.06	−88.54	23.48
H	*p*-C_6H_4CN	−6.28	−78.83	−30.78	−54.56	24.28	−45.02	33.81
							(−57.91)	(20.92)
p-C_6H_4CN	H	−6.28	−85.79	−38.76	−47.63	38.16	−67.87	17.92
H	*p*-C_6H_4OH	−87.19	−152.57	−23.61	−125.43	27.14	−121.31	31.26
							(−123.55)	(29.01)
p-C_6H_4OH	H	−87.19	−160.59	−31.63	−120.84	39.74	−138.35	22.24
Ph	Ph	−13.18	−78.80	−23.85	−38.21	40.59	−53.31	26.16
p-C_6H_4CN	Ph	19.20	−52.57	−30.00	−9.24	43.33	−31.78	20.80
Ph	*p*-C_6H_4CN	19.20	−54.23	−31.66	−13.84	40.39	−26.11	28.12
							(−30.90)	(23.33)
p-C_6H_4OH	Ph	−60.65	−127.34	−24.92	−85.80	41.54	−102.60	24.74
Ph	*p*-C_6H_4OH	−60.65	−127.44	−25.02	−85.97	41.47	−101.91	25.53
p-C_6H_4OH	*p*-C_6H_4CN	−29.34	−102.78	−31.67	−63.07	39.71	−75.90	26.88
p-C_6H_4CN	*p*-C_6H_4OH	−29.34	−101.12	−30.01	−59.59	41.54	−81.33	19.79
CH_2CH_2CH	CO_2H	−128.71	−215.29	−44.81	−187.58	27.71	−178.84	36.45
CO_2H	CH_2CH_2CH	−128.71	−209.32	−38.84	−164.75	44.57	−172.66	36.66

[a] $\Delta H_{2-Rea} = \Delta H^f$ (**2**) − ΔH^f (**1**) − ΔH^f (OH^-). [b] $\Delta H_{7-2} = \Delta H^f$ (**7**) − ΔH^f (**2**). [c] $\Delta H_{5-2} = \Delta H^f$ (**5**) − ΔH^f (**2**), similarly values in parentheses correspond to $\Delta H_{10-2} = \Delta H^f$ (**10**) − ΔH^f (**2**).

dangers of simplifying assumptions regarding the nature of the transition state in such reactions, *i.e.* the migrating group appears not to behave as a formal nucleophile in terms of the substituent effects. Certainly there is no theoretical evidence here to support the accepted interpretation of an early transition state.[1]

The Effect of Substituent X *on the Migration of* R.—Comparison of substituent effects on K or k_2 directly is experimentally complex because of the composite nature of the observed rate constant [eqn. (3)]. Nevertheless, it can be readily established for a pair of substituents R and X from isotopic labelling experiments which one will migrate in preference to the other. It also follows from eqn. (3) that the relative rates of the two isomeric reactions are related to the difference in free energy between (**1**) and (**7**), and not directly to the barrier for the rearrangement step (**2**) to (**3**). Since (**1**) and OH^- are common to both reactions, only the relative free energies of the two isomeric transition states (**7**) need be compared. Under these circumstances, it becomes apparent that the group X may have a signifcant role to play in determining the relative stability of transition state (**7**). We discuss initially calculations (Table 3) for two specific pairs of substituents (R/X = H or Ph[1] and cyclopropyl or CO_2H[8]), for which migratory preferences have been experimentally established by isotopic labelling.

The rearrangement of phenylglyoxal via *transition state* (**7**) (R/X = H/Ph). The hydroxyl ion-catalysed rearrangement of phenylglyoxal to phenylglycolic acid has been established[1] as proceeding *via* hydrogen migration in preference to phenyl migration. The results in Table 1 with X = H indicate little difference between R = H and R = Ph in enthalpic contribution to the rate constant k_2. The classical explanation for the observed specificity would be that an aldehyde [*i.e.* (**2**); R = Ph, X = H] is more susceptible to nucleophilic attack than a ketone [*i.e.* (**2**); R = H, X = Ph], and that therefore the migration is determined by the value of the equilibrium constant K and not the rate constant k_2. The MNDO calculations indeed predict the isomer R = Ph, X = H to be 7.5 kcal mol^{-1} less stable than R = H, X = Ph. However, the barrier for [1,2] migration (*i.e.* ΔH_{7-2}) for R = H, X = Ph is 14.0 kcal mol^{-1} higher in energy than for R = Ph, X = H, a difference that arises largely from the substituent effect of the group X! Overall therefore, the absolute energy of (**7**; R = Ph, X = H) corresponding to migration of the phenyl group *via* route (a) in the Scheme is 6.5 kcal mol^{-1} lower than that for hydride transfer (**7**; R = H, X = Ph, Table 3), in apparent contradiction with experiment. We note at this point that a similar result was obtained for the pair of substituents R/X = H and *p*-cyanophenyl. Although such results are within the limits of accuracy of the MNDO method, this does suggest that alternative explanations such as those involving single-electron-transfers should be considered.

The rearrangement of phenylglyoxal involving single-electron-transfer. If the migrating group R = H, only one mode of SET is possible, giving (**5**). However, if R = Ph, an SET can occur to give either the biradical (**5**), or the species (**10**) *via* electron-transfer to the aryl group itself. We were indeed able to locate two triplet states corresponding to (**5**) or (**10**) with X = H, R = Ph, and one state corresponding to (**5**) with X = Ph, R = H (Table 3).

Discussing firstly the specific case of X = H, we note that the intermediate biradicals (**5**) or (**6**) are not significantly stabilised compared with glyoxal, irrespective of the nature of the migrating group R. Thus triplet (**5**) is 39.4 kcal mol^{-1} higher than (**2**) when R = H, and 35.9 kcal mol^{-1} higher when R = Ph, values that effectively exclude the possibility of such electron-transfer. The triplet state of (**10**) (R = Ph) is also high in energy [31.50 kcal mol^{-1} relative to (**2**)]. The corresponding transition state (**7**) is 8.9 and 4.5 kcal mol^{-1} lower than (**5**) and (**10**) respectively, indicating that neither SET pathway involving the migration of the phenyl group is favoured.

The situation is different when X = Ph, since the phenyl group can stabilise the adjacent radical centres in (**5**) or (**6**). In this case (**5**; X = Ph, R = H) is now only 23.5 kcal mol^{-1} higher than (**2**), a stabilisation of 15.9 kcal mol^{-1} relative to (X = R = H). The energy of (**5**; X = Ph, R = H) is now calculated to be lower than that of the transition state (**7**; X = Ph, R = H) by as much as 17.5 kcal mol^{-1} (Table 3).

The subsequent fate of a biradical such as (**5**; X = Ph, R = H) is also of some interest, since the process resembles quite closely a [1,2] hydrogen atom migration. We had previously shown that such a process in a simple radical system has a prohibitively high energy.[9] It was not possible to directly study the [1,2] hydrogen atom migration of (**5**) to (**3**) on the singlet surface as discussed above. However, the related conversion of singlet (**6**; R = X = H) into (**4**) has a relatively low barrier (8 kcal mol^{-1}), as noted above. This latter process is probably facilitated by the 'oxy-anion' effect,[22] and therefore the barrier for [1,2] hydrogen atom migration in (**5**) is probably somewhat higher, but not so large as in a conventional radical.[9] If this is true also for the singlet conversion of (**5**; X = Ph, R = H) into (**3**), then paths (b) or (c) may indeed constitute viable routes for the migration of *hydrogen* rather than phenyl. We suggest therefore that the observed migratory preference in phenylglyoxal might be rationalised by a mechanism involving an intramolecular SET from the oxy-anion substituent to the carbonyl group followed by a [1,2] hydrogen transfer. We are unaware of any such previous proposal in the literature for this reaction.

How can this hypothesis be tested experimentally? One approach might be to investigate the effect of a *para* substituent attached to group X = aryl (Table 3) on the rate of migration of the group R = H, *via* the effect on the two constants K and k_2. The entries in Table 3 include the enthalpy of reaction of [(**1**) + OH^-] giving (**2**). Changes in this quantity should reflect the substituent effect on X on the equilibrium constant K (assuming no entropic differences). The *p*-CN substituent on X has a surprisingly large effect on the stability of (**2**), promoting its formation by 7.4 kcal mol^{-1} relative to X = Ph (with R = H) and by 6.2 kcal mol^{-1} (with R = Ph). Such β-activation of a dicarbonyl compound should be verifiable experimentally. The *p*-CN group on X is also predicted to act on k_2 by reducing the barrier to [1,2] hydride migration by 2.9 kcal mol^{-1}. However, such a group also promotes the SET process *via* (**5**) by 5.6 kcal mol^{-1}, which would also favour k_2. We predict therefore that electron-withdrawing groups on the non-migrating substituent X should enhance the rearrangement of arylglyoxals, but that this effect would not differentiate between paths (a), (b), or (c) in the Scheme.

In contrast to these results, an electron-donating substituent on X such as *p*-hydroxy appears to have only very small effects on K, the barrier to migration, and the SET process leading to (**5**).

The rearrangement of R/X = *cyclopropyl*/CO_2H. It has been noted experimentally for this system that the ester (or acid) group migrates in preference to the cyclopropyl group, and also that the cyclopropyl substituent slows down the rate of rearrangement compared with a simple alkyl substituent (*e.g.* X = Me, R = CO_2H).[8] Our calculations are consistent with both these observations. We find the barrier for the conversion of (**2**) into (**3**) with R = CO_2H, X = cyclopropyl is 6.8 kcal higher than the corresponding barrier with R = CO_2H, X = H (Table 3). The intermediate (**2**) is also more stable by 6.0 kcal mol^{-1} for the combination (R = CO_2H, X = cyclopropyl) than for the alternative (R = cyclopropyl, X = CO_2H), due to enhancement of the electrophilic characteristics of the α-carbonyl group by the ester substituent. Overall, the transition

Table 4. Calculated energies of intermediate species for R = Ar in paths (b) and (c) in kcal mol^{-1}

X	R	(8)	(9)	ΔH_{8-2} [a]	ΔH_{9-2} [b]
H	Ph	−89.43		15.02	
H	*p*-C_6H_4CN	−64.76	−75.99	14.07	2.84
H	*p*-C_6H_4OH	−139.10	−150.70	13.47	1.87
Ph	Ph	−79.78	−78.48	−0.98	0.32
p-C_6H_4CN	Ph	−60.66	−51.79	−8.09	0.75
Ph	*p*-C_6H_4CN	−54.04	−51.76	0.19	2.47
p-C_6H_4OH	Ph	−129.82	−127.86	−2.84	−0.52
Ph	*p*-C_6H_4OH	−130.41	−128.89	−2.97	−1.45
p-C_6H_4OH	*p*-C_6H_4CN	−103.82	−102.99	−1.04	−0.21
p-C_6H_4CN	*p*-C_6H_4OH	−110.83	−102.09	−9.71	−0.97

[a] $\Delta H_{8-2} = \Delta H^f$ (8) − ΔH^f (2). [b] $\Delta H_{9-2} = \Delta H^f$ (9) − ΔH^f (2).

state (7) is 22.8 kcal mol^{-1} higher in energy for the combination X = CO_2H, R = cyclopropyl than for the isomeric X = cyclopropyl, R = CO_2H and clearly indicates that only the ester or acid group should migrate. The energy difference between R = CO_2H or cyclopropyl for the migration step (*i.e.* ΔH_{7-2}) is actually much smaller (10.9 kcal mol^{-1}) when X = H in both cases, again clearly illustrating that both substituents have a very important joint role to play in controlling the rate of this rearrangement. There is no reported experimental evidence that this specific reaction occurs with any opening of the cyclopropyl ring.[8] It is therefore unlikely that an SET mechanism is occurring with this combination of substituents, since the formation of a biradical such as (**5**; X = cyclopropyl, R = CO_2H) should result in the formation of products corresponding to opening of the ring. Our calculations (Table 3) also show that the SET process is not favoured in this case. Nevertheless, observation of ring opening in a cyclopropyl group may indeed provide a convenient method of obtaining experimental evidence for the operation of an SET process in the benzilic acid-type rearrangements.

The Benzilic Acid Rearrangement Proper (R = X = Ph).—The preceding results for phenylglyoxal suggest that an SET mechanism involving the formation of a species such as (**5**) or (**10**) may be particularly favourable for the rearrangement of benzoin itself (R = X = phenyl). There are however several important differences to be expected between the migration of the group R = H and that of R = aryl. Previous results[9] indicated that in simple radicals, [1,2] hydrogen migration was a relatively high-energy concerted process, whereas migration of a group such as phenyl was predicted to be a comparatively facile stepwise reaction, proceeding *via* a cyclic intermediate. The analogues of these intermediates for the benzilic acid reaction would be species such as (**8**) or (**9**). For phenyl migration in phenylglyoxal, MNDO does indeed predict such intermediates to occur on the pathway for conversion of triplet (**5**; R = Ph, X = H) into (**3**) and of singlet (**6**; R = Ph, X = H) into (**4**) *via* (**8**) and (**9**) respectively (Table 4). Thus (**8**; R = Ph, X = H) was found to be 15.0 kcal mol^{-1} less stable than (**2**) and the barrier to its formation from (**5**) was quite high (35 kcal mol^{-1}). We also note at this point that the charge and spin distribution clearly indicated that the negative charge was located on the oxygen atom shown for (**8**) (as opposed to other representations involving location of the negative charge on the phenyl ring or the other oxygen) and that therefore (**8**) should be susceptible to significant stabilisation by the substituent X. This is indeed found to be true for benzoin itself, where (**8**; R = X = Ph) is now 1.0 kcal mol^{-1} *more* stable than (**2**) and 26.5 kcal mol^{-1} more stable than triplet (**5**). The latter itself is now 15.1 kcal mol^{-1} lower in energy than the transition state (**7**) (Table 3). The isomer (**9**), differing only in the position of the proton, is similar in energy to (**8**), but as expected shows a smaller substituent effect due to X (Table 4). These results do raise the possibility that species such as (**8**) or (**9**) might be capable of being trapped under suitable circumstances.

Since a great deal of information regarding substituent effects is available where R = X = aryl, we chose to study two such systems as models (Table 3). These results will be discussed with reference to the effect on K, on k_2 and on the SET and the species resulting from this. The effect of replacing phenyl by *p*-cyanophenyl is to favour the formation of (**2**) by 7.8 kcal mol^{-1} when on the group R and only by slightly less when on group X (6.2 kcal mol^{-1}), as was noted above for the arylglyoxal system.

In contrast, little effect is predicted on k_2(ΔH_{7-2}, Table 3) when the substitution is on R, whilst an *increase* in the barrier is calculated when such substitution is on X. This is in contrast to the previous calculations (Table 1) for the case of X = H rather than phenyl, which indicated that substituents on the R group had a rather greater effect on the barrier to [1,2] migration.

Two triplet states of (**2**; X = Ph, R = *p*-cyanophenyl) were characterised, corresponding to single-electron-transfers to give (**5**) and (**10**), the latter being the more stable species (by 4.8 kcal mol^{-1}). For the isomeric combination (X = *p*-cyanophenyl, R = Ph), only (**5**) could be characterised and not (**10**), presumably due to the relative stabilisation of (**5**) by group X. These results mean that if an SET to give (**5**) occurs, electron-withdrawing substituents are favoured on X and *not* R, contrary to experiment. On the other hand, an SET to form (**10**) shows little discrimination between R and X in terms of the *para* substitution (Table 3). An electron-donating group such as *p*-OH has a much smaller effect on K, k_2, and the energy of the SET process.

In summary, these results imply that electron-withdrawing substituents in the rearrangement of substituted benzoins act principally by influencing the equilibrium constant K, with a much smaller effect on the rate constant k_2. These results are to be contrasted with those previously discussed for arylglyoxals, where it was predicted that both K and k_2 are subject to substituent effects. Clearly, the group X does not play a passive role in such reactions! We also predict that there may be two types of SET process possible, with differing substituent effects. Electron-transfer to give (**10**) is the most consistent with experimental observation. The energetics of the electron-transfer appear to indicate that such mechanisms have to be seriously considered as an alternative or complementary process to the classical reaction mechanism.

The Role of the Positive Counter-ion.—In solvents such as water, the role of the counter-ion to the hydroxide ion appears

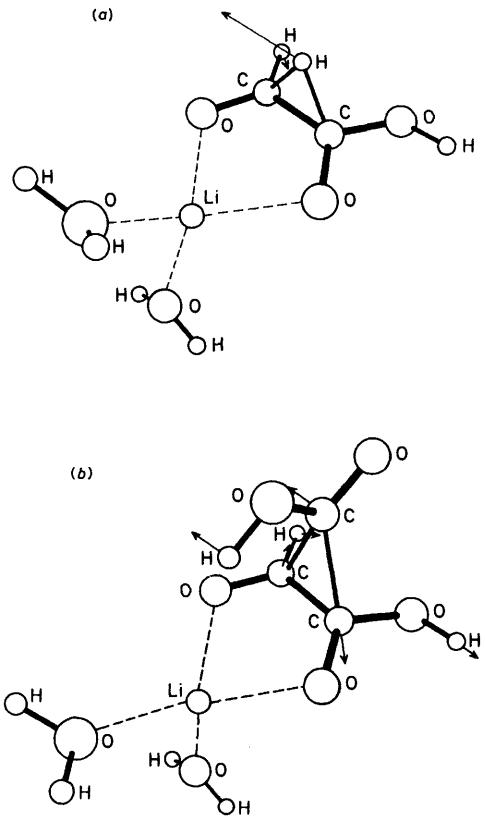


Figure 6. Transition states on the reaction pathway between (**2**) and (**3**) for (*a*) R = H, (*b*) R = CO_2H with the inclusion of a co-ordinated $Li(H_2O)_2^+$ counter-ion. Arrows indicate the calculated MNDO displacement co-ordinates for the imaginary frequency

not to be important. However, when the reaction is carried out in less polar solvents, it has been suggested [25] that the positively charged ion does indeed play an active role by co-ordination to the two carbonyl oxygens, prior to nucleophilic attack by OH^- and concomitant R^- migration. We chose to model this by calculating the barriers to migration of two groups R = H and CO_2H with X = H in both cases and with $Li(H_2O)_2^+$ co-ordinating to the two oxygen atoms of the erstwhile carbonyl groups as in (**12**) (Figure 6). The calculations show that the intrinsic barrier to migration is actually increased, by 4 kcal mol^{-1} in the case of R = H and by 15 kcal mol^{-1} in the case of R = CO_2H. The reason for this can be seen in the calculated overall charge on the whole of the migrating group (Table 1). A group with little opportunity to delocalise negative charge such as methyl typically has a charge of *ca.* −0.41 at the transition state, compared with a CO_2H group with a value of −0.69. The addition of a positive counter-ion such as $Li(H_2O)_2^+$ reduces the negative charge on the migrating group quite significantly, the acid group for example now having the value −0.47 and with a corresponding barrier to reaction quite similar to a methyl group. If the counter-ion appears to play no role in promoting the intrinsic ability of a group to migrate, its effect must be to displace the equilibrium away from (**1**) and towards the co-ordinated system (**12**). This hypothesis was investigated by calculating the enthalpy of reaction for the two equilibria [reactions (4) and (5)].

$$(1) + OH^- = (2) \quad (4)$$

$$(11) + H_2O = (12) \quad (5)$$

We note initially that the heat of formation of OH^- is predicted by MNDO to be too high by 36 kcal mol^{-1}, whereas the corresponding values for alkoxide anions are correctly reproduced.[24] If this correction is applied, it is found that ΔH for reaction (5) (−34.5) is 3.5 kcal mol^{-1} more exothermic than for reaction (4) (−31.0). Such a calculation does not take into account any entropic factors or solvation effects, but it does provide a possible indication that co-ordination to a counter-ion might affect the value of the equilibrium constant K and hence the observed kinetics of benzilic acid-type rearrangements.

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