Acyloxy-shifts in open and closed shell systems—intramolecular nucleophilic substitution reactions in disguise

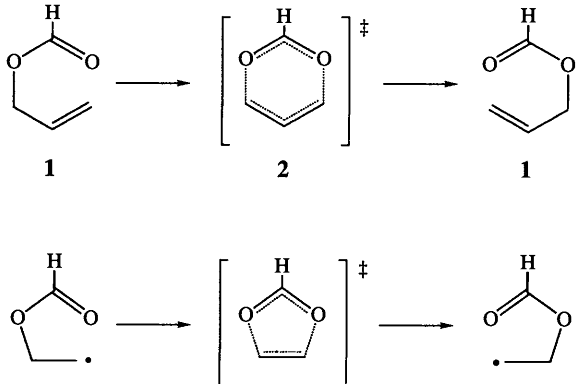
Hendrik Zipse

Inst. Org. Chemie, TU Berlin, Str. des 17. Juni 135, D-10632 Berlin, Germany

The 1,3-acyloxy shift in allyl formate is compared to the 1,2-acyloxy-shift in the 2-formylethyl radical at various theoretical levels. The Becke3LYP hybrid density functional gives the best agreement with experiment. The barrier for the closed shell rearrangement is 22 to 27 kcal mol^{-1} higher than for the open shell transformation. Both reactions can be described as intramolecular nucleophilic substitution reactions, in which the formyloxy group functions as both the nucleophile and the leaving group. In the framework of the valence bond curve crossing model, the difference in the barriers is mainly due to the energy required to excite the C=C double bond to the triplet state.

Introduction

Nucleophilic substitution reactions in closed shell systems involving allylic substrates (S_N2' reactions) have counterparts in open shell systems, in which the allylic double bond is replaced by a single methylene group.[1] While the same basic characteristics of the reaction mechanism were found in open and closed shell cases, the barrier was drastically lower in the former. How general is this 'methylenology principle'? Can it be applied to a broader range of reactions involving carbon–carbon double bonds? To this end, the 1,3-acyloxy shift in allyl formate **1** is compared here to the 1,2-acyloxy-shift in the 2-formylethyl radical **3** with various theoretical methods (Scheme 1).



Scheme 1

Results and discussion

Even though the rearrangement of **1** itself has not been investigated experimentally, the 1,3-shifts of related allyl acetates and allyl trifluoroacetates have barriers between +35 and +45 kcal mol^{-1} (1 cal = 4.184 J) in the gas phase.[2] The barriers involving the trifluoroacetyl group are 1–1.4 kcal mol^{-1} lower than for the corresponding acetates. Since [α-$^2H_2$] allyl trifluoroacetate has a barrier of +36.5 kcal mol^{-1}, the value for **1** should be *ca.* +38 kcal mol^{-1}. The allylic shift of *p*-nitrobenzoyl occurs more readily than benzoyl or acetyl in chlorobenzene solution.[3] A labelling study with ^{18}O-enriched carboxylates indicated the reaction to proceed mainly intramolecularly, *i.e.* without formation of free acetate anions or allylic cations. The study of the reaction mechanism is, however, hampered by small amounts of free acid, which form during the reaction and catalyse the rearrangement.[4]

The 1,2-acyloxy shift in radicals has, ever since its discovery by Tanner[5] and Surzur,[6] remained a mechanistic mystery. Intermolecular versions of this intramolecular rearrangement are unknown. An unusually large solvent effect has been found for the barrier to rearrangement in the 2-acetyl-2,2-dimethylethyl radical, which is +16.8 kcal mol^{-1} in *tert*-butylbenzene and +12.7 kcal mol^{-1} in water.[7] Also, the reaction appears to be remarkably sensitive to the presence of neighbouring groups. Thus, the barrier is much higher in 3-acyloxytetrahydropyran-2-yl radicals (+13.9 kcal mol^{-1})[8] than in highly substituted carbohydrate radicals of analogous structure (+8.7 kcal mol^{-1}).[9] Finally, studies using isotopically labelled acyl groups show complete transposition of carbonyl to ether oxygen positions only in some, but not all cases.[8,10]

When the experimental characteristics of the 1,2- and 1,3-acyloxy rearrangements are compared, the methylenology principle appears to work well also in this case. Both reactions are considered to be borderline cases between concerted rearrangements and stepwise, ion-forming processes. In both cases, the use of isotopically labelled esters did not yield a clear mechanistic picture. Also, both reactions appear to be accelerated in more polar media. The barriers of the open shell system are, however, much lower. The following theoretical investigation compares the mechanistic details of both reactions.

The potential energy surface for **1** and **3** has been studied with the Becke3LYP hybrid density functional (restricted for **1** and unrestricted for **3**) as implemented in GAUSSIAN 94, with the 6-31G* basis set.[11a] In selected cases, the geometry was optimized at the UMP2/6-31G* level as well. Single point calculations at the MP2 and QCISD levels with the 6-31G* and 6-311G** basis sets have been added to evaluate relative energies. The Kohn–Sham orbitals obtained from Becke3LYP-calculations were analysed with UNICHEM 3.0.[11b] The barriers at various theoretical levels for the 1,3-formyl shift in **1** and the 1,2-formyloxy shift in **3** are collected in Table 1. The barrier obtained for **1** at the Becke3LYP/6-31G* level is rather close to the estimate above. The agreement is even better when a somewhat larger basis set is used and the small zero point correction is included. The barriers are significantly larger at the PMP2 or QCISD levels, with little influence of basis set size.[12] Very much the same trend can be identified for the open shell model. The barriers are lowest with the Becke3LYP method, the larger basis set giving again a somewhat lower value. Here, the Becke3LYP barriers appear to be somewhat below the true barrier, which is expected to lie close to 17 kcal mol^{-1}. Barriers derived from PMP2 or QCISD single point calculations are higher than this value by 8–9 kcal mol^{-1}. As the last two entries in Table 1 show, this is not due to significantly different

Table 1 Barriers for the [3,3]-sigmatropic shift in **1** and [2,3]-sigmatropic shift in **3** (in kcal mol^{-1})

Method	ΔE(2-1)	ΔE(4-3)	ΔΔE
Becke3LYP/6-31G*//Becke3LYP/6-31G*	+41.4	+14.8	+26.6
ΔZPE(Becke3LYP/6-31G*)[a]	−1.5	−0.6	−0.9
PMP2/6-31G*//Becke3LYP/6-31G*	+47.4	+25.3	+22.1
PMP2/6-311G**//Becke3LYP/6-31G*	+49.1	+26.5	+22.6
QCISD/6-31G*//Becke3LYP/6-31G*	+49.9	+24.7	+25.2
QCISD/6-311G**//BeckeELYP/6-31G*	+51.2	+26.1	+25.1
Becke3LYP/6-311G**//Becke3LYP/6-311G**	+40.3	+13.4	+26.9
PMP2/6-31G*//UMP2/6-31G*	—	+24.2	—
UMP2/6-31G*//UHF/3-21G[b]	—	+23.2	—

[a] Zero point vibrational energy difference. [b] Ref. 12.

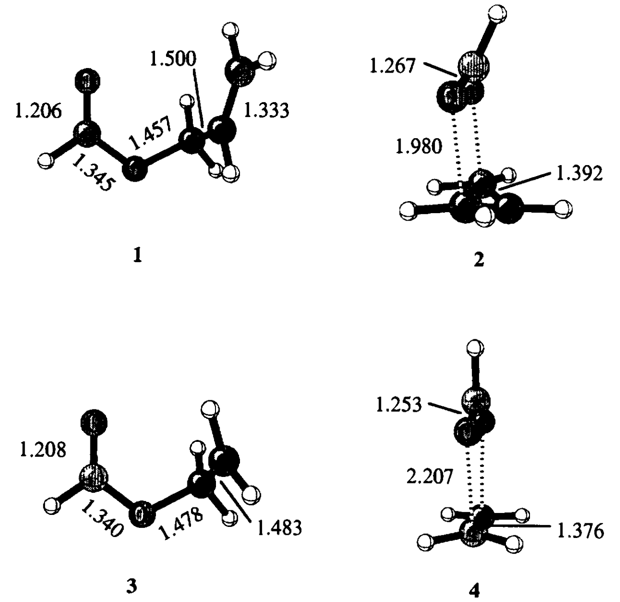


Fig. 1 Stationary points in the reaction of allyl formate (**1**) and 2-formylethyl radical (**3**) optimized at the Becke3LYP/6-31G* level of theory

geometries obtained with the MP2 and DFT methods. Also, an earlier theoretical study of this reaction gave an extrapolated UMP2/6-31G*//UHF/3-21G barrier of 23.2 kcal mol^{-1}.[13] The last column of Table 1 lists the differences between the barriers computed with various methods. Variations in the differences are significantly smaller than in the barriers themselves and the barrier for **1** is found to be higher by 22–27 kcal mol^{-1} compared to that for **3**. We can therefore conclude that a variety of theoretical methods can be used to reproduce the large difference in activation barrier expected from experimental results.

The ground and transition state geometries for both systems are shown in Fig. 1 together with selected bond distances as obtained with the Becke3LYP/6-31G* method. Various conformers of **1** have been studied and the most favourable one is shown in Fig. 1. The extended all-*trans* conformer is less favourable by 1.4 kcal mol^{-1}. The same situation is found for **3**, in that the conformer of lowest energy has the formyl group twisted away from the methylene terminus by around 80°. The extended all-*trans* conformation of **3** is less favourable by 0.3 kcal mol^{-1} in this case. Only one concerted transition structure can be located for the formal [3,3]-sigmatropic shift of **1**. This is in contrast to the Cope- and Claisen-rearrangements, in which chair- as well as boat-transition structures are found.[12,14] A second remarkable feature of **2** is the non-planar allyl system containing a slightly pyramidalized central carbon atom, reminiscent of transition structures for S_N2' substitution reactions.[15] Transition structure **2** is also unusual in that the orientation of the formyl group precludes efficient interaction of the formyl and allyl group π-systems as expected in [3,3]-sigmatropic rearrangements. The out-of-plane bending angle of the formyl group relative to the plane described by the forming/breaking bonds amounts to 31°. In the open shell transition structure **4**, the formyl and ethylene π-systems are perfectly orthogonal to each other. This leads, in turn, to efficient overlap between the formyl lone pairs and the ethylene π-system. Even though the 1,2-acyloxy shift in systems such as **3** has been viewed as an 'open shell pericyclic reaction' involving five electrons and the 1,3-acyloxy shift in **1** has been termed 'dioxa-Cope rearrangement' at times, the transition structures found here certainly predict a different type of reaction. The strong involvement of the formyl lone pairs in both cases can only be reasonably understood as an *intramolecular nucleophilic substitution reaction*, in which the carbonyl lone pairs feature as nucleophiles and the C–O bonds adjacent to the allyl group (in **1**) or to the radical centre (in **3**) take on the role of the leaving group. Additionally, both transition structures **2** and **4** might be described as 'loose' in that bond breaking is far more advanced than bond making.

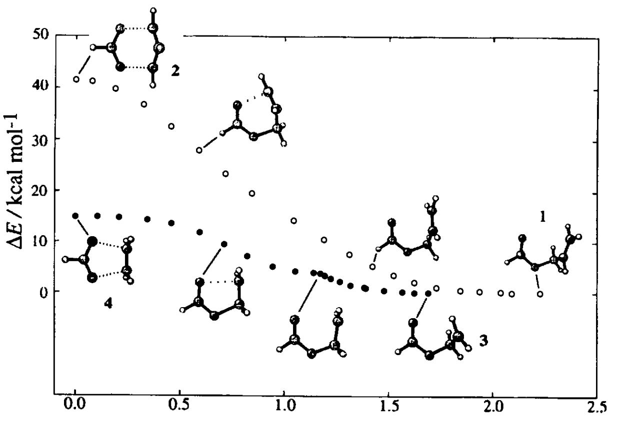


Fig. 2 Reaction pathways for the formyl shift in **1** and **3** at the Becke3LYP/6-31G* level. Selected structures are shown. *r* = Reaction coordinate.

The characterization of the formyloxy shifts as S_N2' or $S_{RN}2'$ reactions receives further support when the complete reaction pathways down from transition structures **2** and **4** are analysed. These are shown in Fig. 2 with selected structures occurring along the pathway. The reaction coordinate *r* is defined as the difference between the breaking and the forming C–O bonds. Starting from the most favourable ground state conformations **1** and **3**, respectively, the reaction proceeds by first rotating around the central C–O bond to adjust the position of the formyl group relative to the allyl/ethylene moieties. Once this 'preorientation' is achieved, breaking of the old and making of the new C–O bond ensues. At no point along the reaction pathways is the formyl π-system oriented such that efficient participation in the bond making/bond breaking processes is possible.

Analysis of the Kohn–Sham orbitals for transition state **4** shows the FMOs to be composed out of two sets of orbitals which are orthogonal to each other (Fig. 3). The first set includes p-type orbitals at the formyl oxygen atoms as well as the ethylene carbon atoms. These four orbitals combine to give four molecular orbitals (MO17, MO18, MO20 and MO21 in Fig. 3), which are to be occupied by five electrons, giving MO20 as the singly occupied molecular orbital (SOMO) of the open shell system. Straightforward symmetry arguments predict the shape of the SOMO to be as found in Fig. 3, with little contribution from the formyl carbon atom and similar contributions from the formyl oxygen and ethylene carbon atoms. Indeed, the spin density as calculated with the DFT method is distributed mainly over the formyl oxygen and ethylene carbon

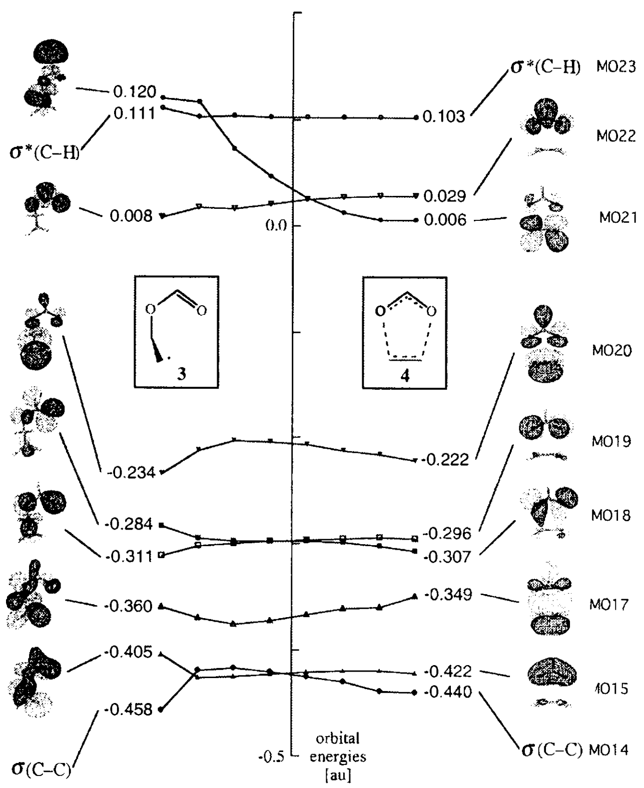


Fig. 3 Selected Kohn–Sham orbitals obtained from Becke3LYP/6-31G* calculations for stationary points **3** and **4**

atoms, with coefficient 0.27 at oxygen and 0.23 at carbon. The second set of MOs is composed of three p-type orbitals of the formyl group, which combine to give a typical set of three allylic molecular orbitals (MO15, MO19 and MO22). As we move from transition state **4** to ground state **3** (from right to left in Fig. 3), little variation can be seen in the energy as well as composition of these latter orbitals. In contrast, the four orbitals of the first set show significant variation along the reaction pathway. The MO20 of **4** connects to the SOMO of ground state **3** without intersecting with other molecular orbitals. The SOMO of the ground state consists mainly of one p-type orbital at the terminal methylene group. MO18 in **4** converts to the next highest occupied molecular orbital (NHOMO) in **3**, which mainly consists of one carbonyl oxygen lone pair. The lowest unoccupied molecular orbital (LUMO) of **4** (MO21) increases dramatically in energy to finally end up as σ*(C–O) orbital in **3**. We can therefore conclude that the 'active' set of MOs in **4** has the SOMO, the nonbonding carbonyl lone pair, and the σ*(C–O) orbital in **3** as main contributors. The fourth orbital involved can be described as a mixture of oxygen lone pairs and σ(C–H) orbitals in **3**. The FMOs found for transition state **2** are rather similar as discussed for the *syn*-S_N2' reaction with disparate leaving groups/nucleophiles.[15] The molecular orbitals cannot, however, be classified as strictly as for transition state **2** due to the lower symmetry of **4**. The partial charges predicted for the formyl groups from the Mulliken population analysis are −0.30 for **1**, −0.41 for **2**, −0.31 for **3**, −0.29 for **4**. Similar values are obtained by fitting the molecular electrostatic potential. The formyl group carries a partial negative charge in the transition state of both systems, which is not very different from the charge in the ground state. Due to the loose structures of **2** and **4**, however, charge separation is much larger in the transition states. We can conclude from the analysis of molecular orbitals and charge as well as spin density distributions that both reactions can most readily be interpreted as nucleophilic substitution reactions.

Why is the closed shell barrier around 25 kcal mol^{-1} higher than the open shell barrier despite all these similarities? A rationalization of the barrier lowering can be based on the valence bond curve crossing method of Shaik and Pross.[16] According to this theoretical model, the barrier height in substitution reactions can be estimated by the expression: $\Delta E_a = f^*G - B$, with G as the vertical excitation energy necessary to obtain the product electronic state from the electronic ground state of the starting point, f a curvature factor describing the fraction of G entering into the activation barrier, and B as the transition state resonance energy. Given that B and f are rather constant for a given reaction type and combination of nucleophile/leaving group, one is left with the initial gap as the most important factor here. Interpreting the rearrangement reaction as intramolecular nucleophilic substitution reaction, the relevant electronic excitation is electron transfer from the attacking nucleophile (the carbonyl lone pair) to the leaving group-substrate bond (the central C–O bond) for both the open and closed shell system. Due to the neighbouring radical centre, the C–O bond in **3** is weaker and therefore lends itself easier to reduction as compared to the same bond in **1**. Since the central C–O bond lengths in **1** and **3** are, however, rather similar (Fig. 1) this contribution to the barrier lowering should be rather small. This charge-transfer excitation has to be accompanied by a complementary excitation within the formyl-π-system to shift the C–O double bond. The excitation energy required for this process must also be expected to be rather similar for both systems. While these excitations are sufficient to describe the product electronic state in the open shell system, an additional factor is necessary in the closed shell case. The two electrons forming the allylic double bond, which are coupled to a pair in the ground state, have to be uncoupled to allow for the formation of the new C–O bond. The energy necessary for this step can be approximated by typical vertical singlet–triplet gaps for simple alkenes, at *ca.* 95–100 kcal mol^{-1}. Given that the f-factor equates to 0.25 for perfectly parabolic curves and assuming values between 0.25 and 0.3 for typical ionic substitution reactions, one would therefore predict the barrier for rearrangement of **1** to be higher by at least 25–30 kcal mol^{-1} compared to the barrier for **3**.

Conclusions

Acyloxy shifts in open and closed shell compounds show many similarities. Most importantly, both reactions are best described as intramolecular substitution reactions. The most interesting consequence of this similarity is, that characteristics for one of the systems might also be relevant to the other. Take for example the catalytic effects of small amounts of acid frequently noted in studies of the closed shell system. Investigations of free radical 1,2-acyloxy shifts have not paid attention to this possible complication, even though the great range of pre-exponential factors and activation barriers is difficult to reconcile with one single mechanism.[8] Also, the rate of 1,3-acyloxy transfer has long been known to depend on the ionic strength of the medium, but no such effect has been noted for open shell systems.[17] It remains to be seen as to how far open and closed shell systems also exhibit analogous behaviour in these latter two points.

Supplementary material available: tables with absolute energies as well as structures for all stationary points have been deposited with the British Library Supplementary Publications scheme, Suppl. Pub. S7163. For details of the Supplementary Publications scheme, see 'Instructions for Authors (1996)', *J. Chem. Soc., Perkin Trans. 2*, 1996, Issue 1.

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft. Computational resources were provided by the Zentraleinrichtung

Rechenzentrum TU Berlin and the Konrad–Zuse–Zentrum für Informationstechnik Berlin. I am indebted to Professor S. Shaik for thorough discussions concerning the curve crossing model and to R. Hertwig for assistance with UNICHEM. Thanks are also due to Professor H. Schwarz for continuing support of our research.

References

1 H. Zipse, *J. Am. Chem. Soc.*, 1994, **116**, 10773.

2 E. S. Lewis, J. T. Hill and E. R. Newman, *J. Am. Chem. Soc.*, 1968, **90**, 662.

3 E. A. Braude, D. W. Turner and E. S. Waight, *J. Chem. Soc.*, 1958, 2396; 2404.

4 Y. Pocker, *J. Chem. Soc*, 1965, 4318.

5 D. D. Tanner and F. C. P. Law, *J. Am. Chem. Soc.*, 1969, **91**, 7535.

6 J. M. Surzur and P. C. R. Teissier, *C. R. Acad. Sci., Ser. C, Paris*, 1967, **264**, 1981.

7 L. R. C. Barclay, J. Lusztyk and K. U. Ingold, *J. Am. Chem. Soc.*, 1984, **106**, 1793.

8 A. L. J. Beckwith and P. J. Duggan, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1673.

9 H.-G. Korth, R. Sustmann, K. S. Groeninger, M. Leising and B. Giese, *J. Org. Chem.*, 1988, **53**, 4364.

10 A. L. J. Beckwith and P. J. Duggan, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1777.

11 (*a*) GAUSSIAN 94, Revision B.3, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, Gaussian, Inc., Pittsburgh, PA, 1995; (*b*) UNICHEM 3.0, Cray Research, Inc., 1995.

12 Y. L. Pascal, J. Levisalles and J. M. Normant, *Tetrahedron*, 1993, **49**, 7679.

13 S. Saebo, A. L. J. Beckwith and L. Radom, *J. Am. Chem. Soc.*, 1984, **106**, 5119.

14 (*a*) H. Y. Yoo and K. N. Houk, *J. Am. Chem. Soc.*, 1994, **116**, 12047; (*b*) O. Wiest, K. A. Black and K. N. Houk, *J. Am. Chem. Soc.*, 1994, **116**, 10336; (*c*) H. Jiao and P. v. R. Schleyer, *Angew. Chem.*, 1995, **107**, 329.

15 (*a*) W.-D. Stohrer, *Angew. Chem.*, 1983, **95**, 642; (*b*) R. D. Bach and G. J. Wolber, *J. Am. Chem. Soc.*, 1985, **107**, 1352.

16 (*a*) S. S. Shaik, H. B. Schlegel and S. Wolfe, *Theoretical Aspects of Physical Organic Chemistry—The S_N2 Mechanism*, Wiley, New York, 1992; (*b*) A. Pross, *Theoretical and Physical Principles of Organic Reactivity*, Wiley, Chichester, 1995.

17 A. G. Catchpole and E. D. Hughes, *J. Chem. Soc.*, 1948, 1.

Paper 6/02777F
Received 22*nd April* 1996
Accepted 21*st June* 1996