# [1,2]–Acyloxy Shifts in Radicals. A Computational Investigation of Substituent and Solvent Effects

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# [1,2]-Acyloxy Shifts in Radicals. A Computational Investigation of Substituent and Solvent Effects

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**Abstract:** Three possible pathways for the acyloxy rearrangement in (acyloxy)ethyl radicals have been investigated with ab initio quantum chemical methods. For migrations of formyloxy, acetyloxy, and (trifluoroacetyl)oxy groups the concerted [3,2]-acyloxy shift represents the most favorable pathway. The barrier for the concerted [1,2]-acyloxy shift is higher by approximately 4 kcal/mol in all three cases, while a stepwise mechanism through a ring-closure/ring-opening sequence is even less favorable. Calculations using the hybrid Becke3LYP density functional and a variety of basis sets predict the barrier for the acetyloxy shift to be higher by 3 kcal/mol than the barrier for the (trifluoroacetyl)oxy shift. This value is less than half what has been determined experimentally before. The effects of aqueous solvation have been studied with the AM1−SM2 and the SCIPCM continuum models and by explicitly including two water molecules into the system. In all three cases, only small solvent effects have been found for the acetyloxy rearrangement, in contrast to previous experimental evidence. Proton catalysis has been studied for the formyloxy rearrangement at the Becke3LYP level and has been found to lower the gas phase barrier by more than 10 kcal/mol. On the basis of these results, it is suggested that acid catalysis might be an important aspect of acyloxy rearrangements in solution.

## Introduction

The [1,2]-acyloxy shift in radicals has, ever since its discovery by Tanner[1] and Surzur,[2] remained a mechanistic mystery in that it was not possible to find one mechanism that would adequately explain all experimental facts. Intermolecular versions of this intramolecular rearrangement are unknown as of yet. The various mechanistic hypotheses considered for this reaction include a stepwise mechanism (pathway **A** in Scheme 1) leading through cyclic 1,3-dioxolanyl radicals. This pathway was ruled out early on when it was shown that the rate of ring opening of these intermediates proceeds much too slow to account for the observed rate of acyloxy rearrangement.[3] Also, while 2-cyclopropyl-substituted 1,3-dioxolanyl radicals undergo rapid opening of the cyclopropyl ring, no such process was observed for the [1,2]-shift of the (cyclopropylacyl)oxy residue.[3c] Most of the experimental results can be rationalized assuming a concerted [2,3]-sigmatropic rearrangement (pathway **B**). This pathway results in complete carbonyl to ether oxygen transposition, which has indeed been observed in studies using isotopically labeled substrates.[4] The few cases in which isotopic scrambling was observed have been rationalized by assuming a competition between pathways **B** and **C**. Unusually large solvent effects have finally been explained by assuming a charge-separated transition state as in pathway **D**, even though it was left open, whether this structure represents a genuine transition state or a discrete intermediate. Recent results by Crich et al., however,

## Scheme 1
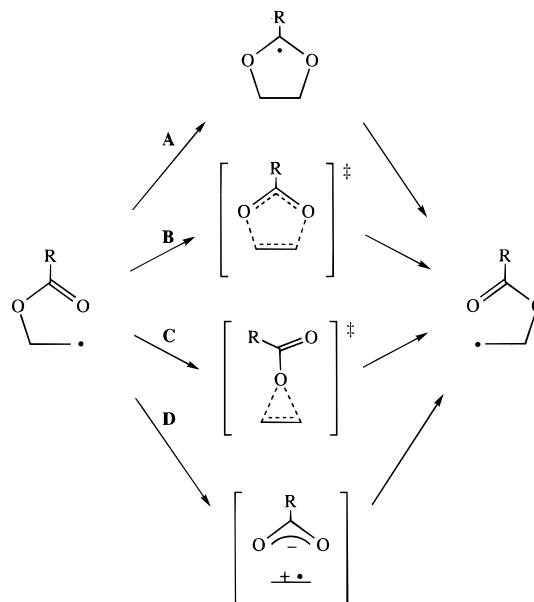


make the formation of an intimate ion pair rather unlikely.[5] No clear mechanistic rationalization has been achieved yet of the large neighboring group effects on the rearrangement rate.[4,6] An early theoretical study by Radom et al. has shown that pathway **B** poses the lowest barrier for [1,2]-formyloxy migration and that the corresponding transition structure shows significant charge separation.[7] We have recently compared the open shell [1,2]-formyloxy with the closed shell [1,3]-formyloxy rearrangement in a theoretical study and have found both

⊗ Abstract published in *Advance ACS Abstracts,* January 1, 1997.

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(2) Surzur, J. M.; Teissier, P. *C. R. Acad. Sci., Ser. C* **1967,** *264,* 1981.

(3) (a) Beckwith, A. L. J.; Tindal, P. L. *Aust. J. Chem.* **1971,** *24,* 2099. (b) Perkins, M. J.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1975,** 77. (c) Barclay, L. R. C.; Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1982,** *104,* 4399.

(4) (a) Beckwith, A. L. J.; Duggan, P. J. *J. Chem. Soc., Perkin Trans. 2* **1992,** 1777. (b) Beckwith, A. L. J.; Duggan, P. J. *J. Chem. Soc., Perkin Trans. 2* **1993,** 1673.

(5) (a) Crich, D.; Yao, Q.; Filzen, G. F. *J. Am. Chem. Soc.* **1995,** *117,* 11455. (b) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **1994,** *116,* 2631.

(6) Korth, H.-G.; Sustmann, R.; Groeninger, K. S.; Leising, M.; Giese, B. *J. Org. Chem.* **1988,** *53,* 4364.

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**Table 1.** Relative Energies (kcal/mol) for Stationary Points in the Acyloxy Shift of 2-(Formyloxy)ethyl Radical (**1**), 2-(Acetyloxy)ethyl Radical (**6**), and 2-[(Trifluoroacetyl)oxy]ethyl Radical (**11**)

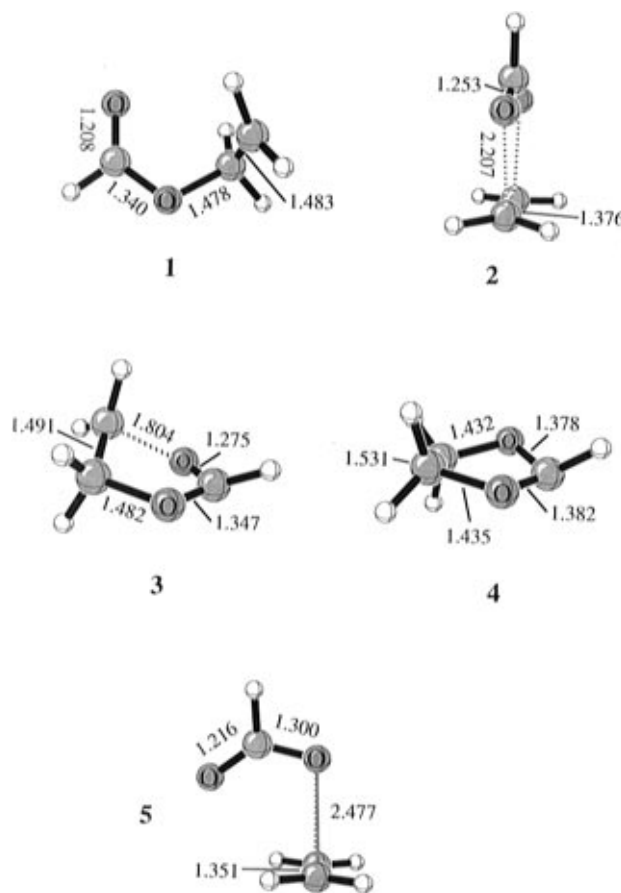| structure R | | $\Delta E$ (B3LYP/6-31G(d) //B3LYP/6-31G(d)) | $\Delta ZPE$ (B3LYP/6-31G(d)) | $\Delta E$ (PMP2/6-31G(d) //B3LYP/6-31G(d)) | $\Delta E$ (QCISD/6-31G(d) //B3LYP/6-31G(d)) |
|---|---|---|---|---|---|
| H | **1** | 0.0 | 0.0 | 0.0 | 0.0 |
| | **2** | +14.8 | −1.1 | +25.3 | +24.7 |
| | **3** | +28.0 | +0.2 | +35.6 | +34.3 |
| | **4** | +12.1 | +2.5 | +15.1 | +13.3 |
| | **5** | +19.0 | −1.9 | +31.9 | +25.7 |
| CH₃ | **6** | 0.0 | 0.0 | 0.0 | 0.0 |
| | **7** | +16.6 | −0.6 | +26.6 | +26.4 |
| | **8** | +28.0 | +0.3 | +35.1 | +34.3 |
| | **9** | +12.0 | +2.7 | +14.8 | +13.2 |
| | **10** | +20.1 | −1.7 | +32.5 | +26.6 |
| CF₃ | **11** | 0.0 | 0.0 | 0.0 | 0.0 |
| | **12** | +14.6 | −0.6 | +28.0 | +24.1 |
| | **13** | +23.5 | +0.4 | +31.2 | +29.6 |
| | **14** | +6.2 | +2.7 | +9.4 | +7.0 |
| | **15** | +18.7 | −1.4 | +31.5 | +27.2 |

reactions to be rather similar.[8] On the basis of these results, we have proposed both reactions to be intramolecular nucleophilic substitution reactions, in which the acyloxy group functions as the nucleophile as well as the leaving group. We are now investigating here whether substituent as well as solvent effects can also be rationalized on this basis and whether alternative mechanistic scenarios such as pathway **A** or **C** can be excluded.

## Theoretical Methods

All quantum mechanical calculations have been performed with Gaussian 94.[9] Unless specified otherwise, geometry optimizations have been performed with the hybrid Becke3LYP density functional[10] as implemented in Gaussian 94 together with the split valence 6-31G basis set, augmented by polarization functions at all non-hydrogen atoms.[11] This level of theory will in the following be termed "B3LYP/6-31G-(d)". Analytical second derivatives were used to calculate vibrational frequencies for all stationary points at this level. If not noted otherwise, relative energies are reported without zero-point energy corrections. Relative energies are also evaluated by single-point energy calculations at the PMP2/6-31G(d) and QCISD/6-31G(d) levels of theory. Partial charges as well as spin densities discussed in the text are derived from Mulliken population analyses of the Kohn−Sham orbitals (B3LYP/6-31G(d)). In most cases investigated here, changes in charge distribution calculated from monopole charges fitted to the molecular electrostatic potential are comparable. The AM1−SM2 calculations were performed using AMSOL 4.1.[12]

## Results

**Gas Phase Calculations.** Three reaction pathways for the [1,2]-acyloxy migration have been found in the parent system 2-(formyloxy)ethyl radical (**1**). Structures of all stationary points found for this system are shown in Figure 1, and relative



**Figure 1.** Stationary points in the [1,2]-acyloxy migration of 2-(formyloxy)ethyl radical (**1**) (B3LYP/6-31G(d)).

energies are given in Table 1. The most favorable pathway leads through transition structure **2**, in complete agreement with the earlier study by Radom et al.[7] As suggested earlier, this structure can best be rationalized as the transition state of an intramolecular nucleophilic substitution reaction, in which the carbonyl lone pair functions as the nucleophile and the central C−O bond as the leaving group.[8] This process will in the following be termed a "[3,2]-formyloxy shift". The formyloxy moiety in **2** carries an overall negative charge of −0.29e, which is slightly less than in **1** (−0.31e). The "charge separate transition state" **2** therefore arises not so much through separation of charges within a given molecular framework, but through separation of charged molecular fragments instead. The second pathway entails formation of 1,3-dioxolanyl radical (**4**) through

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(9) 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.

(10) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Hertwig, R. H.; Koch, W. *J. Comput. Chem.* **1995**, *16*, 576.

(11) (a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (b) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654. (c) Hariharan, P. C.; Pople, J. C. *Theor. Chim. Acta* **1973**, *28*, 213.

(12) AMSOL 4.1: Cramer, C. J.; Lynch, G. C.; Hawkins, G. D.; Truhlar, D. G.; Liotard, D. A., 1994.

a sequence of ring closure and ring opening. Only the most favorable conformation of **4** is shown. The transition structure for ring closure (**3**) is located +28.0 kcal/mol above **1**, while the dioxolanyl radical intermediate is less stable than **1** by 12.1 kcal/mol. Reaction through this pathway is unlikely to play any significant role, much in agreement with most experimental studies and Radom's previous theoretical study.

Transition structure **5** converts the ground state **1** into its mirror image by way of a process which can best be termed a "[1,2]-formyloxy shift" and pictorially represented as pathway **C** in Scheme 1. The barrier for this process of +19.0 kcal/mol is slightly less than for the ring-closure/ring-opening sequence through dioxolanyl radical (**4**), but more than 4 kcal/mol higher than for the [3,2]-shift. The structure of **5** can best be described as "loose" in that the breaking and the newly forming C—O bonds are rather long (2.477 Å). The formyloxy moiety in **5** carries an overall negative charge of −0.25e, which is somewhat less than in **1** or **2**. The spin density in **5** is distributed over the ether oxygen and ethylene carbon atoms with coefficients of +0.63 and +0.16, respectively. As what kind of reaction can the [1,2]-shift be described? The large separation between the formyloxy and ethylene fragments invites the interpretation of **5** as resulting from simultaneous homolytic cleavage of the old and formation of the new C—O bond. Alternatively, **5** can be seen as the transition state for an intramolecular nucleophilic substitution, in which the ether oxygen lone pair (and not the carbonyl oxygen lone pair as in **2**) serves as the nucleophile and the central C—O bond as the leaving group. This mechanistic scenario can account for the spin density as well as the charge distribution in **5**.

In conclusion, rearrangement of **1** appears to proceed most readily along the [3,2]-shift pathway, while other alternatives such as the ring-closure/ring-opening sequence or the [1,2]-shift face much higher barriers. No transition structure for a [3,1]-shift could be found, in which the carbonyl and ether oxygen atoms exchange their positions.

**Substituent Effects.** In order to investigate the effects of substituents in the migrating acyloxy group, the unimolecular chemistry of the 2-(acetyloxy)ethyl radical (**6**) and the 2-[(trifluoroacetyloxy]ethyl radical (**11**) was also studied.

Introduction of the electron-donating methyl group in **6** (Figure 2) is expected to increase the charge density in the acyloxy moiety. Given the partially negatively charged formyl groups in the [3,2]- and [1,2]-formyloxy shift transition states, introduction of the methyl group should lead to an increased barrier for both processes. This is indeed the case (Table 1). The barrier for the [3,2]-acyloxy shift in **6** is 1.8 kcal/mol higher than in **1**. The transition state structure **7** for this process is rather similar to **2**. The spin density is distributed over the two acetyl oxygen atoms and the two ethylene carbon atoms with a coefficient of +0.25 on all centers. The acetyloxy group carries an overall negative charge of −0.28e in **7**, only slightly less than the corresponding value of −0.30e in ground state **6**. The cyclic dioxolanyl radical **9** is less favorable than the open shell ground state **6** by +12.0 kcal/mol. This energy difference is almost identical to the value found for the unsubstituted 1,3-dioxolanyl radical (**4**). The barrier for formation of **9** from **6** is also comparable to the barrier for cyclization of **1**. Reaction through the ring-closure/ring-opening sequence is therefore as unlikely for **6** as it is for **1**. The introduction of the methyl group has very much the same effect on the [1,2]-acyloxy shift pathway as on the [3,2]-acyloxy shift. The barrier of this process is increased from +19.0 kcal/mol for **1** to +20.1 kcal/mol for **6**. The charge of the acyloxy group amounts to −0.22e, which is less than in **6** or in **7**. The spin density is located on
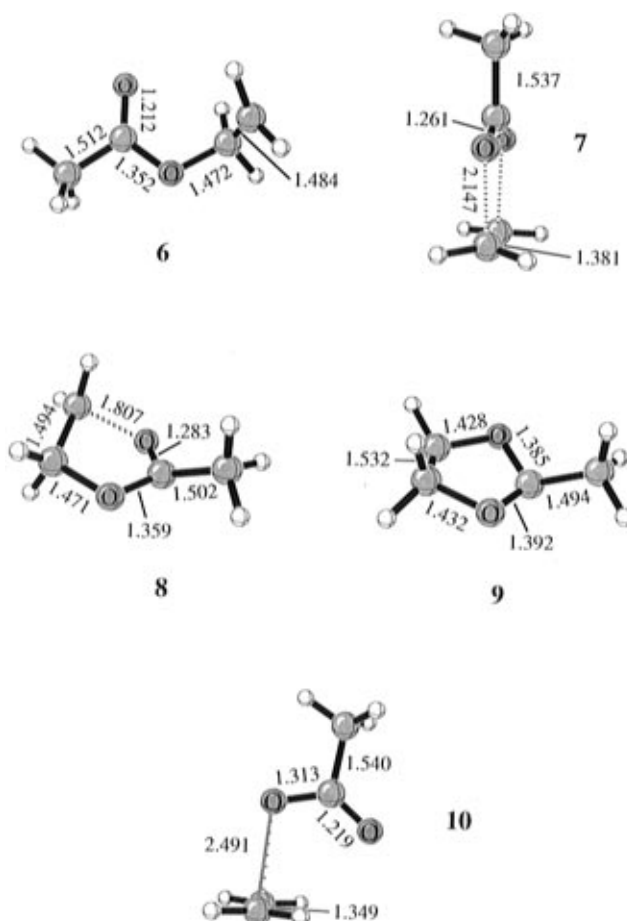


**Figure 2.** Stationary points in the [1,2]-acyloxy migration of 2-(acetyloxy)ethyl radical (**6**) (B3LYP/6-31G(d)).

the ether oxygen and ethylene carbon atoms with coefficients of +0.67 and +0.15, respectively. One can conclude then that introduction of the methyl group increases the barriers for both concerted pathways by a small margin.

On the basis of its known powerful electron-withdrawing properties, the trifluoromethyl group in **11** is expected to lead to an opposite effect. Surprisingly then, this is not the case. The barrier for the [3,2]-acyloxy shift in **11** is lower than the barrier for the same process in **1** by a mere 0.2 kcal/mol. If differences in zero-point vibrational energies (Table 1) are included, the formyloxy shift is even preferred! The (trifluoroacetyl)oxy moiety in transition structure **12** (Figure 3) carries an overall negative charge of −0.34e, which is identical to the value found for ground state **11**. The spin density in **12** is distributed over the acyloxy oxygen atoms and the ethylene carbon atoms with coefficients of +0.24 and +0.26, respectively. The cyclic dioxolanyl radical intermediate **14** appears to be stabilized through the trifluoromethyl group, since the energy difference to the acyclic ground state **11** amounts to only +6.2 kcal/mol. This is only half the value found for the other two systems **1**/**4** and **6**/**9**, and it appears that the trifluoromethyl group is stabilizing by approximately 6 kcal/mol. This is in complete contrast to the known destabilizing effect fluoro and trifluoromethyl substitution has on radicals.[13] One can only speculate that the stabilizing effect found here is due to the simultaneous presence of electron-donating and electron-withdrawing radical substituents, i.e., a manifestation of cap-

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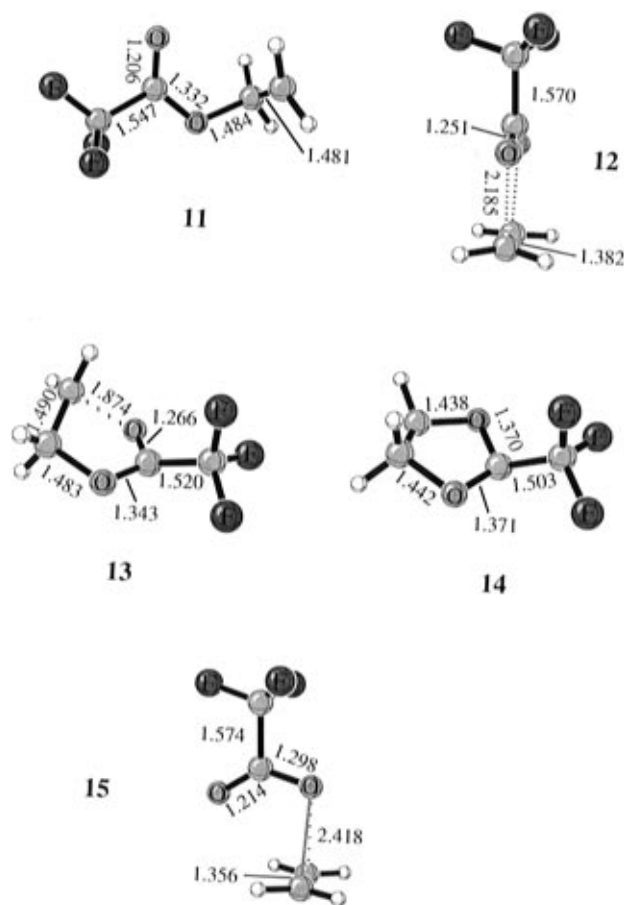
**Figure 3.** Stationary points in the [1,2]-acyloxy migration of 2-[(trifluoroacetyl)oxy]ethyl radical (**11**) (B3LYP/6-31G(d)).

**Table 2.** Relative Energies (kcal/mol) for Stationary Points in the [3,2]-Acyloxy Shift of 2-(Formyloxy)ethyl Radical (**1**), 2-(Acetyloxy)ethyl Radical (**6**), and 2-[(Trifluoroacetyl)oxy]ethyl Radical (**11**)[a]

| method[b] | 1 | 2 | 6 | 7 | 11 | 12 |
|---|---|---|---|---|---|---|
| B3LYP/6-31G(d) | 0.0 | +13.7 | 0.0 | +17.2 | 0.0 | +14.0 |
| B3LYP/6-311+G(d,p) | 0.0 | +12.1 | 0.0 | +15.6 | 0.0 | +12.5 |
| B3LYP/6-311++G(2d,2p) | 0.0 | +12.0 | 0.0 | +15.6 | 0.0 | +12.6 |
| B3LYP/6-311+G(df,p) |  |  |  |  | 0.0 | +12.9 |

[a] Relative energies include the unscaled differences in zero-point vibrational energies. [b] Using B3LYP/6-31G(d) geometries.

acyloxy migration. Finally, the cyclization/ring-opening sequence constitutes the least favorable pathway in all three cases. The most favorable [3,2]-acyloxy shift shows an increased barrier on introduction of the methyl group, but little variation on incorporation of the trifluoromethyl group. The only known experimental measurement of the activation energies for acetyloxy and (trifluoroacetyl)oxy migration in otherwise identical systems predicts the barrier for the latter process to be lower by 8.1 kcal/mol.[15] Unfortunately, these measurements have been performed in different solvents (*tert*-butylbenzene vs Freon 113) and different temperature ranges. From our calculations, we predict a barrier lowering of only 3.2 kcal/mol, based on B3LYP/6-31G(d) energies and including differences in zero-point vibrational energy. The corresponding QCISD values predict a similar trend in substituent effects, while the MP2 values predict the (trifluoroacetyl)oxy shift to be the least favorable. In order to ensure that the small predicted substituent effects are not a consequence of inferior basis set size, a series of single-point energy calculations with extended basis sets at the B3LYP level have been performed for the stationary points involved in the [3,2]-acyloxy shift. The results are collected in Table 2. It can readily be seen that the *absolute* barriers do not show any significant variations beyond the 6-311+G(d,p) basis set, and that the *relative* barrier heights are virtually identical for all chosen basis sets. This finding is much in line with the generally low basis set dependence of DFT calculations. As integration grid size is always a concern in density functional calculations, the calculations using the 6-311+G(2d,2p) basis set were performed for **6** and **7** not only with the pruned (72,302) grid used by default in Gaussian 94 but also with a spherical product (96,32,64) grid.[1] With the latter choice, the absolute energies for both stationary points are lowered by only $2 \times 10^{-5}$ hartree as compared to the default grid and the rearrangement barriers are not affected. In summary it appears rather unlikely that more refined gas phase calculations will yield a barrier difference for the [3,2]-acyloxy shifts in **6** and **11** anywhere close to the experimental value.

**Solvent Effects.** The only published measurement of solvent effects on the barrier of 1,2-acetyloxy shifts has been obtained for 2-(acetyloxy)-2-methylprop-1-yl radical, which rearranges to the corresponding tertiary radical with an activation barrier of $+17.9 \pm 1.9$ kcal/mol in *tert*-butylbenzene and of $+12.7 \pm 0.9$ kcal/mol in water.[15] This dramatic lowering of the activation barrier by 5.2 kcal/mol has been explained with the charge separate transition state, which presumably is better solvated than the ground state. Several methods exist for modeling solvent effects on reaction barriers.[16,17] None of these existing methods have been validated for open shell species. To escape the risk of artifacts of a particular method, we have utilized several conceptually different methods in the study of solvent effects on acyloxy rearrangements and have compared the results.

todative stabilization.[14] Besides this thermochemical stability, radical **14** also appears to be stabilized kinetically in that the barrier to ring opening is larger for **14** than for **9** or **4**. This is in remarkable agreement with the experimental observation that 2-trifluoromethyl-substituted 1,3-dioxolanyl radicals can be observed for a longer period of time even at elevated temperatures, in marked contrast to other 2-alkyl-substituted 1,3-dioxolanyl radicals.[3c,15] Despite the comparatively favorable thermochemistry of radical **14**, the barrier for formation of this intermediate through transition structure **13** is significantly higher than for either the [3,2]- or the [1,2]-acyloxy shift. The latter process faces a barrier of 18.7 kcal/mol starting from **11**. The structural characteristics of the [2,1]-shift transition structure **15** are by and large comparable to that of **5** and **10**. The overall charge of the (trifluoroacetyl)oxy group in **15** is −0.31e, slightly less than in **11**. The spin density is distributed over the ether oxygen and ethylene carbon atoms with coefficients of +0.58 and +0.20, respectively.

We can conclude that, in all three systems studied here, the concerted [3,2]-formyloxy shift represents the most favorable reaction pathway for acyloxy migration. The overall charge distributions found in the transition structures of this process are rather similar to those in the corresponding ground states. No major charge rearrangement appears to occur on going from the ground to the transition state. The concerted [1,2]-acyloxy shift is the second most favorable pathway for acyloxy migration in all three cases. The barrier for this process is consistently higher by approximately 4 kcal/mol than the barrier for the [3,2]-

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(15) Barclay, L. R. C.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 1793.

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**Table 3.** Free Energies of Solvation (kcal/mol) and Cumulative Mulliken Charges of the Acyloxy Groups in Ground and Transition States of the [3,2]-Acyloxy Shifts in 2-(Formyloxy)ethyl Radical (**1**), 2-(Acetyloxy)ethyl Radical (**6**), and 2-[(Trifluoroacetyloxy)ethyl Radical (**11**)

| structure | | $\Delta G_{SOLV}{}^a$ | | $\Delta G'_{SOLV}{}^b$ | | $q[RCO_2]_{AM1,GAS}$ | | $q[RCO_2]_{AM1,SM2}$ | |
|---|---|---|---|---|---|---|---|---|---|
| R | | UHF | HE | UHF | HE | UHF | HE | UHF | HE |
| H | **1** | −3.83 | −3.83 | −3.68 | −3.64 | −0.20 | −0.21 | −0.20 | −0.21 |
| | **2** | −4.01 | −4.42 | −3.94 | −4.06 | −0.27 | −0.34 | −0.34 | −0.41 |
| | **(2−1)** | **−0.18** | **−0.59** | **−0.26** | **−0.42** | **−0.07** | **−0.13** | **−0.14** | **−0.20** |
| CH₃ | **6** | −3.02 | −3.01 | −2.80 | −2.75 | −0.21 | −0.21 | −0.20 | −0.21 |
| | **7** | −3.87 | −4.13 | −3.14 | −3.25 | −0.34 | −0.37 | −0.42 | −0.43 |
| | **(7−6)** | **−0.85** | **−1.12** | **−0.35** | **−0.50** | **−0.13** | **−0.16** | **−0.22** | **−0.22** |
| CF₃ | **11** | −0.02 | +0.12 | −0.21 | −0.03 | −0.25 | −0.26 | −0.27 | −0.28 |
| | **12** | −4.09 | −3.83 | −1.19 | −1.48 | −0.42 | −0.41 | −0.63 | −0.53 |
| | **(12−11)** | **−4.07** | **−3.95** | **−0.98** | **−1.45** | **−0.17** | **−0.15** | **−0.36** | **−0.25** |

$^a$ $\Delta G_{SOLV}$ as calculated with AM1 charges. $^b$ $\Delta G_{SOLV}$ as calculated with B3LYP/6-31G(d) charges.

**AM1−SM2.** As the first method for evaluating solvent effects for this reaction, we have employed the AM1−SM2 solvation model, which has been developed for water as a solvent.[16,18,19] The SM2 free energy of solvation $\Delta G_{solv}$ is composed of two factors, $\Delta G_{ENP}$ and $\Delta G_{CDS}$. The first term includes long-range effects such as mutual solvent−solute polarization, while the CDS term is parametrized to include short-range effects such as specific solute−solvent interactions and cavitation energies. As it is not clear for our current purpose whether calculations with the half electron (HE) or the unrestricted Hartree−Fock (UHF) method give superior results, we have used both methods in parallel. Given the fact that both HE and UHF overestimate the gas phase barrier for the [3,2]-formyloxy rearrangement by more than 40 kcal/mol, we have used the AM1−SM2 method to provide solvation free energy *differences* between the ground and transition states for [3,2]-acyloxy shifts only. This strategy has been successfully used before to calculate solvent effects for systems in which the gas phase situation was not described correctly by the AM1 method.[19] The free energy of solvation differences collected in Table 3 therefore describe only the lowering of the barrier on going from the gas phase to aqueous solution. In all cases, the AM1−SM2 solvation model predicts the barrier to be lower in aqueous solution than in the gas phase; that is, all solvation free energy differences between ground and transition states ($\Delta\Delta G_{SOLV}$) are negative. The barrier lowering is, however, rather small for the formyloxy shift. In this system, the transition state **2** is better solvated than the ground state by only 0.18 kcal/mol at the UHF level. The solvent effect on the acetyloxy shift is only slightly larger with a predicted barrier lowering of −0.85 kcal/mol, much in contrast to the experimental measurement. It is only for the (trifluoroacetyl)oxy group that a significant solvent effect on the barrier can be found. Transition state **12** is better solvated than ground state **11** by more then 4 kcal/mol. Comparison of the cumulative UHF/AM1 charges of the acyloxy groups $q[RCO_2]$ in ground and transition states (Table 3) shows that the degree of barrier lowering is tightly connected to the degree of solvent-induced charge separation. This effect is smallest for **1** and largest for **11**. In the latter case, the ground state charge distribution hardly changes between the gas and aqueous phases, while the corresponding transition state **12** has a much more negatively charged acyloxy group in aqueous solution (−0.63e) than in the gas phase (−0.42). We have to note, however, that the UHF/AM1 gas phase charge distribution differs significantly from the B3LYP/6-31G(d) gas phase charge distribution. We have therefore repeated the calculation of the AM1−SM2 free

energies of solvation with the gas phase B3LYP/6-31G(d) charge distribution. The resulting free energy differences $\Delta\Delta G'_{SOLV}$ (Table 3) are all negative again. The predicted effect for the formyloxy shift is slightly larger now, while that for the acetyloxy and (trifluoroacetyl)oxy shifts is much smaller. The successful quantitative prediction of solvent effects will therefore be highly dependent on the chosen charge distribution in the solution phase. Comparison of the UHF and HE results also shows that no major difference exists between the solvent effects predicted by these two methods. In summary the maximum solvent effect predicted for the acetyloxy rearrangement amounts to −1.12 kcal/mol with the HE/AM1 method, much less than found experimentally.

**SCIPCM.** The self-consistent isodensity surface polarized continuum model (SCIPCM) has recently been developed by Frisch et al.[9] It follows in philosophy the polarized continuum models of Tomasi et al.,[20] but uses a cavity which is defined through a self-consistently optimized surface of constant electron density. Since this solvation treatment can be used in combination with the B3LYP/6-31G(d) quantum mechanical method, it is possible to obtain a much better estimate for the solvent-induced charge reorganization in ground and transition states. Despite the fact that the current implementation of this model does not perform well in reproducing solvation free energies of negatively charged systems,[21] application of an almost parameter-free solvation model seems very desirable for our purpose. The SCIPCM calculations were performed with a dielectric constant of $\epsilon = 78.54$ for water and the 0.001 au isodensity surface. In order to facilitate comparison with the AM1−SM2 results, the same gas phase B3LYP/6-31G(d) geometries were utilized. As found with the AM1−SM2 solvation model, the SCIPCM model predicts the barriers for [3,2]-acyloxy shifts to be lower in the aqueous than in the gas phase (Table 4). The effects are, however, rather small in all three cases. The largest barrier lowering of 1.6 kcal/mol is found for the (trifluoroacetyl)oxy rearrangement. The barrier lowering for the acetyloxy shift is very small (0.5 kcal/mol), again far from the experimental value. Comparison of the gas and solution phase charge distribution (Table 4) again shows a solvent-induced enhancement of charge polarization. The effects are, however, not as dramatic as predicted with the AM1−SM2 model. In order to quantitatively compare theoretical and experimental solvent effects, it would be necessary to repeat the SCIPCM calculations with the dielectric constant of *tert*-butyl benzene and then compare the results for both solvents. Given the very small differences between gas phase

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**Table 4.** Aqueous Phase Barriers for the [3,2]-Acyloxy Rearrangement (kcal/mol) as well as Cumulative Mulliken Charges of the Acyloxy Groups in the 2-(Formyloxy)ethyl Radical (**1**), 2-(Acetyloxy)ethyl Radical (**6**), and 2-[(Trifluoroacetyl)oxy]ethyl Radical (**11**) As Calculated with the SCIPCM/B3LYP/6-31G(d)[a] Method

| structure | $\Delta E^d$ (SCIPCM/ B3LYP/6-31G(d)// B3LYP/6-31G(d)) | $q[RCO_2]^b$ (SCIPCM/ B3LYP/6-31G(d)) | $q[RCO_2]^c$ (B3LYP/ 6-31G(d)) |
|---|---|---|---|
| **1** | 0.0 | −0.32 | −0.31 |
| **2** | +14.0 | −0.35 | −0.28 |
| **6** | 0.0 | −0.32 | −0.30 |
| **7** | +16.1 | −0.34 | −0.29 |
| **11** | 0.0 | −0.37 | −0.34 |
| **12** | +13.0 | −0.43 | −0.34 |

[a] A dielectric constant of $\epsilon = 78.54$ has been used in combination with the 0.001 au isodensity surface. [b] Obtained from solution phase SCIPCM/B3LYP/6-31G(d) Mulliken charges. [c] Obtained from the gas phase B3LYP/6-31G(d) Mulliken charges. [d] Gas phase B3LYP/6-31G(d) geometries have been used.

and aqueous phase barriers obtained already, however, these additional calculations have not been performed.

All calculations of solvent effects have up to now utilized the gas phase optimized structures of ground and transition states. Given the very small effects obtained, we have to wonder whether this choice severely limits the predictive power of the continuum models. Solvent-induced structural reorganization should be most significant in transition structures **2**, **7**, and **12**, as already indicated by the solvent-induced charge reorganization. The structure of transition state **2** was therefore reoptimized at the SCIPCM/B3LYP/6-31G(d) level using a dielectric constant of $\epsilon = 78.54$ and the 0.001 au isodensity surface. The obtained transition structure (not shown) is structurally very similar to **2**. The breaking/forming C−O bonds are slightly longer than before (2.238 Å), while the C−C bond length in the ethylene fragment (1.378 Å) and the C−O bond length in the formyl group (1.255 Å) are virtually unchanged. The formyloxy group carries a negative charge of −0.35e after reoptimization with the SCIPCM model, which is identical to the value obtained from the SCIPCM single-point calculation on the gas phase optimized structure of **2**. From this result, we can be confident that the calculation of solvent effects with continuum solvation models yields reliable results even with gas phase optimized structures.

**B3LYP/6-31G(d) Supermolecule.** As a final point in this study of solvent effects on the [3,2]-acyloxy shift we have added two water molecules to ground state **1** and transition state **2** and reoptimized both stationary points. This "supermolecule" approach is particularly well suited to provide insight into the influence of specific solvent effects on substrate structures and into variations of specific solute−solvent interactions between ground and transition states. On the downside, this method is not well suited to provide an average description of solvation. To find the most favorable orientation between water molecules and the substrates, a series of structurally different complexes between the frozen substrate **1** or **2** and one water molecule (in its experimental geometry) have first been investigated. The information obtained from this study was then used to assemble starting configurations for the complexes of **1** and **2**. Ground state **16** and transition state **17** (Figure 4) were obtained after reoptimization. Only very small differences can be found between the solvated and the unsolvated ground and transition states. The most notable change can be detected in the forming/breaking C−O bonds in **17**, which are slightly larger at 2.241 Å than in transition state **2** at 2.207 Å. It is worth noting that the explicit consideration of two solvent molecules leads to much the same (small!) variation in transition state structure as does
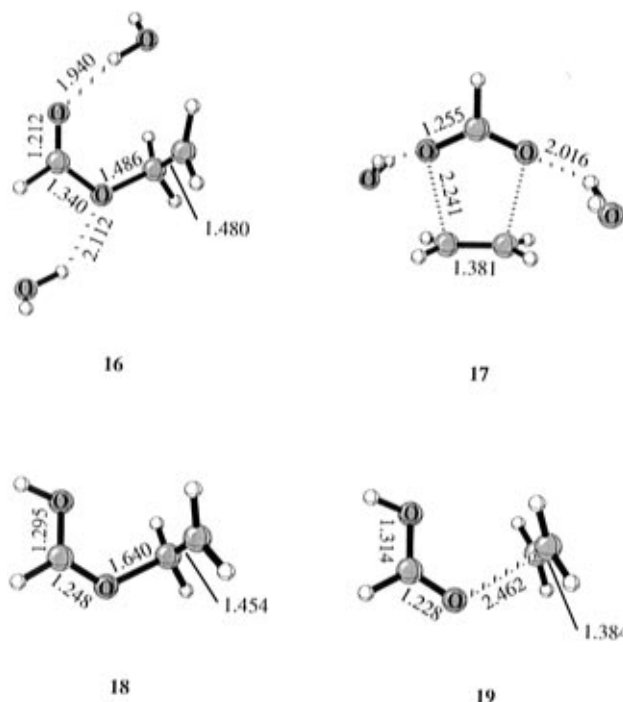


**Figure 4.** Ground and transition states in the water- and the proton-catalyzed [1,2]-acyloxy migration of (formyloxy)ethyl radical (B3LYP/6-31G(d)).

the use of the SCIPCM continuum model. The barrier for the [3,2]-formyloxy shift in **16** is +14.5 kcal/mol, which is 0.3 kcal/mol less than in the gas phase, almost identical to the combined B3LYP/6-31G(d)/AM1−SM2 prediction, and 0.5 kcal/mol more than predicted with the SCIPCM continuum model.

**Possibility of Acid Catalysis.** Given the fact that neither the substituent nor the solvent effect observed for this reaction can be reproduced with satisfactory accuracy, it appears that our theoretical studies leave out essential parts of the experimental system. The experimental setup involves formation of the (acyloxy)ethyl radicals from their closed shell precursors using the $TiCl_3/H_2O_2$ couple for reactions in water, while reactions in apolar media have been initiated by UV photolysis of peroxides. For water as the solvent this raises the point of general acid catalysis of the rearrangement. We have pointed out before[8] that acid catalysis appears conceivable for this type of reaction since the closely related [1,3]-acyloxy rearrangement is known to show general acid catalysis.[22]

The most extreme way of modeling the effects of acid catalysis is by inclusion of a proton in the system. One must, of course, keep in mind that free protons are not available in aqueous solution and that the effects of acid catalysis will accordingly be smaller in solution than calculated here in the gas phase. Protonation of **1** leads to structure **18** as the most favorable conformer (Figure 4). Protonation causes elongation of the carbonyl C−O double bond and considerable shortening of the C−O bond between the carbonyl group and the ether oxygen atom. The most noticeable change in bond length can, however, be observed for the C−O bond between the ether oxygen and the ethylene moiety, which is much longer in **18** (1.640 Å) than in **1** (1.478 Å) or **16** (1.486 Å). These changes in bond lengths actually suggest that structure **18** can also be thought of as the adduct between formic acid and ethylene radical cation. It is not surprising then that the rearrangement pathway for **18** is rather similar to that of other distonic radical

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cations formed by addition of neutral nucleophiles to ethylene radical cations.[23] The only pathway found here leads through transition state **19**, which moves the formic acid moiety from one end of the ethylene subunit to the other. In structural terms, **19** is most closely related to transition structure **5** of the parent system. The barrier for the proton-catalyzed process amounts to +3.6 kcal/mol at the Becke3LYP/6-31G(d) + $\Delta$ZPE level of theory, *10.1 kcal/mol less* than for the most favorable rearrangement pathway in the neutral parent system. Two conclusions can immediately be drawn from this result. First, given the enormous effect observed in the protonated model system and the rather small effect obtained from explicitly including two water molecules, one must conclude that acid catalysis will be at least as important as solvation, even for rather weak acids. Second, if the acid-catalyzed pathway preferentially follows through transition structures like **19**, then the acid-catalyzed pathway will be at least in part responsible for the scrambling observed in isotopically labeled acyloxy groups.

## Conclusions

From the various mechanistic scenarios studied here, the concerted [3,2]-acyloxy shift is the most favorable in all cases. Rearrangement of the (trifluoroacetyl)oxy group faces the lowest and rearrangement of the acetyl group faces the largest barrier. All solvent models utilized here agree in predicting the [3,2]-acyloxy shift to proceed more readily in aqueous solution than in the gas phase. Despite the fact that all these results are in qualitative agreement with experimental observation, we have to note that the predicted substituent and solvent effects are considerably smaller than observed experimentally. This can in principle be due either to deficiencies in computational methodology or to the fact that the experiment proceeds through a pathway not studied here. In aqueous solution this can potentially be the reaction through an ion-pair intermediate. One would then, of course, expect exchange processes of the ions formed in such an intermediate with ions present in solution. In light of the known dependence of the rate of the closed shell [3,3]-acyloxy shift on the concentration of acids,[22] one has to wonder, however, whether the open shell [3,2]-acyloxy rearrangement is also prone to acid catalysis. A dramatic lowering of the rearrangement barrier can indeed be found for the [1,2]-formyloxy rearrangement upon protonation. It therefore appears desirable that future experimental investigations of acyloxy rearrangements pay attention to the effects of solution pH and buffer concentration.

**Supporting Information Available:** Tables with absolute energies as well as structures for all stationary points (8 pages). See any current masthead page for ordering and Internet access instructions.

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