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Methylene Group Transfer in Carbonyl Compounds Discovered *in Silico* and Detected Experimentally**

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Abstract: Previously unknown transformation of aldehydes, ketones and carboxylic acid derivatives leads to the formation of substituted oxiranes, aziridines and azirines as shown by DFT and MP2 computations. Formations of 2,2-dimethyloxirane-d₈ from acetone-d₆, phenylazirine-d₂ from benzonitrile and 2-methyl-2-(4-hydroxyphenyl)oxirane from 4-hydroxyacetophenone were detected experimentally by electrospray ionization mass-spectrometry with heated desolvating capillary. This reaction is a truly concerted process characterized by high activation barriers (activation enthalpies 320-480 kJ/mol).

Transformation of carbonyl compounds and derivatives of carboxylic acids builds a nucleus of contemporary organic chemistry. There are numerous known reactions employing carbonyl compounds resulting in deep and variegated structural changes affording synthesis of useful products or intermediates.^[1-5]

Here we report a so far unpublished reaction, non-catalytic scrambling of a methylene moiety of the carbonyl compounds and/or derivatives of carboxylic acids located *in silico* and experimentally detected by ultrahigh resolution mass spectrometry with electrospray ionization.

While scanning the approach of the methyl group of one acetone molecule to the carbonyl group of the other molecule of acetone, we have observed a characteristic maximum whose geometry was later used for the location of the corresponding transition state **TS1** (Scheme 1, Figure 1).



Scheme 1. Computed reaction of two acetone molecules yielding acetaldehyde and 2,2-dimethyloxirane.

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Figure 1. Transition states for formation of 2,2,-dimethyloxirane and acetaldehyde from two acetone molecules computed by two different theoretical approaches. Similar structures (interatomic distances in Å are shown) and thermodynamic parameters (enthalpies in kJ mol⁻¹, entropies in J mol⁻¹ K⁻¹ are shown) were computed. Blue arrows show displacement vectors in the TS.

IRC Analysis confirmed formation of acetaldehyde 2 and 2,2dimethyloxirane 3 from two molecules of acetone 1 as a truly concerted process characterized by multidirectional movement of hydrogen atom and CH₂ group (Figure 1).

This discovery prompted us to search experimental evidence of the occurrence of this transformation under experimental conditions. Taking into account the high activation barrier and significantly endothermic character of oxirane formation (Table 1), we attempted to verify the computational results experimentally via mass-spectrometric analysis of acetone- d_6 solution passing through heated desolvating capillary of electrospray (ESI) ionization source.^[6]

This new method proved its versatility for detecting reactive intermediates and products in reactions with high activation barriers.^[6] Moreover, via coupling a heated desolvating capillary with ESI, reaction rates of some reactions can be increased for up to five orders of magnitude, thus making feasible a wide range of synthetic reactions not possible in a single phase.^[7] This is achieved via creating interface with huge surface-to bulk ratio.^[8] A series of the most recent studies proved reliability and fruitfulness of this method.^[9] In our experiments we have used deuterated substrates for further increasing the sensitivity.

Scheme 2 summarizes the results of two independent experiments that reliably and reproducibly demonstrated formation of 2,2-dimethyloxirane-d₈ in the temperature interval 200-300 °C.

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Table 1. Scope of the Intermolecular CH₂ group transfer.^{a,b}

Starting compounds	Products	TS	ν, cm ⁻¹	∆H≠,	ΔН,	ΔS [≠] ,	ΔS,
				kJ mol ⁻¹	kJ mol ⁻¹	J mol ⁻¹ K ⁻¹	J mol ⁻¹ K ⁻¹
		TS1	531 <i>i</i>	393	134	-50	-37
H ₃ C CH ₃ H ₃ C CH ₃		- a					
<u> </u>		TS2	756 <i>i</i>	402	134	-67	-33
			1001	402	101	07	00
		сн ₃	0.451	100	100		
	L A	_{CH3} IS3	6457	406	130	-96	-29
C ₆ H ₅ CH ₃ H ₃ C CH ₃	С6Н5 Н	H ₃					
		CH ₃ TS4	804 <i>i</i>	423	146	-63	-46
FH ₂ C CH ₃ H ₃ C CH ₃	FH ₂ C H	СН3					
		CH TS5	1072 <i>i</i>	456	151	-46	-33
	F ₃ C H	СН3					
	ľ ľ Å	CF ₃ TS6	7307	389	146	-63	-50
F2HC CH3 H3C CF3	F ₂ HC H	CH3					
0 0 		CF3 TS7	520 <i>i</i>	359	113	-63	-25
0 0 0 0		TS8	1030 <i>i</i>	161	18/	-46	-13
		F	10007	-0-	10-1	40	10
F CH ₃ H ₃ C F	H ₃ C ⁻ F	CH ₃					
	Î / _ ·	Me TS9	1004 <i>i</i>	473	192	-63	-50
MeO CH ₃ H ₃ C OMe		Ha					
0 0 		TS10	626 <i>i</i>	431	197	-29	-2
0 0	H ² NH ₂ O		445;	254	107	75	
		1311	445/	301	197	-75	-42
Me ₂ N CH ₃ H ₃ C H	H NMe ₂	сн ₃					
	Î	F TS12	190 <i>i</i>	347	151	-29	-25
Me ₂ N CH ₃ H ₃ C F		CH					
Me	CH3	TS13	625 <i>i</i>	427	117	-54	-29
	0 N	1013	0201	721	117	-34	-23
	нас н	CH ₃					
		CH3					
N N		TS14	820 <i>i</i>	444	197	-59	-42
H CH ₃ H ₂ C	н н	CH3					U
		TS15	745 <i>i</i>	498	201	-54	-67
					-	_	
H ₃ C ⁻ ⁻ CH ₃ H ₃ C ⁻		`CH3	0.40	40.4	470		
Ĭ IN		1516	849 i	494	178	-1	13
H ₃ C CH _{3 C6} H ₅	н ₃ с н	°C ₆ H ₅					

 $a_{\omega}B97XD/6-31G(d,p)/SMD; {}^{b}TS1-TS13$ in acetone, TS14-TS16 in acetonitrile.

Inspired by these results we further studied the scope of this new transformation computationally and experimentally.

Computational screening of various combinations of the starting carbonyl compounds showed that this transformation has a general character (Table 1). Imine as well as derivatives of carboxylic acids: esters, fluoroanhydrides, amides, and nitriles also gave *in silico* the corresponding products. Notable decrease of the activation barrier was computed for the reactions having CF_3 group as a CH_2 acceptor (**TS7**) or dimethylacetamide as a CH_2 group donor (**TS11** and **TS12**).

The activation barriers computed for the reaction of nitriles with acetone were the highest among the studied reactions. This did not prevent experimental detection of the corresponding azirine formed in the reaction with benzonitrile, although it was necessary to apply a higher temperature (Scheme 3).

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Scheme 2. Experimental detection of protonated 2,2-dimethyloxirane-d₆ **4**. Results of two independent experiments are shown. Second reaction product, acetaldehyde-d₄ was not observed, since its molecular weight is beyond the detection range. Measured HRMS data of protonated acetone **5** are shown for reference.



Scheme 3. Experimental detection of deuterated azirine formation from benzonitrile and acetone-d₆. Formation of **4** is also observed due to the self-reaction of acetone-d₆ (Scheme 2). Second reaction product of both reactions, acetaldehyde-d₄, was not observed, since its molecular weight is beyond the detection range.



Scheme 4. Experimental detection CD₂ group transfer from acetone-d₆ to 4-hydroxyacetophenone **7** at 200 °C. Formation of **4** is also observed due to the self-reaction of acetone-d₆ (Scheme 2). Second reaction product of both reactions, acetaldehyde-d₄, was not observed, since its molecular weight is beyond the detection range. Computed imaginary frequencies (cm⁻¹), activation and reaction enthalpies (kJ mol⁻¹), activation and reaction entropies (J mol⁻¹ K⁻¹) (ω B97XD/6-31G(d,p)/SMD(acetone).

When either of different starting compounds can be a CH_2 group donor, two different reactions can take place (Scheme 4, 5). At 200 °C only the product of CD_2 group transfer from acetone-d₆ via **TS17** was observed (together with **4**, Scheme 4), whereas at the temperatures approaching 300 °C both reactions took place simultaneously (Scheme 5). Noteworthy, another product of the CH_2 group transfer from 4-hydroxyacetophenone, 4hydroxybenzaldehyde was also observed.



Scheme 5. Experimental detection of CH₂ group transfer from 4-hydroxyacetophenone **7** to acetone-d₆ **1** at 300 °C. Formation of **4** and **8** is also observed due to the self-reaction of acetone-d₆ (Scheme 2) and CD₂ group transfer from **1** to **7** (Scheme 4). Second reaction product, acetaldehyde-d₄, of the self-reaction of acetone-d₆ was not observed, since its molecular weight is beyond the detection range. Computed imaginary frequencies (cm⁻¹), activation and reaction entropies (J mol⁻¹), activation and reaction entropies (J mol⁻¹) (ω B97XD/6-31G(d,p)/SMD(acetone).

Interestingly, computations of the alternative pathway in the reaction of acetone 1 with acetonitrile provided trisubstituted oxirane 11 and dihydrogen (Scheme 6, Figure 2a) instead of expected 3 and HCN.

This transformation together with an intramolecular reaction leading to the formation of the corresponding oxirane 6 and degenerate CH₂ group transfer in 7 (Scheme 7, Figure 2b) outlines the wide scope of the new reaction.



Scheme 6. Computed reaction of acetone with acetonitrile (ω B97XD/6-31G(d,p)/SMD(acetonitrile). Computed imaginary frequency (cm⁻¹), activation and reaction enthalpies (kJ mol⁻¹), activation and reaction entropies (J mol⁻¹ K⁻¹).



Figure 2. Computed transition states for formation of oxirane 11 (left, ω B97XD/6-31G(d,p)/SMD(acetonitrile)) and degenerate rearrangement in 14 (right, ω B97XD/6-31G(d,p)/SMD(heptane)).

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In conclusion, we have located computationally and detected experimentally a previously unknown reaction of carbonyl compounds – pericyclic transfer of a CH_2 unit from one carbonyl group to another. Although the activation barriers are high, they might decrease by appropriate choice of a catalyst and accurate tuning of the conditions of microdroplets generation,^[10] giving access to practically important transformations. These findings demonstrate potential of thorough computational studies of simple molecules and versatility of heated capillary electrospray mass spectrometry experimental detection of thermodynamically unstable products in the reactions with high activation barriers.



Scheme 7. Computed intramolecular formation of oxirane 13 and degenerate rearrangement in 14 (ω B97XD/6-31G(d,p)/SMD(heptane)). Computed imaginary frequencies (cm⁻¹), activation and reaction enthalpies (kJ mol⁻¹), activation and reaction entropies (J mol⁻¹ K⁻¹).

Experimental Section

DFT Computations were carried out using the long-range corrected hybrid functional with damped atom—atom dispersion (ω B97XD)¹¹ as implemented in the GAUSSIAN 09 software package¹² on the 6-31G(d,p) basis. MP2 computations applied the same basis. Solvent effects were accounted by carrying out optimizations in the SMD force field¹³ (acetone, acetonitrile or heptane).

All chemicals were of reagent grade or higher. Methanol (Lab-Scan, HPLC grade) was used as a solvent for MS experiments. For measuring mass spectra a custom built QExactive Orbitrap mass spectrometer (Thermo) equipped with ion funnel and extended metal desolvating capillary and electrospray ionization source was used.^[14] Mass spectra were recorded by Orbitrap in positive ion mode with the resolving power of 140 000. Heating of capillary was performed using lab power supply OJE QJ3003C III implemented in series mode. Mass-spectra treatment and modelling were performed with Thermo Xcalibur 3.0 software.



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Keywords: carbonyl compounds • *ab initio* calculations • MS spectrometry • heated capillary • DFT

- 1 F. A Carey, R. J. Sundberg, *Advanced Organic Chemistry, Part B: Reactions and Synthesis.* Springer, New York, Fifth Edition **2007.**
- D. Caine in Carbon-Carbon Bond Formation, Vol. 1, R. L. Augustine, Ed. Marcel Dekker, New York, **1979**, Chpt. 2.
- 3 C. H. Heathcock, Modern Synthetic Methods 1993, 6, 1.
- 4 Modern Aldol Reactions, R. Mahrwald Ed. Wiley-VCH, Weinheim, 2004.
- 5 S. Masamune, W. Choy, J. S. Petersen, L. R. Sita. *Ang. Chem. Int. Ed. Engl.* **1985**, *24*, 1-30.
- R. M. Bain, C. J. Pulliam, R. G. Cooks, *Chem. Science* 2015, *6*, 397-401, and references therein.
- 7 a) R. Augusti, H.Chen, L. S. Eberlin, M. Nefliu, R. G. Cooks, *Int. J. Mass Spectrom.* 2006, 253, 281-287; b) J. K. Lee, S. Kim, H. G. Nam, R. N. Zare, *Proc. Natl. Acad. Sci. USA* 2015, *112*, 3898-3903; c) S. Banerjee, R. N. Zare, *Angew. Chem. Int. Ed.* 2015, *54*, 14795-14799.
- 8 Y. Li, X.Yan, R. G. Cooks, Angew. Chem. Int. Ed. 2016, 55, 3433-3437.
- a) Z. Wei, X. Zhang, J. Wang, S. Zhang, X. Zhang, R. G. Cooks, *Chem. Sci.* 2018, *9*, 7786; b) X. Yan, H. Cheng, R. N. Zare, *Angew. Chem. Int. Ed.* 2017, *56*, 3562-3565; c) R. M. Bain, S. Sathyamoorthi, R. N. Zare, *Angew. Chem. Int. Ed.* 2017, *56*, 15083-15087.
- 10 R. M. Bain, C. J. Pulliam, F. Thery, R. G. Cooks, Angew. Chem. Int. Ed. 2016, 55, 10478-10482.
- 11 J. D. Chai, M. H.Gordon, *Phys. Chem. Chem. Phys.*, **2008**, *10*, 6615-6620.
- 12 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, 2009.
- 13 A. V. Marenich, C. J. Cramer, D. G. Truhlar, J. Phys. Chem. B, 2009, 113, 6378-6396.
- 14 Y. Kostyukevich, E. Nikolaev, Analytical chemistry 2018, 90, 3576-3583.

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