

Accepted Article

Title: Formation of a Tunneling Product in the Photo-Rearrangement of o-Nitrobenzaldehyde

Authors: Dennis Gerbig and Peter Richard Schreiner

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Angew. Chem. Int. Ed. 10.1002/anie.201705140 Angew. Chem. 10.1002/ange.201705140

Link to VoR: http://dx.doi.org/10.1002/anie.201705140 http://dx.doi.org/10.1002/ange.201705140

WILEY-VCH

COMMUNICATION

WILEY-VCH

Formation of a Tunneling Product in the Photo-Rearrangement of o-Nitrobenzaldehyde

Dennis Gerbig^[a] and Peter R. Schreiner*^[a]

Abstract: The photochemical rearrangement of o-nitrobenzaldehyde to o-nitrosobenzoic acid, first reported in 1901, has been shown to proceed via a distinct ketene intermediate. In the course of matrix isolation experiments in various host materials at temperatures as low as 3 K, we re-investigated the ketene in its electronic and vibrational ground states and show here that hitherto unreported Htunneling dominates its reactivity, with half-lives $t_{1/2}$ of a few minutes. Unexpectedly, the tunneling product is different from onitrosobenzoic acid formed in the photoprocess: Once prepared by irradiation, the ketene spontaneously rearranges to an isoxazolone via an intriguing mechanism initiated by H-tunneling. High-level computations reveal that this isoxazolone is neither thermodynamically nor kinetically favored under the experimental conditions, and that formation of this unique tunneling product constitutes a remarkable and new example of tunneling control.

The photochemical conversion of *o*-nitrobenzaldehyde (1) to *o*-nitrosobenzoic acid (2) is a puzzling reaction that has attracted considerable attention since its original discovery by Ciamician and Silber.^[1] Its significance lies in its diverse applications, in particular, in the use of nitro-compounds as photo-cleavable protecting groups in the context of "caging", *i.e.*, activation upon photoirradiation, of physiologically active reagents.^[2] The latter provide great opportunities for the continuing development of phototherapy as a biocompatible alternative to traditional systemic drug applications.

The rearrangement of **1** has been shown to proceed *via* initial hydrogen transfer from the formyl to the adjacent nitro group, yielding a ketene (**3**) as the primary photoproduct.^[3] The intermediacy of **3** could unequivocally be established by means of matrix isolation infrared spectroscopy^[4] as well as by ultrafast transient visible, infrared and stimulated Raman spectroscopies.^[5] Inherent vibrational excitation of "hot" **3** or continued irradiation in the visible range then effect a secondary rearrangement to final product **2** *via* hydroxyl group transfer in a process akin to the concept of shuttle catalysis.^[6]

We turned our attention to this intriguing reaction within the broader scope of our studies on tunneling control^[7] that must be considered as a way of understanding and ultimately controlling chemical reactions as a viable alternative to the well established principle of kinetic vs. thermodynamic control. Tunneling control was originally identified for the novel family of hydroxycarbenes:[7a, 8] Despite the existence of a kinetically preferable reaction pathway to the corresponding vinyl alcohol, many hydroxycarbenes exclusively rearrange to their

 [a] Dr. Dennis Gerbig, Prof. Dr. Peter R. Schreiner, Ph.D. Institute of Organic Chemistry Justus–Liebig University Heinrich–Buff–Ring 17, 35392 Giessen, Germany E-mail: prs@uni-giessen.de

Supporting information for this article is given via a link at the end of the document.

corresponding aldehyde (the thermodynamic product) by hydrogen tunneling through a high but narrow barrier.^[7a] In principle –but not shown yet– a reaction product that is neither thermodynamically nor kinetically favored cannot be synthesized from the same starting material by conventional means, but may be accessible exclusively by tunneling. We demonstrate here that this is indeed possible and consequently term this the *tunneling product*.

As it turns out, **3** still shows exceptional reactivity even when there is insufficient energy to overcome thermal barriers and in the absence of ultraviolet or visible radiation. In the following, we provide evidence that ground state **3** undergoes an intramolecular rearrangement initiated by hydrogen tunneling, yielding the unique tunneling product **4**, which is distinctly different from the thermodynamically and kinetically favored photoproduct **2** (Scheme 1).



Scheme 1. Photorearrangement of *o*-nitrobenzaldehyde (1): product **2** is favored kinetically and thermodynamically, while hitherto unobserved isoxazolone (**4**) is the product only accessible *via* a tunneling reaction.

In our investigations, we employed the matrix isolation technique to generate ground state **3** to study its reactions under cryogenic conditions. For that purpose, **1** was evaporated under high vacuum conditions and co-deposited with a large excess of either neon, argon, krypton, xenon, or dinitrogen onto an optically transparent support as cold as 3 K at the time of measurement. After photogeneration of **3** within the so-obtained matrix by 313 nm light, we were able to discern new signals in the ketene region of the infrared spectrum as well as a new absorption in the visible range of the ultraviolet-visible spectrum.

Much to our surprise, we observed the rapid decay of the ketene signals within minutes, which was not attributable to photochemical bleaching of the matrix (Fig. 1). The first-order decay process was accompanied by the concomitant emergence of a new signal in the infrared, located at higher frequencies than the carbonyl signal of **2** (Table 1). To exclude the possibility that the observed reaction was a mere result of infrared stimulation by globar radiation inside the spectrometer, we covered the vacuum shroud immediately after generation of **3** and foregoing initial spectra recording, only to find its expected signals had already vanished upon the follow-up measurement.

COMMUNICATION

WILEY-VCH



Figure 1. Decay of ketene intermediate (3, downward arrows) and concurrent emergence of tunneling product (4, upward arrows) in neon at 3 K (top trace) and argon at 8 K (bottom trace) within a 45 min period in the dark.

As there is insufficient thermal energy under our cryogenic conditions, **3** cannot overcome any reaction barrier in a classic fashion. Thus, only a quantum mechanical tunneling process provides a satisfactory explanation for the observed reactivity. The tunneling rate constants show an expected dependence on the matrix host material,^[9] with the tunneling half-lives ($t_{1/2}$, Table 2) increasing in the order of neon < argon < krypton < xenon: Guest molecules are likely to be increasingly stabilized by London dispersion interactions in the solid host material. Molecular nitrogen, on the other hand, strongly stabilizes **3** likely by coordination,^[10] thereby increasing $t_{1/2}$ by more than an order of magnitude. Rates measured in argon at 8 K and 20 K are also identical within the experimental margin of error, which further supports a tunneling mechanism.

Table 1. Infrared signals v in wavenumbers (cm⁻¹) of the ketene intermediate (3) and 1-hydroxy-benzo[*c*]isoxazol-3(1*H*)-one (4) in neon and argon (values for other host materials are given in the SI); theoretical values v_{theor} and *l*_{rel} (in km mol⁻¹) computed at B3LYP/6-311++G(*d*,*p*) (unscaled; results from anharmonic frequency computations in curly brackets).

	v(Ne) ^[a]	$\nu(Ar)^{[b]}$	ref. ^[c]	V _{theor} ^[d]	I _{theor}	approx. description
3	2122.8	2118.3	2118	2188.1 {2145.2}	1156 {794}	v(C=C=O)
	2109.2	2108.1	2107	{2140.0}	{108}	[1]
	1232.6	1230.5	[e]	1256.1 {1230.8}	110 {137}	δ(NOH), δ(CCC) arom.
4	3606.6	3581.5 3577.8	3580 3577	3783.9	108	ν(OH)
	1821.3 1814.8 1810.8	1805.7 1799.7	1804 1799	1847.6	577	v(C=O)
	1057.2	1063.3 1061.1 1059.0 1057.7	[e]	1069.6	131	ν(C–O), ring deform.

[a] Measurement at 3 K. [b] Measurement at 8 K. [c] values in Ar from [4] [d] gas phase values [e] not observed [f] combination δ (NOH), δ (CCC) arom. + v(C–O).

We performed quantum chemical computations to shed light on the tunneling mechanism and the ensuing rearrangement product. The newly emerging infrared signal in the carbonyl region matches closest the spectral features of 1-hydroxybenzo[*c*]isoxazol-3(1*H*)-one (**4**), which has been suggested as a possible trace product alongside **2** in a prior matrix isolation study (Scheme 1).^[4]

Table 2. Experimentally and theoretically obtained half-lives $t_{1/2}$ in minutes of the ketene intermediate (3) generated from *o*-nitrobenzaldehyde (1) in different matrix materials by irradiation with 313 nm light.

	τ _{1/2} (Ne)	τ _{1/2} (Ar)	τ _{1/2} (Kr)	τ _{1/2} (Xe)	$\tau_{1/2}$ (N ₂)	
experimental	1.7±0.1 ^[a]	2.0±0.2 ^[b]	2.2±0.1 ^[b]	3.5±0.1 ^[b]	81±4 ^[a]	
theoretical ^[c]	11					

[a] Measurement at 3 K. [b] Measurement at 8 K. [c] computed for gas-phase at CCSD(T)/cc-pVTZ//MP2/aug-cc-pVDZ at 0 K.

The structure of 3 as initially generated prohibits the direct formation of isoxazolone (4): Since the torsional movement of the NOOH moiety along the C=N bond is not feasible due to the quinoid nature of 3, an intramolecular [1,3]-hydrogen transfer initiated by tunneling followed by instantaneous ring formation appears as a viable pathway. This mechanistic proposal is further substantiated by repeating the experiment with 1 deuterated at the formyl group (d_1-1) : intermediate d_1-3 is persistent in the absence of ambient light for at least several days. A hydrogen/deuterium kinetic isotope effect this large (computed as >10⁶, vide infra) is highly indicative of a tunneling process due to the pronounced influence of the mass of the tunneling particle on the rate constant.^[11] We could indeed reproduce the kinetic isotope effect computationally by assessing the tunneling rate constants of 3 with the semiclassical Wentzel-Kramers-Brillouin (WKB)[7a, 11] approximation (Table 2): While we obtain a value of several minutes for 3 at the CCSD(T)/cc-pVTZ//MP2/aug-cc-pVDZ level of theory, the half-life of d_1 -3 amounts to several years.



reaction coordinate

Figure 2. Schematic reaction path from ketene (3) to isoxazolone (4). Quantum mechanical tunneling (QMT) only occurs through the narrowest barrier.

In the course of these tunneling computations, we mapped the intrinsic reaction path^[12] of the transformation (Figure 2): It is evident that the traversed enthalpic barrier only applies to the

COMMUNICATION

initial [1,3]-hydrogen shift and that ring formation and rehybridization of the isoxazolone nitrogen in fact occur subsequently in a *barrierless* fashion (*cf.* Supplementary Materials). Accordingly, additional stationary points along the reaction path could not be located.

Upon further inspection of the ground state potential energy surface around **3**, which was also established at the CCSD(T)/cc-pVTZ//MP2/aug-cc-pVDZ level of theory, it is apparent that the formation of the usually observed photoproduct **2** is thermodynamically preferred over that of **4** (Scheme 2).



Scheme 2. Reaction pathways open to the ketene intermediate (3) computed at CCSD(T)/cc-pVTZ//MP2/aug-cc-pVDZ + zero point vibrational energy (ΔH_0); ground state enthalpies in black, transition state enthalpies in red. Reaction to *o*-nitrosobenzoic acid (2) does not occur despite being favored kinetically *and* thermodynamically.

Moreover, the enthalpic barrier separating **2** from precursor **3** in its ground state is by far the lowest, which should, under consideration of classic Transition State Theory (TST),^[13] strongly favor the formation of **2** kinetically as well. In stark contrast, however, neither reaction to **2** (nor back to **1**) occurs, but only **4** forms in the dark process: Its appearance is entirely attributable to tunneling through a substantially higher, yet sufficiently narrow barrier (Figure 2). This observation marks another example of tunneling control and, to the best of our knowledge, the first report of an exclusive tunneling product.

Note that **4** can in principle transform into **2** *via* a transition state close in energy to the entrance channel (approx. +2.2 kcal mol⁻¹; *cf.* Supplementary Materials). While this pathway is not operative under matrix isolation conditions, it might well be relevant in solution at ambient temperatures, similarly to closely related compounds.^[14] Besides tunneling in the rearrangement of **3**, photoproduct **2** and its deuterated analog O-*d*-**2** undergo conformational tunneling between *E*- and *Z*-conformers, thus mimicking the behavior of many other carboxylic acids.^[9, 15] Experimental details and kinetic data regarding these processes are provided in the Supplementary Materials.

By unveiling the spontaneous rearrangement of ground state 3 in cryogenic matrices due to a tunneling process, we could add yet another intriguing mechanistic feature to the rich chemistry of the o-nitrobenzaldehyde system more than a century after the original conception of its photorearrangement.^[1] We anticipate that the explicit consideration of tunneling and the extent of control it exerts on reactivity is not limited to this particular system but is of general nature, thereby affecting the design of chemical reactions beyond the classic limits of TST.

Experimental Section

Matrix isolation. Experiments at 8 K were conducted on a Leybold cryostat system consisting of a RGD 210 closed-cycle refrigerator cold head and a RW2 compressor unit. Experiments at 3 K were carried out on a Sumitomo cryostat system with a RDK 408D2 closed-cycle refrigerator cold head and a F-70 compressor unit. For infrared measurements, the vacuum shroud was equipped with polished potassium bromide windows. A polished cesium iodide window mounted in the sample holder on the cold head served as the matrix substrate. For ultraviolet-visible measurements, both the vacuum shroud and the sample holder were outfitted with polished barium fluoride windows. Temperatures of the matrices were determined with silicon diodes at the base of the sample holders. Deposition temperatures were varied for the matrix host gases, with 3 K for neon, 12 K for argon, 15 K for dinitrogen, 25 K for krypton, and 30 K for xenon. For irradiation of the matrices, a 200 W Osram HBO 200 high pressure xenon(mercury) lamp was used in conjunction with a Bausch & Lomb monochromator. For wavelengths ≥ 405 nm, a Schott 375 nm cutoff filter was added to the beam path.

Spectroscopic measurements. Infrared spectra of matrix experiments at 8 K were recorded on a Bruker Equinox IFS55 Fourier-transform infrared spectrometer, matrix experiments at 3 K were measured on two Bruker Vertex 70 instruments (standard potassium bromide or wide-range beamsplitters). Spectral data were recorded in the range from 6000 to 400 cm⁻¹ with a resolution of 0.5 cm⁻¹. Measurements in the ultraviolet-visible region were conducted on Jasco V-670 and V-760 spectrophotometers in the range of 190–800 nm with a resolution of 1 nm

Kinetics. Tunneling kinetics of matrix-isolated **3** (2) were evaluated by recording infrared spectra in regular intervals for a period of several hours after 30–60 s irradiation of the matrix with 313 nm light. Between repeated measurements, the optical path was blocked to avoid prolonged irradiation of the matrix by the instrument globar. Additionally, a 3.6 μ m cutoff filter was installed to effectively block infrared light > 2700 cm⁻¹ and prevent obscuring the ground state reactivity of **3** (2) due to vibrational overtone excitation.

Chemicals. Samples of **1** were sublimed before use. Synthesis of d_1 -**1** was performed *via* reduction of methyl *o*-nitrobenzoate to d_3 -*o*-nitrobenzylic alcohol with lithium aluminium deuteride and subsequent Swern oxidation. The crude product was purified by flash column chromatography as well as sublimation and showed an estimated isotopic purity of > 90% for deuterium. For matrix isolation, host gases of 99.999% purity were used.

Computational. All computations employing density functional^[16] and Møller-Plesset^[17] perturbation theory were performed with Gaussian09^[18] in revision E.01. Intrinsic reaction paths were mapped using the Hratchian predictor-corrector algorithm and projected frequencies were computed along the paths.^[19] Coupled cluster^[20] energies for each point on a path were determined with CFOUR 1.0.^[21] WKB computations were carried out with Wolfram Mathematica 10.^[22]

Biochemistry 1978, 17, 1929-1935.

Phys. 2008, 10, 3872-3882.

COMMUNICATION

[1]

[2]

[3]

[4]

[5]

[6]

[7]

[8]

Keywords: matrix isolation • nitrobenzaldehyde • photochemistry • physical organic chemistry • tunneling

G. Ciamician, P. Silber, Ber. Dtsch. Chem. Ges. 1901, 34, 2040-2046.

a) J. A. Barltrop, P. J. Plant, P. Schofield, Chem. Commun. London

1966, 822-823; b) A. Patchornik, B. Amit, R. B. Woodward, J. Am.

Chem. Soc. 1970, 92, 6333-6335; c) J. Engels, E. J. Schlaeger, J. Med.

Chem. 1977, 20, 907-911; d) J. H. Kaplan, B. Forbush, J. F. Hoffman,

a) P. De Mayo, S. Reid, Q. Rev. Chem. Soc. 1961, 15, 393-417; b) M.

a) S. Laimgruber, W. J. Schreier, T. Schrader, F. Koller, W. Zinth, P.

Gilch, Angew. Chem. Int. Ed. 2005, 44, 7901-7904; b) S. Laimgruber, T.

Schmierer, P. Gilch, K. Kiewisch, J. Neugebauer, Phys. Chem. Chem.

a) P. R. Schreiner, H. P. Reisenauer, D. Ley, D. Gerbig, C.-H. Wu, W. D. Allen, *Science* **2011**, *332*, 1300-1303; b) D. Ley, D. Gerbig, P. R.

a) P. R. Schreiner, H. P. Reisenauer, F. C. Pickard, A. C. Simmonett,

W. D. Allen, E. Mátyus, A. G. Császár, Nature 2008, 453, 906-909; b) D.

Gerbig, H. P. Reisenauer, C.-H. Wu, D. Ley, W. D. Allen, P. R.

Schreiner, J. Am. Chem. Soc. 2010, 132, 7273-7275; c) D. Gerbig, D.

Ley, H. P. Reisenauer, P. R. Schreiner, *Beilstein J. Org. Chem.* 2010, 6, 1061-1069; d) D. Gerbig, D. Ley, P. R. Schreiner, *Org. Lett.* 2011, 13,

V. George, J. C. Scaiano, J. Phys. Chem. 1980, 84, 492-495.

B. N. Bhawal, B. Morandi, ACS Catalysis 2016, 6, 7528-7535.

Schreiner, Org. Biomol. Chem. 2012, 10, 3781-3790.

S. Kuberski, J. Gebicki, J. Mol. Struct. 1992. 275. 105-110.

3526-3529; e) D. Ley, D. Gerbig, J. P. Wagner, H. P. Reisenauer, P. R. Schreiner, J. Am. Chem. Soc. **2011**, *133*, 13614-13621.

- [9] M. Pettersson, E. M. S. Maçôas, L. Khriachtchev, J. Lundell, R. Fausto, M. Räsänen, J. Chem. Phys. 2002, 117, 9095-9098.
- [10] K. Marushkevich, M. Räsänen, L. Khriachtchev, J. Phys. Chem. A 2010, 114, 10584-10589.
- [11] W. H. Miller, N. C. Handy, J. E. Adams, J. Chem. Phys. 1980, 72, 99-112.
- [12] a) K. Fukui, J. Phys. Chem. 1970, 74, 4161-4163; b) K. Fukui, Acc. Chem. Res. 1981, 14, 363-368.
- [13] a) H. Eyring, J. Chem. Phys. 1935, 3, 107-115; b) M. G. Evans, M. Polanyi, Trans. Faraday. Soc. 1935, 31, 875-894.
- [14] Y. V. Il'ichev, M. A. Schwörer, J. Wirz, J. Am. Chem. Soc. 2004, 126, 4581-4595.
- [15] a) E. M. S. Maçôas, L. Khriachtchev, M. Pettersson, R. Fausto, M. Räsänen, *Phys. Chem. Chem. Phys.* 2005, *7*, 743-749; b) S. Amiri, H. P. Reisenauer, P. R. Schreiner, *J. Am. Chem. Soc.* 2010, *132*, 15902-15904.
- [16] a) A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098-3100; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648-5652.
- [17] C. Møller, M. S. Plesset, Phys. Rev. 1934, 46, 618-622.
- [18] M. J. Frisch et al., Gaussian Inc., Wallingford CT, 2009.
- [19] a) H. P. Hratchian, H. B. Schlegel, *J. Phys. Chem. A* 2002, 106, 165-169; b) H. P. Hratchian, H. B. Schlegel, *J. Chem. Phys.* 2004, 120, 9918-9924.
- [20] J. Čížek, J. Chem. Phys. 1966, 45, 4256-4266.
- [21] CFOUR v. 1.0, 2010, http://www.cfour.de. See SI for full citation.
- [22] Mathematica 10.0, Wolfram Research Inc., 2014, http://www.wolfram.com.

4

WILEY-VCH

COMMUNICATION

COMMUNICATION

Triggered by Tunneling: The ketene intermediate derived from photoexcited *o*-nitrobenzaldehyde rearranges to a hitherto unobserved tunneling-exclusive isoxazolone product under cryogenic conditions, thereby constituting a new reactivity paradigm in chemistry.



Dennis Gerbig, Peter R. Schreiner*

Page No. – Page No.

Formation of a Tunneling Product in the Photo-Rearrangement of o-Nitrobenzaldehyde