Kinetics Hot Paper

International Edition: DOI: 10.1002/anie.201708413
German Edition: DOI: 10.1002/ange.201708413

"On-Droplet" Chemistry: The Cycloaddition of Diethyl Azodicarboxylate and Quadricyclane

*Ryan M. Bain[+], Shyam Sathyamoorthi[+], and Richard N. Zare**

Dedicated to Professor K. Barry Sharpless and Professor R. Graham Cooks

Abstract: *Sharpless and co-workers previously studied the [2σ+2σ+2π] cycloaddition of diethyl azodicarboxylate (DEAD) and quadricyclane and reported that the addition of water to the neat reagents caused an acceleration in the reaction rate, giving birth to what has been called "on-water" chemistry. We have examined the same reaction in aqueous microdroplets (ca. 5 μm diameter) and find that the cycloaddition reaction is accelerated even further (by a factor of 10^2) compared to that of the "on-water" reaction reported previously. The trends of acceleration in solvents other than water demonstrated by Sharpless and colleagues were replicated in the corresponding microdroplet experiments. We also find that DEAD reacts with itself to form a variety of hydrazine carboxylates and intercept intermediates of this reaction in microdroplets to validate a mechanism proposed herein. We suggest that "on-droplet" chemistry, similar to "on-water" chemistry, may be a general process of synthetic interest.*

Water, long the solvent of choice for biochemical reactions, has seen increased use in organic synthesis.[1] The seminal discovery by Breslow and co-workers[2] of the rate acceleration of Diels–Alder cycloadditions in water suggested that the poor solubility of hydrophobic reagents may promote, rather than hamper, certain classes of reactions. Indeed, the exploration of reactions at the organic–aqueous interface has become a topic of research in the synthetic community.[3] In these reactions, an organic phase floats atop a bulk water layer. Termed "on-water" chemistry by Sharpless and co-workers,[4] these reactions now encompass a diverse range of transformations including cycloadditions,[5] sigmatropic rearrangements,[6] aldol reactions,[7] and Grignard additions.[8] In almost all cases, an acceleration of several to several hundred-fold has been noted relative to reactions conducted in organic solvents or even under neat conditions. Mellouli et al. examined "on-water" cycloaddition reactions in biphasic microfluidic systems and investigated the role of surface-to-volume ratios on conversion rates, demonstrating that acceleration can be ascribed to the increased rate of conversion at the surface.[9] Water is an ideal solvent in terms of safety and cost. Additionally, many reactions conducted "on-water" allow for the facile isolation of products, which often precipitate and can be collected by simple filtration rather than after an often complex and time-consuming workup.[4a]

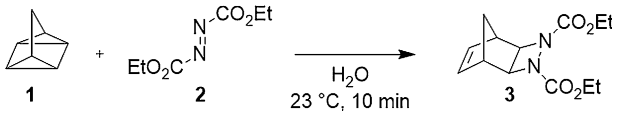
Work from our group,[10] as well as others,[11] has demonstrated that reactions in microdroplets generated through electrospray ionization (ESI) are often orders of magnitude faster than their counterparts in bulk solution. This unique reactivity in the ESI process was first proposed by Augusti et al.[12] during their study of Eberlin transacetalization reactions in which acylium ions were generated by ESI of a tetramethylurea solution and gaseous acetals were subsequently introduced and allowed to react with the acylium ions. In this work, Augusti et al. argued that "polar acetal molecules are collected from the gas phase by the charged droplets and react with the acylium ions distributed at the liquid surface."[12] Recent studies have demonstrated the surface of the microdroplet has a profound influence on rate enhancement; the comparison of bulk-phase with microdroplet and thin-film Hammett substituent plots showed that reagents with more surface activity had a greater increase in reactivity in the microdroplet.[11d] Additional studies have demonstrated that reactivity can also be enhanced at the surface of levitated droplets[13] and in microfluidic systems.[14] Muller, Badu-Tawiah, and Cooks[15] have pioneered "preparative electrospray," where four ESI sources spray simultaneously to generate product at rates on the milligram per minute scale for Claisen–Schmidt condensations and benzoin condensations. This has also been demonstrated in the biphasic oxidation of 4-nitrobenzyl alcohol.[16] These remarkable, confined-volume systems have been implemented to screen novel synthetic routes and optimize flow chemistry.[17] Interestingly, previous reports have demonstrated that the microdroplet products are not simply gas-phase products from ion-molecule reactions.[18] New products, not observed in bulk, can be formed in microdroplet reactions as demonstrated by work from our group with an intramolecular Diels–Alder reaction of 3,5-hexadienyl acrylate which produced a hydrolysis product in droplet rather than the typical bulk-phase cycloadduct.[19]

Intrigued by reports of dramatic acceleration "on water", we set out to investigate the same reactions to determine if they could be accelerated further in the microdroplet environment created by ESI, as the spray process would create an even larger surface-to-volume ratio than previously reported systems. We chose the [2σ+2σ+2π] cycloaddition of diethyl azodicarboxylate (DEAD, **2**) with quadricyclane (**1**) as a model reaction (Scheme 1), first disclosed by Rieber

[*] Dr. R. M. Bain,[+] S. Sathyamoorthi,[+] Prof. R. N. Zare
Department of Chemistry, Stanford University
Stanford, CA 94305 (USA)
E-mail: zare@stanford.edu

[+] These authors contributed equally to this work.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201708413.



Scheme 1. Reaction of quadricyclane (**1**) with diethyl azodicarboxylate (DEAD, **2**) "on water" to form the cycloaddition product (**3**).

et al.[20] and later studied "on water" by Sharpless and co-workers.[4a] In toluene, when quadricyclane is stirred with DEAD, even after 24 h, low conversion (24%) to product occurs. In contrast, Sharpless and co-workers found that "on water", the reaction progresses much further, 42% after 4 h and 69% after 18 h. We report here that in microdroplets generated through ESI, the reaction rate of **1** and **2** is dramatically increased. In addition, we detect the formation of other products and intermediates, demonstrating that the sensitivity of mass spectrometry allows for the uncovering of reaction pathways that may be invisible to other analytical techniques. By combining the reactivity of ESI with the sensitivity of mass spectrometry, this on-line system could be used to explore synthetic chemistry in new and powerful ways.

Microdroplet reactions were performed in a nanoESI[21] source pulled from a theta-tip glass capillary. In this device, there are two capillary channels that are joined together at the exit to allow for rapid mixing of segregated reagent streams before being expelled as microdroplets. This separation allows the reaction time to be solely the droplet flight time from the tip of the nanoESI capillary to the ion transfer capillary of the spectrometer, that is, there is negligible dead time for mixing. The Williams group and the Derrick group have used this theta-tip nanoESI setup to study fast reaction kinetics.[22] Jansson et al.[23] have demonstrated that hydrogen-deuterium exchange in a theta tip nanoESI reaction is orders of magnitude faster in the microdroplet compared to that in bulk. As "on-water" reactions are already accelerated, we reasoned that, for our microdroplet study, segregating reagents until the moment of reaction would yield the most accurate results in terms of kinetics.

One channel of the theta tip glass capillary was loaded with a suspension of **1** in water; the other channel was charged with a suspension of **2** (Experimental Section, Figure 4). Previous work has determined the average flight velocity of these droplets to be approximately 10 m s^{-1} which can be used to convert the distance between the source and the mass spectrometer inlet into a time of flight.[11a,23,24] Using an unreactive internal standard (2-morpholinocyclohexan-1-ol, prepared following the procedure of Chakraborti and Kondaskar;[25] see the Supporting Information) the microdroplet reaction yield can be determined. This is the first example of determining accelerated reaction rates quantitatively in microdroplets, in contrast to other publications where reaction rates had been approximated.[10c,11a,23] Comparing the two flight times in Figure 1, it is apparent that the reaction progresses dramatically as the distance is increased.

With the internal standard present, a calibration curve (see the Supporting Information for the full curve) was constructed to quantify the formation of product in the droplets as a function of time. This rate can then be compared

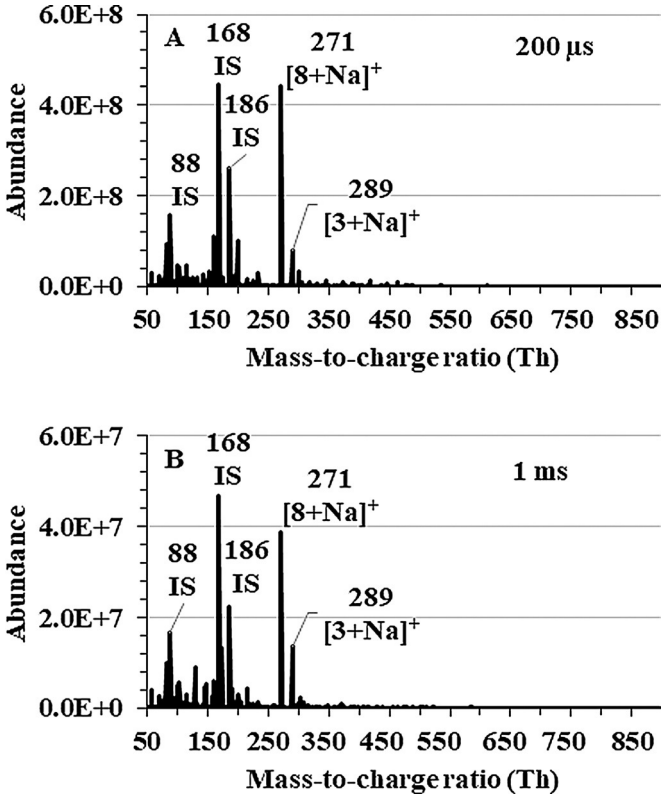


Figure 1. Full-scan positive mode mass spectrum of theta-tip experiments at two different flight times (distances between the MS inlet and the spray source) where **2** in water was loaded into one channel and **1** in water was loaded into the other.

to the "initial-rate region" of our own bulk phase reaction kinetics data (Figure 2b,c). The ratio of the slopes, which represents the ratio of rate constants, gives an acceleration factor for the "on-droplet" reaction. The acceleration factor is 115, given the "on-droplet" rate constant of 0.0023 mol L^{-1} s^{-1} and the "on-water" (linear region) rate constant of 2×10^{-5} mol L^{-1} s^{-1}.

The data in Figure S1 compares the reaction of **1** and **2** in H_2O with that in D_2O at two different microdroplet reaction times (50 and 350 µs). It is apparent that there is a reduction of conversion rate in D_2O by approximately a factor of 5. Remarkably, this is almost the same reduction in rate noted by Sharpless and co-workers "on deuterated water", albeit with the related dimethyl azodicarboxylate (DMAD), where a factor of 4.5 was measured. We attribute this behavior to a solvent isotope effect. Furthermore, we were unable to achieve any detectable reaction acceleration in the microdroplet experiment with toluene, acetonitrile, or chloroform, which is also in agreement with results in bulk.[4a] The cycloaddition in these solvents took multiple days to reach completion. Sharpless and co-workers noted an approximate decrease in reaction rate by a factor of 25 when switching from 1:3 *v*/*v* MeOH:H_2O to 3:1 *v*/*v* MeOH:H_2O with DMAD. In our theta tip experiments with DEAD, the reduction in rate was also evident but by only a factor of five (see Figures S2 and S3). The trend both "on water" and "on droplet" is clear: some amount of heterogeneity is likely

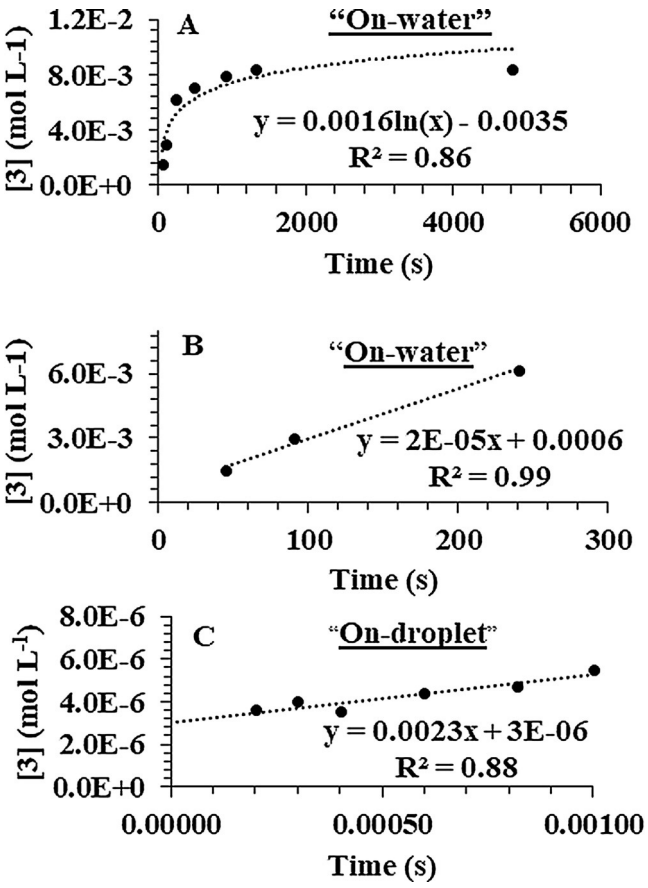


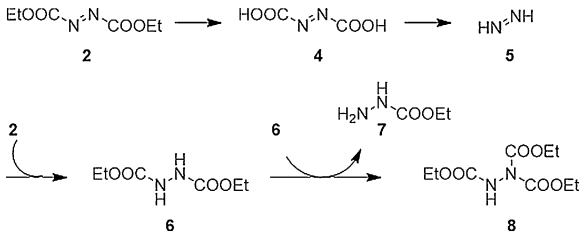
Figure 2. a) Concentration of **3** over time for the bulk-phase reaction b) Linear fit for the first three time points and c) concentration of product over time for the "on-droplet" reaction. (See the Supporting Information for the raw data from which these plots were generated.)

required to observe acceleration. The microdroplet "surface reactivity" is likely the cause of further rate enhancement "on droplet" beyond that seen "on water". Mellouli et al. have demonstrated that small changes in surface-to-volume ratio provided marked changes in the conversions of "on-water" reactions.[9]

At first, on-water acceleration was ascribed by Breslow and co-workers[2c,d] primarily to the accumulation of hydrophobic species at the air–water interface. Later, Jung and Marcus[3c] put forward the idea that the acceleration was caused by "dangling" OH bonds in the hydrophobic phase surrounding water. However, calculations by Thomas, Tirado-Rives, and Jorgensen[26] were unable to ascribe the rate acceleration to unusual participation of water molecule on the water surface. Since then, Beattie, McErlean, and Phippen[27] have proposed that reaction with water at the interface results in both the protonated substrate and free OH^-, which is stabilized by its strong adsorption at the interface. This acid catalysis explanation seems to be fully consistent with our observations. We also know from past experiments on microdroplet chemistry that additional factors causing acceleration may be the lack of three-dimensional solvation at the surface of the water droplet, the speed of two-dimensional diffusion, the large electric field at the water–air interface, and the presence of charged species that preferentially accumulate on the water surface.[10a,16,19,28]

It is important to note here that the ions at 271 Th and 199 Th were found to have no increased reactivity in the microdroplets. This was confirmed by electrospraying **2** (the source of the ion at 271 Th, see below) and varying the flight time. This produced no change in the ratio of **2** to the ions at 271 Th and 199 Th, demonstrating that the formation of these species would not interfere with the cycloaddition kinetic measurements.

Interestingly, in the microdroplet reactions, two base peaks at 271 Th and 199 Th were found to originate from a reaction between water and **2**. At first, the ion at 271 Th was puzzling as it seemed to correspond to a loss of H_2O from **3**, a fragmentation that did not seem plausible given the structure of **3.** Moreover, the product ion scan of isolated **3** did not provide a product ion at 271 Th. This species was also detected when dilute **2** was electrosprayed in 1:1 *v*/*v* MeOH:H_2O, demonstrating that the species did not originate from the product **3** or starting material **1**. Thus, it seemed that the ion at 271 Th was a decomposition product of **2**. In line with this, the hydrolysis of DMAD in similar systems has been previously hypothesized.[9] A molecular formula of $C_9H_{16}N_2O_6Na^+$ was attained from HRMS measurements with an error of less than 3 ppm. Such a molecular formula could be attributed to triethyl hydrazine-1,1,2-tricarboxylate (Scheme 2, species **8**). Indeed, when a 1:1 *v*/*v* mixture of



Scheme 2. Postulated mechanism for the formation of the ions corresponding to species **6** and **8**.

DEAD:toluene was electrosprayed and collected off-line using a similar method as Muller, Badu-Tawiah, and Cooks[15] and subsequently purified by reversed-phase high pressure liquid chromatography, this molecule was isolated. The isolated sample had matching ^{1}H NMR, ^{13}C NMR, and tandem mass spectra with an authentic standard, synthesized separately (see the Supporting Information for details of synthesis). In addition to **8**, diethyl hydrazine-1,2-dicarboxylate (Scheme 2, Species **6**) was also isolated, accounting for the ion at 199 Th. In D_2O, the two most abundant ions at 272 and 201 Th were identified. This is in accord with our structural assignments, as triethyl hydrazine-1,1,2-tricarboxylate has one exchangeable proton and diethyl hydrazine-1,2-dicarboxylate has two exchangeable protons. The structure of product **3** was also confirmed by preparative electrospray followed by purification and ^{1}H NMR spectroscopy.

Using reversed-phase HPLC, pure samples of both molecules were acquired from a 1:1 *v*/*v* mixture of DEAD:-toluene that was stored at room temperature for one week.

When DEAD was incubated in a 1:1 mixture of MeOH:H_2O at room temperature, partial decomposition into both these species, among others, was observed by ^{1}H NMR within 30 min (see the Supporting Information for details). One possible mechanism for the generation of **6** is through the reduction of DEAD by diimide (Scheme 2, species **5**).[29] Hydrolysis of DEAD forms azodicarboxylic acid (Scheme 2, species **4**), the potassium salt of which is often used as a precursor to diimide.[30] Such a process may be slow in toluene, which contains relatively little moisture, but much more rapid in a MeOH:H_2O mixture. Further reaction of two equivalents of **6** forms **8** as well as ethyl hydrazinecarboxylate (Scheme 2, species **7**). Upon nanoelectrospray ionization of DEAD in 1:1 *v*/*v* MeOH:H_2O from a theta tip capillary, multiple species indicating the plausibility of our mechanistic hypothesis were detected in both positive and negative ion modes (Figure 3).

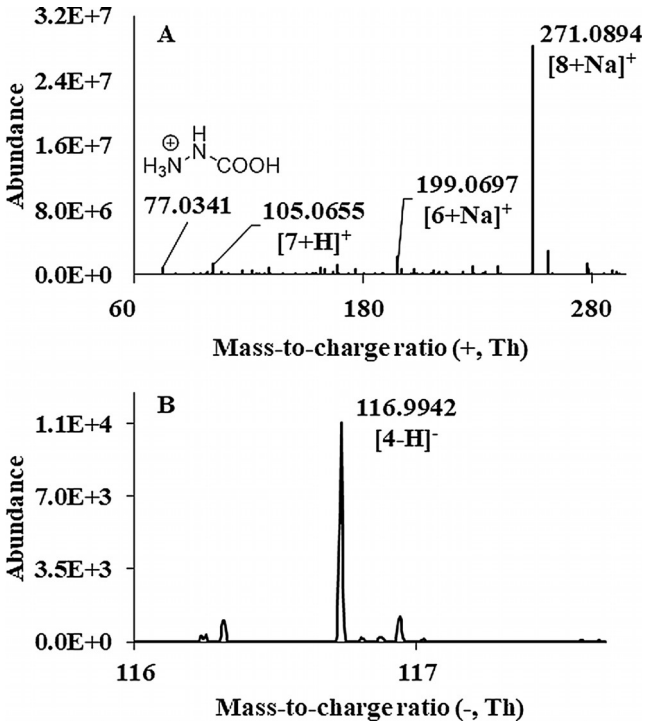


Figure 3. Full-scan positive mode mass spectrum of DEAD in a 1:1 mixture of MeOH:H_2O demonstrates the presence of ions correlating to the species **8**, **7**, and **6** from Scheme 2 and full-scan negative ion mode contains deprotonated **4**.

In summary, we have investigated the cycloaddition of diethyl azodicarboxylate with the strained hydrocarbon quadricyclane in microdroplets generated by nanoelectrospray ionization from theta-tip capillaries. We see a dramatic rate acceleration of this reaction in water microdroplets, two orders of magnitude beyond the already remarkably fast bulk reaction "on water". Furthermore, using a variety of analytical techniques, we have elucidated the structures of several other species that are detected in these droplet reactions and have found evidence suggesting a mechanism for their formation. We suggest that the exploration of "on-droplet" chemistry has great potential for the continued discovery of new, millisecond timescale organic reactions.

Experimental Section

Nanoelectrospray ionization was performed using borosilicate theta-tip capillaries (1.5 mm O.D. 1.0 mm I.D.) purchased from Warner Instruments (Hamden, CT) which were pulled with a P-87 pipette puller (Sutter Instrument, Novato, CA). A scanning electron microscope image (Sigma FE-SEM, Zeiss Microscopy, Thornwood, NY) of a typical tip can be found in Figure 4 and was taken with a Sigma FE-SEM (Carl Zeiss Microscopy, Thornwood, NY). The

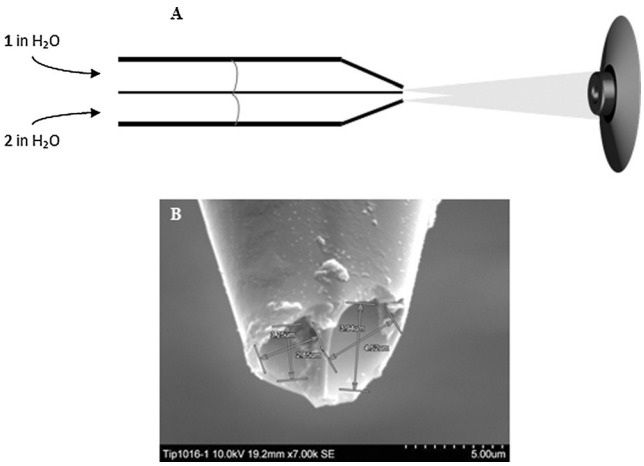


Figure 4. Theta-tip capillary: A) cartoon demonstrating its use with nanoESI and B) SEM image of a typical nanoESI tip used in these experiments.

potential was applied using the instrument HV supply with 1.5–2.0 kV. Interestingly there was no difference when an electrode was placed in each chamber or simply in one chamber. Mass analysis was performed on a hybrid LTQ-Orbitrap XL mass spectrometer (Thermo Fisher Scientific, San Jose, CA). The ion transfer capillary temperature was maintained at 548 K. The capillary voltage was 44 V and the tube lens was 60 V. NanoESI reaction solutions were prepared by dilution of 2 μL of reagent into 10 mL of solvent.

Acknowledgements

We thank a reviewer for calling our attention to Ref. [9]. This work was supported by the Air Force Office of Scientific Research through Basic Research Initiative (AFOSR FA9550-12-1-0400).

Conflict of interest

The authors declare no conflict of interest.

Keywords: accelerated reactions · cycloadditions · kinetics · mass spectrometry · microdroplets

How to cite: *Angew. Chem. Int. Ed.* **2017**, *56*, 15083–15087
Angew. Chem. **2017**, *129*, 15279–15283

[1] a) A. Chanda, V. V. Fokin, *Chem. Rev.* **2009**, *109*, 725 – 748; b) M.-O. Simon, C.-J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415 – 1427; c) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68 – 82; d) B. H. Lipshutz, S. Ghorai, *Green Chem.* **2014**, *16*, 3660 – 3679.
[2] a) D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816 – 7817; b) R. Breslow, U. Maitra, *Tetrahedron Lett.* **1984**, *25*, 1239 – 1240; c) R. Breslow, U. Maitra, D. Rideout, *Tetrahedron Lett.* **1983**, *24*, 1901 – 1904; d) R. Breslow in *Organic Reactions in Water*, Blackwell, Hoboken, **2007**, pp. 1 – 28.
[3] a) R. N. Butler, A. G. Coyne, *Org. Biomol. Chem.* **2016**, *14*, 9945 – 9960; b) S. Narayan, V. V. Fokin, K. B. Sharpless in *Organic Reactions in Water*, Blackwell, Hoboken, **2007**, pp. 350 – 365; c) Y. Jung, R. Marcus, *J. Am. Chem. Soc.* **2007**, *129*, 5492 – 5502.
[4] a) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *44*, 3275 – 3279; *Angew. Chem.* **2005**, *117*, 3339 – 3343; b) J. E. Klijn, J. B. F. N. Engberts, *Nature* **2005**, *435*, 746 – 747.
[5] V. Marchán, S. Ortega, D. Pulido, E. Pedroso, A. Grandas, *Nucleic Acids Res.* **2006**, *34*, e24.
[6] O. Acevedo, K. Armacost, *J. Am. Chem. Soc.* **2010**, *132*, 1966 – 1975.
[7] J. Mlynarski, S. Bas, *Chem. Soc. Rev.* **2014**, *43*, 577 – 587.
[8] L. Cicco, S. Sblendorio, R. Mansueto, F. M. Perna, A. Salomone, S. Florio, V. Capriati, *Chem. Sci.* **2016**, *7*, 1192 – 1199.
[9] S. Mellouli, L. Bousekkine, A. B. Theberge, W. T. S. Huck, *Angew. Chem. Int. Ed.* **2012**, *51*, 7981 – 7984; *Angew. Chem.* **2012**, *124*, 8105 – 8108.
[10] a) J. K. Lee, S. Kim, H. G. Nam, R. N. Zare, *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 3898 – 3903; b) J. K. Lee, S. Banerjee, H. G. Nam, R. N. Zare, *Q. Rev. Biophys.* **2015**, *48*, 437 – 444; c) S. Banerjee, R. N. Zare, *Angew. Chem. Int. Ed.* **2015**, *54*, 14795 – 14799; *Angew. Chem.* **2015**, *127*, 15008 – 15012.
[11] a) R. M. Bain, C. J. Pulliam, S. T. Ayrton, K. Bain, R. G. Cooks, *Rapid Commun. Mass Spectrom.* **2016**, *30*, 1875 – 1878; b) R. M. Bain, C. J. Pulliam, R. G. Cooks, *Chem. Sci.* **2015**, *6*, 397 – 401; c) M. Girod, E. Moyano, D. I. Campbell, R. G. Cooks, *Chem. Sci.* **2011**, *2*, 501 – 510; d) Y. Li, X. Yan, R. G. Cooks, *Angew. Chem. Int. Ed.* **2016**, *55*, 3433 – 3437; *Angew. Chem.* **2016**, *128*, 3494 – 3498; e) R. M. Bain, C. J. Pulliam, S. A. Raab, R. G. Cooks, *J. Chem. Educ.* **2016**, *93*, 340 – 344.
[12] R. Augusti, H. Chen, L. S. Eberlin, M. Nefliu, R. G. Cooks, *Int. J. Mass Spectrom.* **2006**, *253*, 281 – 287.
[13] a) E. A. Crawford, C. Esen, D. A. Volmer, *Anal. Chem.* **2016**, *88*, 8396 – 8403; b) R. M. Bain, C. J. Pulliam, F. Thery, R. G. Cooks, *Angew. Chem. Int. Ed.* **2016**, *55*, 10478 – 10482; *Angew. Chem.* **2016**, *128*, 10634 – 10638.
[14] a) B. Ahmed, D. Barrow, T. Wirth, *Adv. Synth. Catal.* **2006**, *348*, 1043 – 1048; b) A. Fallah-Araghi, K. Meguellati, J. C. Baret, A. El Harrak, T. Mangeat, M. Karplus, S. Ladame, C. M. Marques, A. D. Griffiths, *Phys. Rev. Lett.* **2014**, *112*, 028301.
[15] T. Müller, A. Badu-Tawiah, R. G. Cooks, *Angew. Chem. Int. Ed.* **2012**, *51*, 11832 – 11835; *Angew. Chem.* **2012**, *124*, 12002 – 12005.
[16] X. Yan, H. Cheng, R. N. Zare, *Angew. Chem. Int. Ed.* **2017**, *56*, 3562 – 3565; *Angew. Chem.* **2017**, *129*, 3616 – 3619.
[17] a) M. Wleklinski, C. E. Falcone, B. P. Loren, Z. Jaman, K. Iyer, H. S. Ewan, S.-H. Hyun, D. H. Thompson, R. G. Cooks, *Eur. J. Org. Chem.* **2016**, 5480 – 5484; b) C. E. Falcone, Z. Jaman, M. Wleklinski, A. Koswara, D. H. Thompson, R. G. Cooks, *Analyst* **2017**, *142*, 2836 – 2845; c) H. S. Ewan, K. Iyer, S-H Hyun, M. Wleklinski, R. G. Cooks, D. H. Thompson, *Org. Process Res. Dev.* **2017**, DOI: https://doi.org/10.1021/acs.oprd.7b00218.
[18] R. M. Bain, S. T. Ayrton, R. G. Cooks, *J. Am. Soc. Mass Spectrom.* **2017**, *28*, 1359 – 1364.
[19] S. Banerjee, E. Gnanamani, X. Yan, R. N. Zare, *Analyst* **2017**, *142*, 1399 – 1402.
[20] N. Rieber, J. Alberts, J. A. Lipsky, D. M. Lemal, *J. Am. Chem. Soc.* **1969**, *91*, 5668 – 5669.
[21] M. Wilm, M. Mann, *Anal. Chem.* **1996**, *68*, 1 – 8.
[22] a) L. P. Mark, M. C. Gill, M. Mahut, P. J. Derrick, *Eur. J. Mass Spectrom.* **2012**, *18*, 439 – 446; b) D. N. Mortensen, E. R. Williams, *Anal. Chem.* **2014**, *86*, 9315 – 9321; c) D. N. Mortensen, E. R. Williams, *Anal. Chem.* **2015**, *87*, 1281 – 1287; d) D. N. Mortensen, E. R. Williams, *J. Am. Chem. Soc.* **2016**, *138*, 3453 – 3460; e) D. N. Mortensen, E. R. Williams, *Chem. Commun.* **2016**, *52*, 12218 – 12221; f) A. Radionova, D. R. Greenwood, G. R. Willmott, P. J. Derrick, *Mass Spectrom. Lett.* **2016**, *7*, 21 – 25.
[23] E. T. Jansson, Y.-H. Lai, J. G. Santiago, R. N. Zare, *J. Am. Chem. Soc.* **2017**, *139*, 6851 – 6854.
[24] R. D. Espy, A. R. Muliadi, Z. Ouyang, R. G. Cooks, *Int. J. Mass Spectrom.* **2012**, *325 – 327*, 167 – 171.
[25] A. K. Chakraborti, A. Kondaskar, *Tetrahedron Lett.* **2003**, *44*, 8315 – 8319.
[26] L. L. Thomas, J. Tirado-Rives, W. L. Jorgensen, *J. Am. Chem. Soc.* **2010**, *132*, 3097 – 3104.
[27] J. K. Beattie, C. S. P. McErlean, C. B. W. Phippen, *Chem. Eur. J.* **2010**, *16*, 8972 – 8974.
[28] X. Yan, R. M. Bain, R. G. Cooks, *Angew. Chem. Int. Ed.* **2016**, *55*, 12960 – 12972; *Angew. Chem.* **2016**, *128*, 13152 – 13166.
[29] a) D. J. Pasto, R. T. Taylor, in *Organic Reactions*, Wiley, Hoboken, **2004**; b) J. Stille, T. Anyos, *J. Org. Chem.* **1962**, *27*, 3352 – 3353.
[30] J. W. Hamersma, E. I. Snyder, *J. Org. Chem.* **1965**, *30*, 3985 – 3988.

Manuscript received: August 15, 2017
Revised manuscript received: August 19, 2017
Accepted manuscript online: October 9, 2017
Version of record online: October 24, 2017

