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[11] X-ray crystal-structure determination: The data for 2,2,8,8-tetraallyl-1,3,4,6,7,8-hexahydro-2*H*-pyrimidino[1,2-a]pyrimidine trifluoroacetic acid salt (**1**-CF_3COO^-) and 2,2,8,8-tetraphenyl-1,3,4,6,7,8-hexahydro-2H-pyrimidino[1,2-a]pyrimidine benzoic acid salt (**2**-$C_6H_5COO^-$) were collected on a Nonius DIP 2020 diffractometer at 143(2) K with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods and refined against F^2 by full matrix least-squares with SHELXS-97 (SHELXS-97, G. Sheldrick, Universität Göttingen, **1997**). **1**-CF_3COO^- ($C_{21}H_{30}F_3N_3O_2$): $M_r = 413.48$, monoclinic, space group $C2/c$, $a = 26.1220(3)$, $b = 11.5845(2)$, $c = 24.8791(3)$ Å, $\beta = 117.8239(6)°$, $V = 6658.25(16)$ Å^3, $Z = 12$, $\rho_{calcd} = 1.237$ g cm^{-3}, $F(000) = 2640$, $\mu(Mo_{K\alpha}) = 0.097$ mm^{-1}. A total of 144785 reflections were measured in the range $7 \leq 2\theta \leq 53°$, of which 6785 were unique ($R_{int} = 0.038$). Final R indices: $R_1 = 0.1144$ ($I > 2\sigma(I)$), $wR_2 = 0.3096$ (all data); max./min. residual electron density 1.97/−0.73 e Å^{-1}. **2**-$C_6H_5COO^-$ ($C_{38}H_{37}N_3O_3$): $M_r = 583.71$, monoclinic, space group $P2_1/c$, $a = 10.9899(3)$, $b = 16.4570(4)$, $c = 16.9609(4)$ Å, $\beta = 97.0971(13)$, $V = 3044.06(13)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.274$ g cm^{-3}, $F(000) = 1240$, $\mu(Mo_{K\alpha}) = 0.081$ mm^{-1}. A total of 91531 reflections were measured in the range $3.4 \leq 2\theta \leq 55.2°$, of which 6989 were unique ($R_{int} = 0.081$). Final R indices: $R_1 = 0.061$ ($I > 2\sigma(I)$), $wR_2 = 0.1369$ (all data); max./min. residual electron density 0.25/−0.40 e Å^{-1}. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-163362 (**1**-CF_3COO^-) and -163363 (**2**-$C_6H_5COO^-$). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

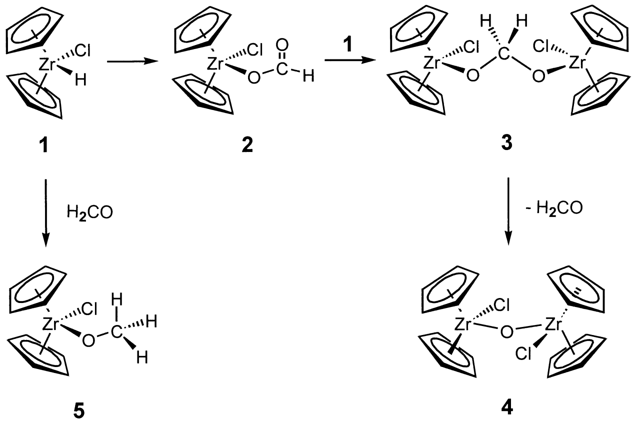
Characterization of Reactive Intermediates by Diffusion-Ordered NMR Spectroscopy: A Snapshot of the Reaction of $^{13}CO_2$ with $[Cp_2Zr(Cl)H]$**

Nils E. Schlörer, Eurico J. Cabrita and Stefan Berger*

Dedicated to Professor Anton Rieker
on the occasion of his 70th birthday

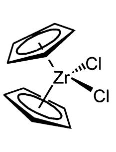
In cases in which the structural characterization of reagents generated in situ or of reactive intermediates is not feasible with conventional methods, DOSY (diffusion ordered spectroscopy) NMR spectroscopy provides a valuable method to obtain additional information.[1] Until now, pulsed field gradient (PFG) spin-echo NMR experiments were employed mainly in organic and pharmaceutical chemistry for the study of aggregation and binding processes.[1d, 2] More recently, however, with the introduction of DOSY NMR spectroscopy the traditional diffusion experiment was subject to a remarkable advance.[3] By presenting the results in a „2D spectrum“—the chemical shift is displayed in one dimension, the diffusion in the other—the resolution and assignment of even complex mixtures are greatly facilitated. The surprising similarity of this concept as well as the manner of presentation led to the description of DOSY NMR spectroscopy as „NMR chromatography“. Although this technique is also extraordinarily well-suited for applications in organometallic and inorganic chemistry in solution, it has attracted little attention.[4] Herein we demonstrate the usefulness of DOSY NMR spectroscopy by presenting a new application.

In the course of the present investigation, DOSY NMR spectroscopy has been successfully applied for the first time to determine the molecularity of an intermediate in the reaction of $[Cp_2Zr(Cl)H]$ (**1**) with CO_2 (Scheme 1). Recently, we succeeded in elucidating the long-standing postulated mechanism of this reaction by low-temperature NMR spectroscopy studies.[5, 6] We were able to observe in situ both the formiato complex **2**, which is formed by insertion of CO_2 into the Zr–H bond of the hydride, and the binuclear diolato complex **3**, which results from reaction with another equivalent of **1**. Although complex **2** was synthesized in an earlier study,[7] the existence of the extremely unstable complex **3** was previously only postulated. However, all our attempts to structurally characterize this species by methods other than ^1H and ^{13}C NMR spectroscopy or to isolate it for a determination of the structure by X-ray structure analysis, failed. Since it was not possible to prove convincingly by spectroscopy that the observed intermediate is a binuclear zirconium compound, we tried to extract additional structural information by means of DOSY NMR spectroscopy.



Scheme 1. The investigated reaction of $[Cp_2Zr(Cl)H]$ (**1**) with CO_2.

Prior to studies aimed to characterize intermediate **3**, we examined the suitability of DOSY NMR spectroscopy for such a system by examining the behavior of two model compounds. With the purpose of determining whether the differences between the mono- and binuclear species lead to a resolution in the diffusion dimension in DOSY spectra, we chose a mixture consisting of the binuclear complex **4**, which has a molecular mass that is almost identical to that of the proposed intermediate, and the mononuclear complex **6**. The ^{13}C



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INEPT DOSY spectrum of this mixture (Figure 1)[8, 9] shows a clear resolution of the Cp signals of the two complexes in the diffusion dimension. As expected, the „heavier“, binuclear compound has the smaller self-diffusion coefficient, which allows the definite assignment of the signals to the corresponding complexes.

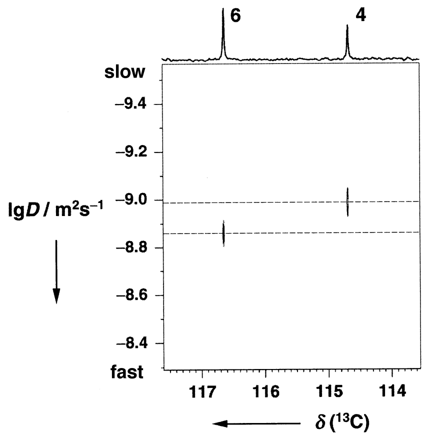

Figure 1. Section of the ^{13}C INEPT DOSY spectrum of a mixture of **4** and **6** in [D$_8$]THF (Cp region), measured at 27 °C.

The relationship between diffusion coefficients and structural properties of molecules is based on the dependence of the self-diffusion coefficients on friction factors, which, in turn, depend on molecular size and the viscosity of the solution. If a molecule is considered as a sphere, the diffusion can be described by the Stokes–Einstein equation (1),[10] in which T is the absolute temperature (in K) and k_B is the

$$D = k_B T/(6\pi\eta r_H) \qquad (1)$$

Boltzmann constant, whereas the viscosity of the solvent is given by η and the hydrodynamic radius of a molecule by r_H. If r_H and η are known, the self-diffusion coefficient can be estimated from this equation. It is known from earlier studies that self-diffusion coefficients that were calculated by using radii obtained from X-ray data correlate well with experimental values.[4b] Therefore, the calculation of self-diffusion coefficients for **4** and **6** was performed by employing radii extracted from X-ray analysis data,[11] which yielded values that are in excellent agreement with the experimental results (Table 1).

Table 1. Experimental and calculated diffusion coefficients and hydrodynamic radii of the studied zirconium complexes.

	Experimental		Calculated	
	r_H [Å][c]	D [m^{2}s^{-1}]	r_H [Å]	D [m^{2}s^{-1}][c]
6	3.0	1.61×10^{-9}	3.1[a]	1.55×10^{-9}
4	3.7	1.31×10^{-9}	3.9[a]	1.30×10^{-9}
5	4.2	1.55×10^{-10}	3.6[b]	1.81×10^{-10}
3	6.3	1.05×10^{-10}	6.1[b]	1.07×10^{-10}

[a] Calculated from X-ray structure data under the assumption of a spherical shape.[11] [b] Calculated from the minimized gas-phase structure (PM3).[13] [c] Calculated by using the Stokes–Einstein equation. For the viscosity the values for THF were used at the corresponding temperatures (T = 25 °C (**6** and **7**), T = –78 °C (**3** and **5**); the value 2.27 cP, at –78 °C, was extrapolated from literature data).[16]

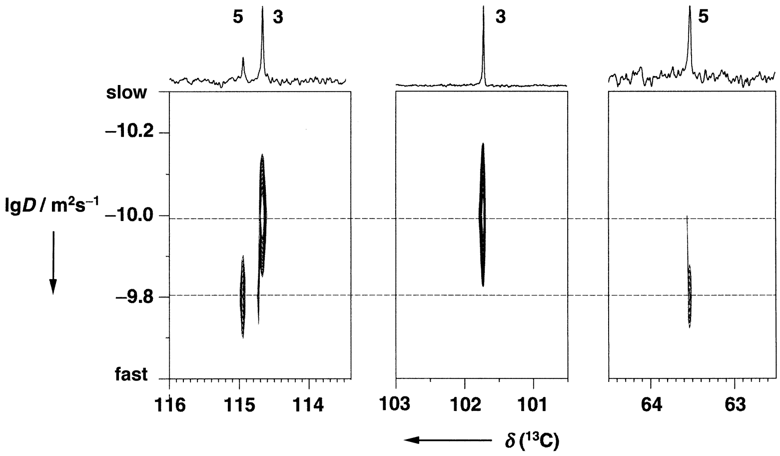

Figure 2. ^{13}C INEPT DOSY spectrum obtained during the reaction of **1** with ^{13}CO$_2$ at –78 °C in [D$_8$]THF. The sections show the signals of **3** (δ = 114.6 (Cp) and 101.7 (CH$_2$)) and **5** (δ = 114.9 (Cp) and 63.5 (OCH$_3$)).

Following these initial investigations, the reaction of ^{13}C-labeled CO$_2$ with **1** was performed at –35 °C, as described elsewhere.[6] As soon as the signal of **3** reached a sufficient intensity,[12] the reaction was stopped by cooling to –78 °C and ^{13}C INEPT DOSY NMR spectra were recorded at this temperature (Figure 2).[9] The signals assigned to compounds **3** and **5** are depicted. As in the model system investigated before, a clear separation was achieved in the diffusion dimension, allowing for the first time an assignment of the Cp signal of **3**, which was not possible from ^{13}C NMR spectra.[13] Signals of Cp and methoxy carbon atoms in **5** possess the same self-diffusion coefficient, which confirms their origin from the same molecule. As was expected for a binuclear compound, the self-diffusion coefficient of intermediate **3**, which was extracted from the signals of Cp and CH$_2$ carbon atoms, is smaller. Like in the first case, the experimental data were compared with the estimated self-diffusion coefficients, which were calculated from the Stokes–Einstein equation. For **3** and **5**, no X-ray data were available; therefore, radii from minimized gas-phase structures were used.[14] This approach has been previously described for organolithium compounds.[4a] Again, the agreement between the experimental and calculated ratio of the self-diffusion coefficients of **3** and **5** is good, especially considering the simplifying models used (Table 1).

With this study it was demonstrated for the first time that DOSY NMR spectroscopy can be applied as a new tool for the characterization of reactive intermediates in organometallic reactions. The straightforward accessibility of this technique, which—if a gradient unit is present—requires no additional equipment, and the simple estimation of self-diffusion coefficients, which is possible without an extended demand on calculations, provide a new tool for the investigation of molecular properties of unstable compounds in solution.

Experimental Section

NMR experiments were performed on a Bruker DRX 400 spectrometer (9.4 T), equipped with a z gradient probe head capable of producing gradients with a strength of 56 G cm^{-1}. All spectra were acquired with a 5 mm TBI probehead. For the DOSY experiments the BPPLED[3, 15] pulse sequence or a modification of the INEPT–DOSY sequence were used.[8] The pulse-field gradients (g) were incremented in 32 steps from 2 % up to 95 % of the maximum gradient strength in a linear ramp. Gradient lengths δ between 1.5 and 2.0 ms, diffusion times Δ between 90 and 200 ms, and an eddy current delay (T_e) of 5 ms were employed. After Fourier transformation and baseline correction, the diffusion dimension was processed by using the Bruker xwinnmr package (version 3.0) and the diffusion values were read directly from the spectra.

For the experiment with a mixture of **4** and **6**, a solution of **4** (0.013 mmol) and **6** (0.041 mmol) in [D$_8$]THF (400 μL) was prepared. For the monitoring of the reaction of **1** with $^{13}CO_2$, **1** (0.050 mmol) and [D$_8$]THF (350 μL) were placed in a pressure-stable NMR tube (Wilmad 522-PP), degassed, and then frozen. $^{13}CO_2$ (0.060 mmol) was condensed in vacuo on top of the frozen mixture. The tube was sealed and transferred into the precooled magnet.

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[9] The ^{13}C INEPT experiment was chosen because during the reaction of [Cp$_2$Zr(Cl)H] with CO$_2$ the Cp region of the ^{1}H NMR spectrum shows a strong overlap of signals, which creates difficulties for processing ^{1}H DOSY spectra. The INEPT spectrum allows not only an easier assignment of signals due to the broader dispersion of carbon chemical shifts but has also the advantage of higher sensitivity than ^{13}C DOSY and an easier set-up because in the experiment the diffusion encoding occurs in the proton frequency.

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[12] Signal-to-noise ratio in the ^{13}C INEPT spectrum: 20:1.

[13] The signal at $\delta = 114.6$ arises from the overlapping Cp signals of the complexes **3** and **4**, which due to their almost identical molecular weight cannot be resolved in the diffusion dimension. However, the assignment of the Cp signal of **3** is clear since the CH$_2$ signal can be used as a reference for the self-diffusion coefficient.

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The First Highly Efficient Asymmetric Synthesis of α-Substituted Methyl Sulfonates[**]

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Dedicated to Professor Dieter Hoppe on the occasion of his 60th birthday

A number of α-substituted sulfonic acids with interesting pharmacological properties is known, and numerous compounds of this class have been isolated, synthesized, and tested for their biological activity. For instance, 6-gingesulfonic acid, which shows anti-ulcer activity, was isolated from *Zingiberis Rhizoma*.[1] Several α-substituted sulfonic acids, which are known as semisynthetic β-lactam antibiotics, have been examined with regard to their antibacterial activity.[2] Cefsulodin, a representative compound of the semisynthetic cephalosporins, shows potent in vivo antipseudomonal activity against *Pseudomonas aeruginosa*.[3] Other compounds such as α-phosphonosulfonic acid derivatives are known as potent squalene synthase inhibitors.[4]

Enantiopure α-substituted sulfonic acids are also employed in synthesis as strongly acidic resolving agents, especially for free neutral amino acids. For example, (S)-(−)-1-phenylethanesulfonic acid ((−)-PES) was found to be an efficient resolving agent for the optical resolution of DL-leucine.[5] The related (+)-2-(2,3,4-trichlorophenyl)ethanesulfonic acid ((+)-TCPES) has been used as resolving agent for antifungal sulfoximines.[6]

Considering their synthesis, enantiopure α-substituted sulfonic acids are commonly obtained from the corresponding racemates by resolution techniques with chiral amines.[7] To the best of our knowledge, only two stereoselective methods are known for the synthesis of optically active α-substituted sulfonic acids. Corey et al. reported the conversion of enantiopure (R)-1-phenylethanol to ((−)-PES) in a multistep procedure.[8] For the synthesis of a squalene synthase inhibitor, the asymmetric α-alkylation of an α-phosphonosulfonate bearing the chirality information within the phosphono moiety was employed. To date this is the only known auxiliary-controlled method for the asymmetric synthesis of α-substituted sulfonates.[9]

In contrast, no method is known to perform asymmetric α-alkylations of metalated sulfonic esters prepared from enantiopure alcohols as auxiliaries. A serious problem during metalation of sulfonic esters could be β-elimination under these basic conditions.

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