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Gas Bubbles in the NMR tube: an Easy Way to Investigate Reactions with Gases in the Liquid Phase

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An easily accessible device for the study of reactions with gases in the liquid phase, consisting of a 10 mm NMR tube with a gas inlet, is presented. This arrangement serves for reaction monitoring and mechanistic studies by acquiring NMR spectra (^{1}H, ^{13}C, ^{31}P) with a resolution that allows one to observe and characterize intermediates that cannot be isolated as pure substances. The quantity of the gas to be consumed is not limited. Examples from organometallic chemistry are presented: the formation of a zirconacyclopentene from a zirconium–alkyne complex and ethylene and investigations on rhodium-catalysed olefin hydrogenation. The qualitative and quantitative evaluation of the measurements and application to reaction kinetics are discussed. An uptake of 0.1 ml of gas per minute at normal pressure (isobaric) is possible without a marked influence of diffusion (stationary conditions). © **1997 John Wiley & Sons, Ltd.**

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INTRODUCTION

To use spectroscopic methods for the study of chemical reactions is common practice because of the advantage of acquiring structural, thermodynamic and kinetic information from the same experiment. We were looking for a method suitable for monitoring reactions with gases 'on-line' and allowing the results to be analysed in a qualitative and (in favourable cases) also quantitative way. NMR spectroscopy seemed to be the most promising method, as it has already been used even to study reactions with gases.[1,2] We now report an accessible device that allows one to carry out these reactions in an NMR tube while taking spectra simultaneously. Examples from organometallic chemistry (stoichiometric and catalytic reactions) are presented.

NMR SET-UP

The reaction cell is a 10 mm NMR tube, equipped with a small PTFE tube as inlet for the reactant gas and a second small opening in the stopper for gas outlet (Fig. 1). The tube is fitted to capillaries made of stainless steel, which serve both to transport the gas and to pass the filled tube through the magnet bore into the probe head. The gas bubbles into the solution, and at the same time it is possible to record spectra without a dramatic loss of resolution. Measurements at different temperatures may be performed as with any other NMR tube.

Gas bubbles generally degrade the homogeneity of the magnetic field, because their magnetic susceptibility differs from that of the surrounding liquid phase. This

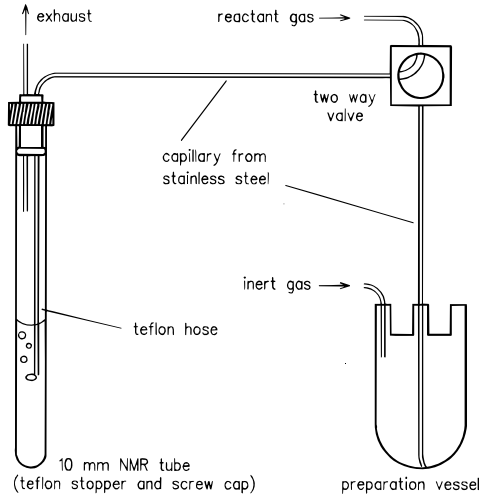

Figure 1. Experimental set-up to investigate reactions with gases in liquid phase by NMR spectroscopy.

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results in slight changes to the local magnetic fields and therefore a distribution of chemical shifts for otherwise equivalent nuclei, i.e. undesired line broadening. We tried to overcome this problem by adjusting the length of the PTFE tube so that it ends just above the receiver coils of the probe, so the bubbles do not enter the region where the actual measurement is made. A sample of triphenylphosphane (methanol solution) in this arrangement gave a linewidth of 5 Hz ($^{31}P\{^1H\}$ NMR) without gas bubbles, and this remained unaffected even at a gas flow rate of 10 ml min^{-1} (the diameter of the PTFE tube is 1 mm and that of the produced bubbles is about 2 mm). In proton NMR, a linewidth of 2 Hz or less is achievable.

If air-sensitive compounds have to be examined, it is not always feasible to prepare the solution in the NMR tube. For such cases, a Schlenk tube is placed in front of the inlet capillary, where the preparation can be carried out or to which the solution can be readily transferred. This preparation vessel can be situated remote from the magnet, the distance being limited only by the length of the capillary. A mercury valve or a similar device must then be fitted to the end of the exhaust tube. The solution is transferred from the vessel to the NMR tube by inert gas pressure, and the reaction is started when the two-way valve is switched from the inert to the reactant gas.

The complete arrangement, as shown in Fig. 1, is airtight; it can be evacuated and purged with an inert gas. Handling of organometallic compounds is thus possible without problems. Slight pressure, up to 3 bar, may also be applied (caution!).

The following applications will not be discussed in detail here with respect to their chemical background and consequences. Instead, we will focus on the measurements themselves and their evaluation.

APPLICATIONS AND RESULTS

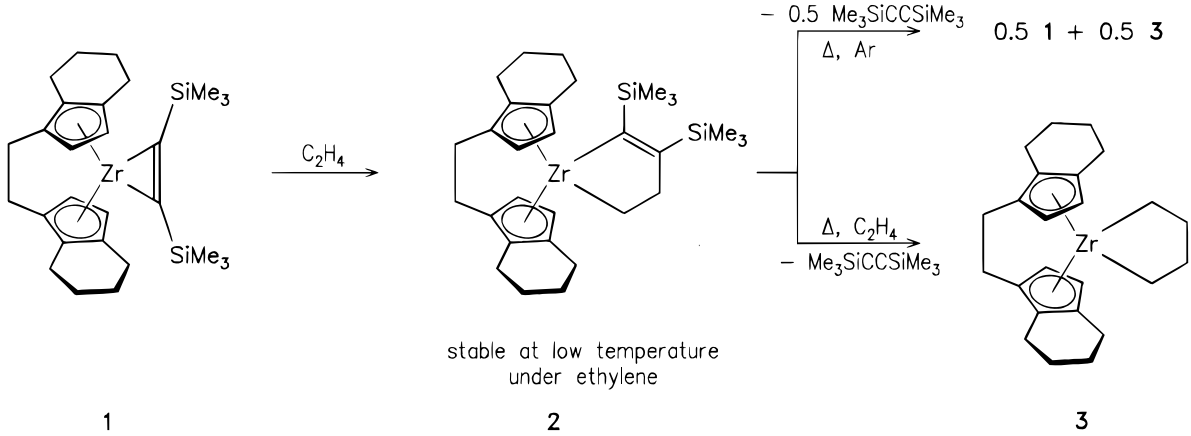
Example 1. Addition of ethylene to a zirconocene–alkyne complex

The first example[3] is an uncommon reaction: the replacement of an alkyne ligand by an alkene in a transition metal complex. This is a stepwise reaction, and by means of the described experimental set-up it was possible to detect the primary product, a zirconacyclopentene (**2**), which results from addition of 1 equiv. of ethylene to the zirconocene–alkyne complex **1** (Scheme 1). This intermediate is only stable at low temperature under an ethylene atmosphere, and its characterization by ^1H and ^{13}C NMR spectroscopy (standard measurement conditions) is straightforward. It is also possible to show the reversibility of this reaction: if the ethylene atmosphere is removed by purging the system with an argon stream, the resonances of the alkyne complex **1** can be detected, together with those of complex **3** and the alkyne.

When the temperature is raised, the alkyne is replaced by a second ethylene molecule to form a zirconacyclopentane (**3**). As stated above, this is an uncommon reaction sequence, because alkene ligands are usually substituted by alkynes.[4] Integration of the proton NMR spectra further shows that the formation of the zirconacyclopentane is quantitative in tetrahydrofuran solution, but occurs with only 75% yield in toluene.

Example 2. Rhodium-catalysed hydrogenation of norbornadiene (nbd) and 1,5-cyclooctadiene (cod)

Frequently, homogeneously catalysed reactions show induction periods where the reaction rate is lower than at a later stage. In most cases, the generation of the catalytically active species from the employed precatalyst (the so-called 'activation' of the catalyst) is responsible for this activation period. Our interest is directed toward the rhodium-catalysed hydrogenation of alkenes.[5,6] Usually, such reactions are followed by sampling small quantities from the solution which are subsequently analysed by chromatographic methods, but this method cannot tell anything about the transition metal species present in the reaction. Further complications arise from the difficulty of completely stopping the reaction at the time the sample is taken, so that no further change in its composition occurs. It therefore seemed an attractive goal to perform these reactions in the NMR tube. The complexes present during the reaction could be detected by ^{31}P NMR spectroscopy, and the progress of the reaction, the degree of conversion from the substrates to the products



Scheme 1. Formation of zirconacycles.

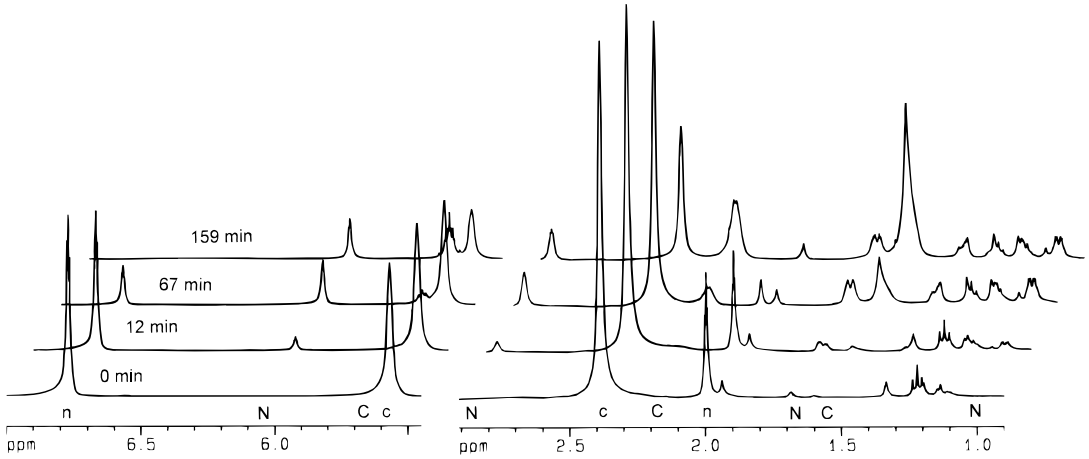
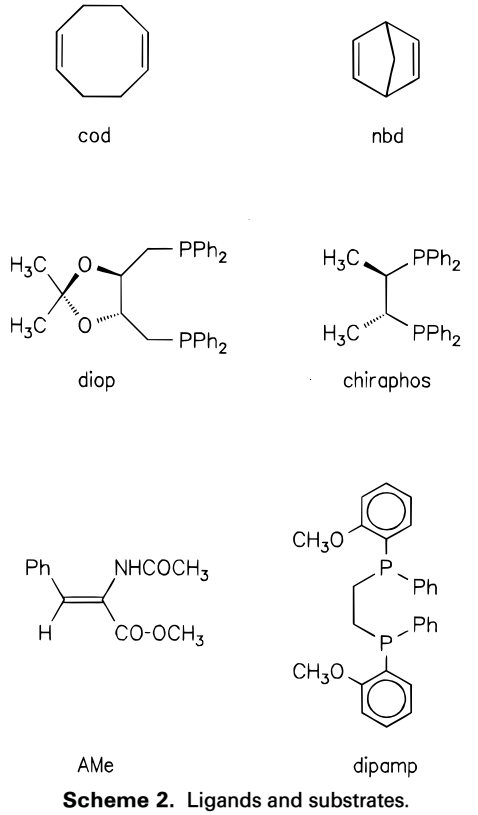


Figure 2. Cuts of the proton spectra taken during the hydrogenation reaction in Example 2. Labelled resonances were used for quantitative evalutation (n, norbornadiene; N, norbornene; c, 1,5-cyclooctadiene; C, cyclooctene). Unlabelled resonances arise primarily from the rhodium complexes.

and the nature of the latter can be examined by ^{1}H NMR spectroscopy.

The rhodium catalysts used for homogeneous hydrogenation reactions are usually prepared as dialkene complexes because they can be handled conveniently. The most commonly used dienes are *cis,cis*-1,5-cyclooctadiene (cod) and norbornadiene (nbd) (Scheme 2). The catalytically active species is generated by reaction with molecular hydrogen ('activation'), and the diene is hydrogenated to yield the mono-alkene. Recently, we showed that in general the norbornadiene complexes $[(P_2)Rh(nbd)]BF_4$ (P_2 = chelating diphosphane) are thermodynamically more stable and react much faster with hydrogen than the corresponding cod complexes.[6] We decided to examine the hydrogenation reaction of the two dienes in our experimental arrangement.



Scheme 2. Ligands and substrates.

A solution of 0.01 mmol of [(diop)Rh(methanol)$_2$]BF_4 and a 50-fold excess of each of the dienes nbd and cod in methanol was transferred to the reaction tube. ^{1}H and ^{31}P NMR spectra were taken as references, and subsequently a slow stream of hydrogen was passed through the solution. Then proton and phosphorus spectra were taken until the dienes had been converted into the monoalkenes (total reaction time about 3 h). Representative examples of the spectra are shown in Figs 2 and 3.

At first, the signals of the free dienes and the phosphorus resonance of the complex $[(diop)Rh(nbd)]BF_4$ were found. Owing to its greater stability, almost exclusively the norbornadiene complex was present. Upon starting the hydrogen stream, its amount rapidly decreased, and simultaneously the resonances of the cyclooctadiene complex grew. The sum, however, remained constant (this can be nicely seen if some triphenylphosphane oxide is added to the solution, which serves as a standard for scaling the ^{31}P NMR integrals). In the proton spectra the conversion of the dienes to the monoenes was clearly visible.

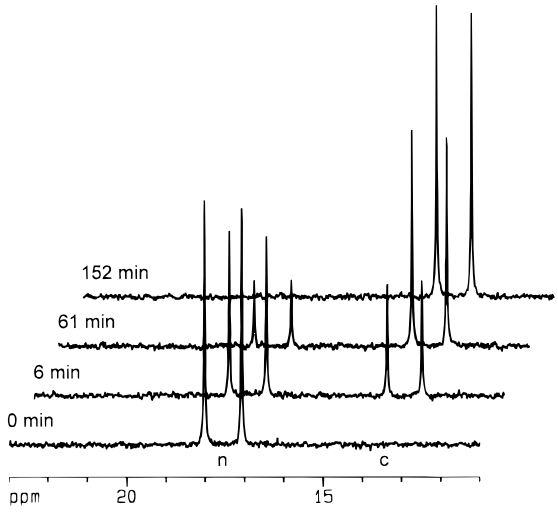


Figure 3. ^{31}P NMR spectra taken during the hydrogenation reaction in Example 2 {n, $[(diop)Rh(nbd)]BF_4$; c, $[(diop)Rh(cod)]BF_4$}. The n : c molar ratios are ∞, 1.5, 0.3 and 0.

When the hydrogenation was continued after consumption of the dienes, reduction of the monoalkenes to the saturated hydrocarbons occurred (e.g., the cyclooctane singlet at δ 1.55 ppm was prominent in the proton spectra).

Example 3. Rhodium-catalysed hydrogenation of (*Z*)-methyl-2-(*N*-acetylamino)cinnamate (AMe)

As a further example, we chose the asymmetric hydrogenation of (*Z*)-methyl-2-(*N*-acetylamino)cinnamate (AMe) with [(dipamp)Rh(cod)]BF_4 as precatalyst. The procedure was the same as in the second example (0.01 mmol of Rh complex, 5.0 mmol of AMe, 5 ml of methanol, monitoring by ^1H and ^{31}P NMR spectroscopy, see Figs 4 and 5). On exposing the mixture to hydrogen, the amount of the cyclooctadiene complex decreased, and a new species, the substrate complex [(dipamp)Rh(AMe)]BF_4, appeared. Only one of the two diastereomeric forms, the so-called 'major' complex, could be found, as the 'minor' complex has an equilibrium concentration of only few per cent[7,8] and was not detected under the measurement conditions chosen.

While the hydrogenation was in progress, as could be seen by the increasing amount of *N*-acetylphenylalanine methyl ester, there was still a reasonable amount of unactivated precatalyst present. The substrate hydrogenation occurred in parallel with the diene hydrogenation, so a lot of the metal centres were still inaccessible to the substrate. This is the reason for the macroscopically observable induction period.[5] Even after complete conversion of the 500-fold excess of the substrate, when the solvent complex [(dipamp)Rh(methanol)$_2$]BF_4 became visible, half of the rhodium was still coordinated by cyclooctadiene and had therefore been unproductive in the desired catalytic reaction (for this reason, Landis and Halpern[8] used solvent complexes instead of diene complexes in their mechanistic studies on asymmetric hydrogenation).

Such an insight into the details of the reaction pathway provides valuable information with respect to the design of the experiments in order to make the most advantageous use of the expensive catalyst. Especially if a catalyst is prepared '*in situ*' from a chiral diphosphane and [Rh(cod)$_2$]BF_4, one cannot always be sure that it is formed in the best and most effective way. Our device allows one to acquire this knowledge quickly by a simple NMR measurement.

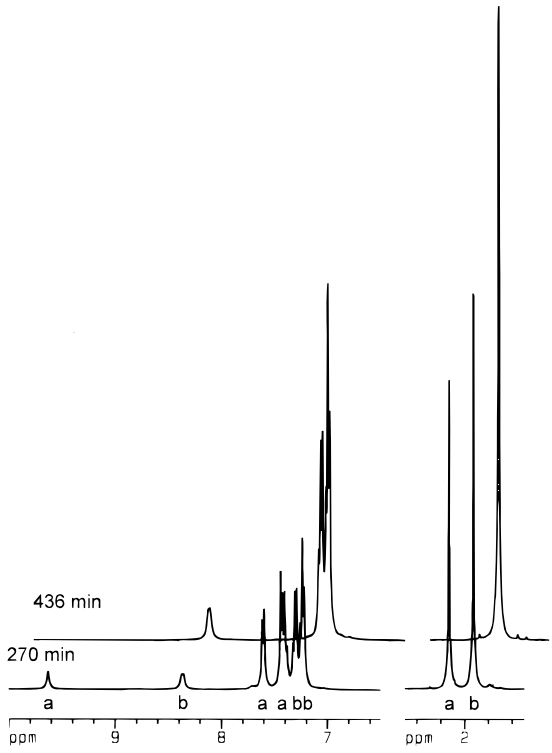


Figure 4. Cuts of the proton spectra taken during the hydrogenation reaction in Example 3. The methyl resonances were used for quantitative evalutation (a, substrate AMe; b, hydrogenated product).

Quantitative evaluation of the results

A complete analysis of the investigated system requires not only a qualitative but also a quantitative treatment of the spectra. A qualitative evaluation is possible without problems. A quantitative discussion, as for a kinetic analysis, however, requires the data to be representative for the system.

As described above, the gas bubbles only into the upper part of the solution under investigation, to avoid distortion of the field homogeneity. Owing to this construction, mixing of the liquid is not very effective, and we have to consider concentration gradients of the dis-

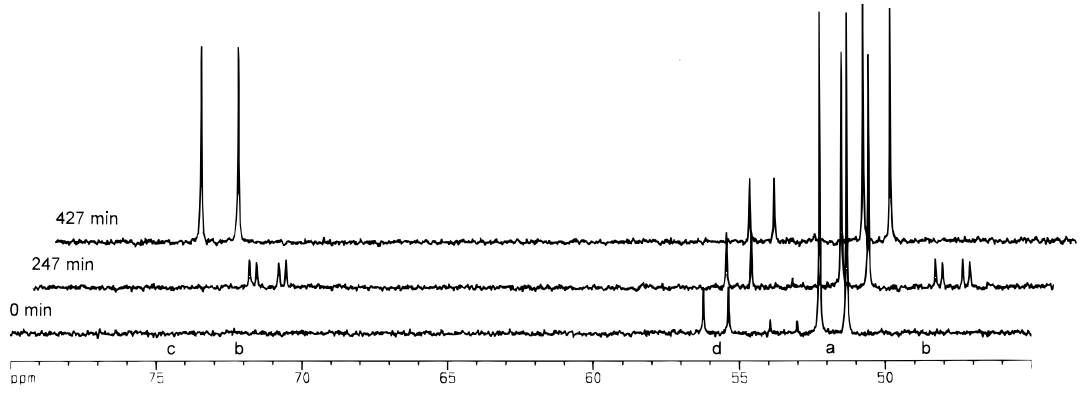


Figure 5. ^{31}P NMR spectra taken during the hydrogenation reaction in Example 3 {a, [(dipamp)Rh(cod)]BF_4; b, [(dipamp)Rh(AMe)]BF_4; c, [(dipamp)Rh(methanol)$_2$]BF_4; d, impurity, presumably [(dipamp)$_2$Rh]BF_4}.

solved gas and also of reactants and products. If diffusion is the rate-determining step in the reaction sequence, we might run into the problem that what we observe in the bottom part of the tube is not representative for the system under kinetically controlled conditions and therefore unsuitable for further analysis.

To check this, we carried out a hydrogenation reaction in the NMR tube and in a specially designed hydrogenation device, where an uptake of up to 10 ml of gas per minute is possible without a marked influence of diffusion.[5,9] *(Z)*-2-(Acetylamino)cinnamic acid was hydrogenated by means of [(chiraphos)Rh(nbd)]BF_4 as precatalyst, a reaction with a similar rate to the examples described above (the conversion of 1 mmol of substrate during 180 min requires a hydrogen consumption of 0.12 ml min^{-1}; Example 2: conversion of 0.61 mmol of the dienes during 100 min requires 0.14 ml min^{-1}). We found the same reaction progress in the NMR tube and in the hydrogenation apparatus (Fig. 6), and we found the same chemical yield and chiral induction in both cases. From this experiment it is clear that such slow reactions can be monitored under practically stationary conditions, the influence of diffusion still being negligible.

A simple quantitative evaluation for Example 2 is shown in Fig. 7. The dialkene/monoalkene molar ratio was determined by integration of the proton NMR spectra (Fig. 2) and used to calculate the degree of conversion, which was then plotted against the reaction time. One immediately sees that the conversion rate for norbornadiene is at least twice that for cyclooctadiene.

The ^{31}P NMR spectra provide the ratio between the two diene complexes. This should be primarily determined by the ratio of the free dienes. The dramatic change of the complex ratio (Fig. 3) is caused by the faster hydrogenation of the norbornadiene, and therefore the amount of the cyclooctadiene complex increases. If we manage to determine a reliable value for the ratio of the formation constants, we will be able to compare the actual value (determined from the ^{31}P NMR spectra) to the expected (calculated from the ratio of the dienes, which is known from the ^{1}H NMR spectra at any point of the reaction). A difference between the experimental and calculated data would indicate that the diene complexes are not in thermodynamic equilibrium under hydrogenation conditions. In this way it should be possible to prove disturbed pre-equilibria, as already suggested.[6]

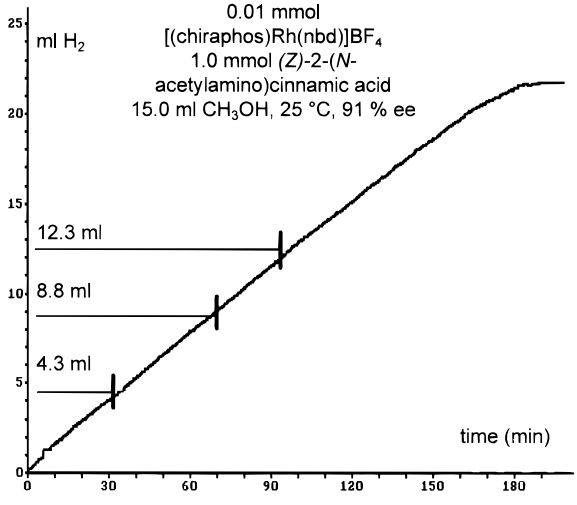


Figure 6. Hydrogen consumption during a rhodium-catalysed hydrogenation reaction. The experiment was conducted in a special hydrogenation apparatus with automatic registration of the gas uptake. The horizontal bars represent the same reaction carried out in the NMR tube in 5 ml of solvent (at the times given samples were taken, the substrate/product ratio was determined by GC and the corresponding H_2 consumption was calculated).

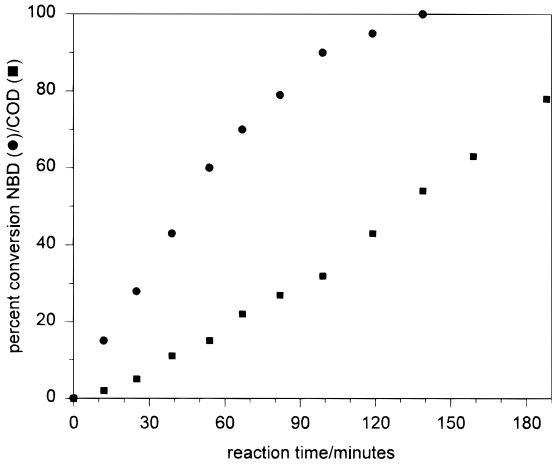


Figure 7. Degree of conversion (Example 2) of (●) norbornadiene to norbornene and (■) cyclooctadiene to cyclooctene as a function of time.

CONCLUSION AND FURTHER APPLICATIONS

Our work clearly demonstrates that it is possible to carry out reactions with gases in the liquid phase within an NMR tube and to monitor their progress by recording spectra simultaneously (^{1}H, ^{13}C and ^{31}P NMR experiments were performed). The scale of the reaction is not limited by the gas volume, as this reactant is supplied continuously. This is a major difference from the method of using pressurized samples, introduced by Roe and co-workers.[2,10] A qualitative evaluation is always possible, and quantitative determinations can also be performed, provided the reaction rate does not exceed a limit given by the diffusion rate in the solution. This should be checked by an independent experiment. If no quantitative analysis is necessary, fast reactions might be retarded by mixing the reactant gas with an inert component. Another way to deal with faster reactions is to use a very thin gas inlet ending at the bottom of the NMR tube (Bargon *et al.* used such an arrangement in their hydrogenation studies,[1] although they did not apply a continuous gas stream). This would help to avoid concentration and temperature gradients by mixing of the liquid, and the fine gas bubbles do not affect the linewidth in the ^{31}P NMR spectra (we achieved without any effort 6 Hz for Ph_3P in methanol). Of course, loss of resolution in the proton spectra is pronounced, but there are problems where this can be tolerated.

Finally, stepwise conversions can easily be followed by proper adjustment of the reaction conditions. All these experiments require no special equipment, the

only necessary device being a 10 mm tube fitted with appropriate gas inlet and outlet.

The application of the apparatus described is, of course, not restricted to hydrogen or ethylene; any diamagnetic gaseous reactant may be introduced. Work concerning reactions with acetylene or carbon monoxide is in progress, and we hope to gain more insight into the mechanisms of organometallic reactions, e.g. the acetylene polymerization.

EXPERIMENTAL

The substances used were commercially availabe or prepared by published procedures. For NMR spectroscopy, a Bruker ARX 400 instrument ($B_0 = 9.4$ T) with a standard 10 mm broadband probe head was used. All experiments were performed with strict exclusion of air.

Observation of the zirconacyclopentene.

Solutions of the alkyne complex **1**[11] in THF-d_8 or toluene-d_8 were transferred to the NMR tube and cooled to 203 K. A gentle stream of ethylene was passed through the solution, and within a few minutes complete conversion to the zirconacyclopentene **2** had occurred (checked by ^{1}H and ^{13}C NMR spectroscopy, characteristic resonances for the metallacyclic carbon atoms: δ 222.8, 174.3, 47.7 and 31.8 ppm in toluene-d_8). Above 240 K, reaction with a second equivalent of ethylene leads to the formation of the zirconacyclopentane **3**; characteristic resonances for the metallacyclic carbon atoms: δ 45.4 and 28.1 ppm in toluene-d_8. Details of the characterization and NMR behaviour of these complexes are available.[3]

General procedure for hydrogenations

A solution of 0.01 mmol of the precatalyst–rhodium complex and an excess of the substrate in 5 ml of methanol–methanol-d_4 (1:1, v/v) was transferred from the preparation flask to the NMR tube by a slow stream of argon. A ^{1}H and a ^{31}P NMR spectrum were taken as reference, and then the reaction was started by switching the gas supply to hydrogen (gas flow rate *ca.* 10–15 ml min^{-1}; at this rate the loss of solvent is not critical).

The ^{1}H NMR spectra were acquired with 30° pulses. To make better use of the receiver's dynamic range, the solvent's methyl resonance was suppressed by presaturation in some cases. The ^{31}P NMR spectra were acquired with the 'inverse-gated' decoupling scheme (1 s cycle, half of each acquisition–decoupling, the remainder relaxation) and the appropriate 'Ernst angle' of about 70° to achieve a maximum signal-to-noise ratio. Since the spin–lattice relaxation times of the involved complexes are similar (for representative examples, values between 0.8 and 1 s were estimated), only a minor error should be introduced by this method. For evaluation on the time-scale, the 'midpoint' of a measurement was taken as the time represented by the spectrum.

Hydrogenation of COD and NBD

A solution of 7.8 mg (0.01 mmol of [(diop)Rh(nbd)]BF_4 was prehydrogenated at atmospheric H_2 pressure for about 15 min[5] to remove the stoichiometric amount of diene. The resulting solvent complex was then treated with a mixture of 55 µl (0.5 mmol) of cod and 55 µl (0.5 mmol) of nbd. During hydrogenation, ^{1}H and ^{31}P NMR spectra were taken in alternating order (2.5 and 10 min measuring times, respectively). The reaction time was 3 h.

Hydrogenation of AMe

The solution was prepared from 7.6 mg (0.01 mmol) of [(dipamp)Rh(cod)]BF_4 and 1.1 g (5.0 mmol) of AMe. During hydrogenation, ^{1}H and ^{31}P NMR spectra were taken in alternating order (2 and 16 min measuring times, respectively). The reaction time was 7 h (total conversion of the substrate).

Acknowledgements

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