Investigating the Kinetics of Homogeneous Hydrogenation Reactions Using PHIP NMR Spectroscopy

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Abstract: The combination of parahydrogen induced polarization (PHIP), kinetics and NMR spectroscopy yields a powerful analytical tool: *quantitative* in situ NMR spectroscopy. Two versions of PHIP NMR experiments are presented to investigate the kinetics of homogeneously catalyzed hydrogenations. The first method, an experimental variation of the ROCHESTER experiment (ROCHESTER = rates of catalytic hydrogenation estimated spectroscopically through enhanced resonances), allows one to determine the hydrogenation rate independently of relaxation and other sources of decay, e.g., subsequent chemical reaction steps. The second method named DYPAS (dynamic PASADENA spectroscopy) uses a variable delay between the end of the hydrogen-addition period and the detection pulse. In principle, all processes during this delay can be described by a set of coupled differential equations. Their solutions can be fitted to the experimental data by a least-squares optimization of the involved kinetic parameters. The DYPAS method can be used to determine the rates of formation as well as the rates of decomposition of stable intermediates and has been applied to the case of freshly hydrogenated and still catalyst-attached product molecules. We provide kinetic data for the formation and decomposition of these unusual product−catalyst complexes during the hydrogenation of different styrene derivatives with a cationic Rh^I catalyst containing a chelating diphosphine ligand. The kinetic measurements indicate that the rate of formation of the catalyst-attached product increases whereas the rate constant of its decomposition diminishes if the para position of the arene ring of styrene carries an electron-donating substituent. In the case of *p*-aminostyrene as the substrate, the detachment step turned out to be rate limiting for the catalytic cycle. With certain substituted styrenes and cationic Rh^I complexes containing *chiral* chelating diphosphine ligands, two geometrically different (diastereomeric) product−catalyst adducts can be discriminated via PHIP NMR spectroscopy. The associated alternative reaction pathways have been analyzed by applying the DYPAS method, which can also be used to investigate the mechanism of an asymmetric hydrogenation.

Introduction

In consequence of the importance for the synthesis of pharmacologically relevant substances, catalytic homogeneous hydrogenations using transition metal complexes are still a field of considerable interest.[1,2] For example, cationic Rh^I complexes containing bidentate phosphine ligands have developed into an important class of catalysts that enable regio- as well as stereoselective hydrogenations.[3−6] Looking at the methodical progress achieved during the past decade, PHIP NMR spectroscopy (PHIP = parahydrogen induced polarization) has developed into a powerful tool to investigate these reactions.[7−10] The main advantage of the method is the associated strong signal enhancement (in the order of 10^3) that qualifies it as a powerful and versatile in situ method. As a prerequisite for the PHIP effect to occur, both former parahydrogen nuclei must be *J*-coupled in the resulting molecule of interest. The PHIP effect allows one to monitor the fate of the two former parahydrogen nuclei during the reaction via spin dynamics.[11,12] Using this in situ method, the hydrogenation of styrene derivatives with cationic Rh^I catalysts has been shown to be partially reversible.[13] In other cases, hydrogen-containing intermediates were detected[14] and reaction products of parahydrogen and organometallic compounds were characterized.[15,16]

In previous applications of PHIP NMR spectroscopy, the main emphasis has been on *qualitative* investigations of homoge-

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neously catalyzed hydrogenation reactions. For a more detailed understanding of catalytic cycles, however, it is important to know not only the structure of possible intermediates but also the rates of their formation and decomposition. Kinetic methods may suggest indirectly the occurrence of certain reaction steps, whereas the short lifetime of many intermediates frequently prevents their direct detection.[17] Because kinetic methods have already proved to be essential for the understanding of homogeneous catalysis, it is highly attractive to combine them with the PHIP effect for *quantitative* in situ investigations. So far, only two experiments have been proposed to determine kinetic parameters via PHIP NMR spectroscopy: One approach combines a continuous-flow NMR technique and the PHIP effect to measure the intensity of polarization under steady-state conditions.[18,19] Accordingly, during the hydrogenation of 1,4-diphenylbuta-1,3-diyne with $[Rh(PPh_3)_2(nbd)]PF_6$[20] as the catalyst precursor, the rates of several reaction steps were determined. This technique provides detailed kinetic information, but it requires a special continuous-flow probehead and the possibility of varying the pressure of H_2 over a wide range. According to the second approach, the rate of product formation can be measured via monitoring the decay of the PHIP intensity that frequently follows first-order kinetics if certain mechanistic and experimental conditions are met. As an example, the hydrogenation of ethyl (*Z*)-α-acetamidocinnamate with [Rh(chiraphos)(nbd)]BF_4 in CD_3OD has been investigated in this fashion.[21]

We propose an analogous experiment that is also based upon satisfying pseudo-first-order conditions during hydrogenation reactions. However, our experimental setup uses a spectrometer-controlled hydrogen addition to the reactive solution, thereby bypassing the problem of a relayed phase transfer of hydrogen from the gas phase into the solution which otherwise prevents the determination of an accurate hydrogenation rate. In addition, the use of conventional NMR equipment provides the possibility of controlling the temperature. Furthermore, the theoretical framework of this experiment provided by R. Eisenberg et al.[21] has been generalized.

Recently, we described the observation of still catalyst-attached product molecules during the hydrogenation of styrene derivatives with cationic Rh^I catalysts containing chelating diphosphine ligands.[22] The detection of this special type of intermediate with the help of in situ PHIP NMR spectroscopy revealed that the rate of detachment is surprisingly low. Therefore, a kinetic method is attractive to draw further conclusions. We show that, in certain cases, the detachment step is rate limiting for the catalytic cycle. We also present a suitable reaction scheme to describe this effect, which is "translated" into a set of coupled differential equations and validated experimentally. In the analogous case of iridium complexes, the corresponding product-catalyst adducts are known to be stable such that they can even be isolated.[23]

Experimental Section

The ^{1}H-PHIP NMR spectra were recorded on a Bruker DRX 200 spectrometer at a proton resonance frequency of 200 MHz. Reagents and solvents were used as obtained from Aldrich. The hydrogenation reactions conducted inside of the NMR magnet were performed at 298 K using a conventional ^{1}H-multinuclear probehead. The hydrogen addition took place during a time interval of 3 s controlled by the spectrometer console via pulse programming. During this time interval, a glass capillary was lowered into the probehead and para-enriched hydrogen gas was bubbled through the reactive solution. The spectra were recorded in a nonspinning mode after a delay of at least 1 s between the end of the hydrogen addition and the 45° detection pulse (to avoid any inhomogeneity of the solution due to bubbles). All spectra were recorded after any polarization stemming from the previous scan had ceased. The enrichment of parahydrogen is achieved via passing H_2 through activated charcoal at 77 K and has been described elsewhere.[18,24] By this means, a steady stream of a nearly 50:50 mixture of ortho- and parahydrogen is obtained. Under these conditions, one-third of the parahydrogen does not contribute to the PHIP intensity as this fraction is compensated by the residual orthohydrogen. This corresponds to a net surplus of 33% parahydrogen.

To determine the intensities of the PHIP signals, the NMR software Nuts was used. The antiphase signals were transformed into inphase signals using the magnitude calculation mode. By this means, the integrals of the transformed signals represent the intensities of the PHIP patterns. To determine values (and their accuracy) for the kinetic parameters involved in the different reaction pathways, the latter were transformed into systems of coupled differential equations that were solved analytically using the software package Mathematica. The experimental data were fitted to these analytical solutions by a least-squares optimization performing the Marquardt−Levenberg algorithm implemented in Sigmaplot. The errors represent the asymptotic standard errors.

Results and Discussion

Hydrogenation Rates Determined by the ROCHESTER Experiment. PHIP NMR spectroscopy detects polarized product molecules (or intermediates) during homogeneously catalyzed hydrogenations. The PHIP effect produces strongly enhanced antiphase signal patterns in the NMR spectrum. The polarized hydrogenation product is represented by the density operator $\sigma_{PHIP} = I_{Z1}I_{Z2}$ (in the case of weak coupling[25]), whereby the numbers indicate the positions of the two former parahydrogen nuclei.[10] The density operator σ_{PHIP} can be transformed into observable magnetization by a 45° detection pulse. The polarization, represented by $\sigma_{PHIP} = I_{Z1}I_{Z2}$, is the subject of longitudinal relaxation. The PHIP intensity is determined both by the chemical formation (according to the rate k_{HYD}) and relaxation. A detailed description of the various relaxation processes is currently in preparation but not the subject of this study. To determine k_{HYD}, it turned out to be sufficient to use a simplified description using only one resulting rate of longitudinal autorelaxation (R^{ZZ}).

It is possible to determine the rate of hydrogenation, k_{HYD}, independently of the relaxation rate and other subsequent reaction steps. The experiment suited to reach this goal is based upon the fact that polarization can be observed during a time interval of several tens of seconds after the end of the hydrogen addition. This fact is a consequence of a small hydrogenation rate (k_{HYD}) being mostly in the order of $k_{HYD} \leq 1\ s^{-1}$ under typical catalytic conditions. Obviously, this method is limited to hydrogenations with $k_{HYD} \leq 1\ s^{-1}$; therewith polarization is observed during a reasonable period of time. Figure 1 outlines the experimental procedure to determine k_{HYD} independently of the relaxation rate (R^{ZZ}) with a ROCHESTER-type experi-

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(25) This density matrix is the result of a hydrogenation conducted inside of the NMR magnet, i.e., under PASADENA conditions (PASADENA = parahydrogen and synthesis allow dramatically enhanced nuclear alignment); see ref 10.

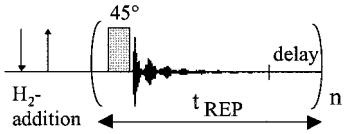
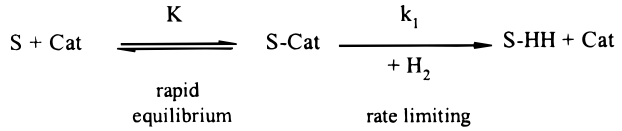


Figure 1. Modified ROCHESTER experiment to determine k_{HYD} independently of the relaxation rate (and independently of subsequent reaction steps). The arrows indicate the up and down motion of the capillary providing a stream of parahydrogen. The number n is typically on the order of 10, and t_{REP} should be at least $2T_1$.

Scheme 1[a]



[a] S: substrate; Cat: active catalyst; S−HH: hydrogenation product.

mental setup (ROCHESTER[21] = rates of catalytic hydrogenation estimated spectroscopically through enhanced resonances). To avoid confusion, we use this acronym throughout this study whenever the experiment as depicted in Figure 1 is used. As described in the Experimental Section, hydrogen is added during the time interval symbolized by the arrows in Figure 1, which indicates the up and down motion of the capillary. During this period of time, para-enriched hydrogen gas is bubbled through the reactive solution at atmospheric pressure. The main advantage of this experimental approach is that no hydrogen atmosphere remains above the sample at the end of the H_2 addition. Therefore, the (most likely rate-determining) step of a relayed hydrogen transfer from the gas phase into the solution is avoided and excluded from consideration. Otherwise, this phase-transfer step complicates the description of the kinetics which then is not governed by a first-order decay of $[H_2]$ anymore.

As already outlined,[21] the starting point for the theoretical framework of this experiment is an approach of J. Halpern et al.[26,27] assuming the mechanism depicted in Scheme 1 for a homogeneously catalyzed hydrogenation, i.e., the product formation follows a pseudo-first-order kinetics if the substrate S is present in large excess. This type of mechanism frequently applies if the hydrogenation is catalyzed by a cationic Rh^I complex containing a chelating diphosphine ligand.[26] According to this mechanism, the kinetics of the product (S−HH) formation can be described by eq 1,

$$\frac{d[S-HH]}{dt} = \frac{k_1 K}{K[S]+1}[S][Cat]_{TOT}[H_2] = k^*_{HYD}[Cat]_{TOT}[H_2] = k_{HYD}[H_2] \quad (1)$$

where $[Cat]_{TOT} = [Cat] + [S-Cat]$. To obtain a pseudo-first-order kinetics, an excess of the substrate S is required. This condition has been met for all experiments throughout this study.

To describe the time dependence of the PHIP intensity, another "reaction" must be considered: the relaxation of $\sigma_{PHIP} = I_{Z1}I_{Z2}$. Neglecting cross-relaxation as well as cross-correlated effects between two dipolar interactions, the decay of $I_{Z1}I_{Z2}$ is mainly determined by the rate of longitudinal two-spin order relaxation, R^{ZZ}. As outlined in Figure 2, $\langle I_{Z1}I_{Z2}\rangle$ can be determined by integration of the associated signals in the magnitude calculation mode. The intensity of a signal group at

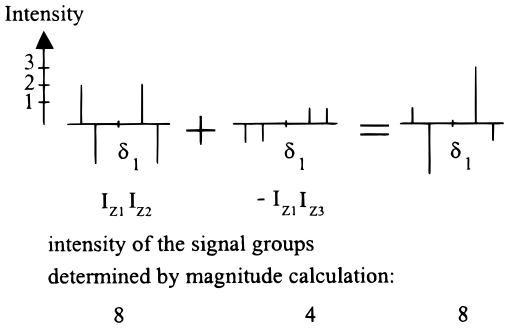
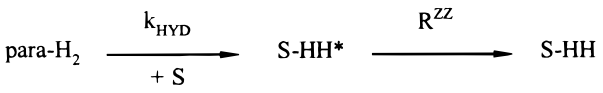


Figure 2. Intensity of polarization (i.e., $\langle I_{Z1}I_{Z2}\rangle$) can be determined by integration of the signal group at the chemical shift of the nucleus 1 (or 2), δ_1 (or δ_2), in the magnitude calculation mode. As long as the expectation values of other longitudinal two-spin order terms $I_{Z1}I_{Zn}$ ($n > 2$) do not exceed $\langle I_{Z1}I_{Z2}\rangle$, they do not contribute to the integral that, therefore, is proportional to $\langle I_{Z1}I_{Z2}\rangle$. The nuclei 1 and 2 are the two former parahydrogen nuclei, whereas nucleus 3 is an additional proton that is involved in relaxation processes leading, e.g., to $I_{Z1}I_{Z2} \rightarrow -I_{Z1}I_{Z3}$.

Scheme 2[b]



[b] S: substrate; Cat: active catalyst; S−HH*: polarized product molecule.

δ_1 is not altered by two-spin order terms $I_{Z1}I_{Zn}$ with $n \neq 1, 2$. In the example depicted in Figure 2, the decay of $\langle I_{Z1}I_{Z2}\rangle$ is dominated by the rate of longitudinal autorelaxation, i.e., $d\langle I_{Z1}I_{Z2}\rangle/dt \approx R_1^{ZZ}\langle I_{Z1}I_{Z2}\rangle$. All processes leading to $I_{Z1}I_{Z2} \rightarrow I_{Z1}I_{Z3}$, i.e., cross-relaxation and cross-correlated interactions, have been neglected, since the corresponding terms are expected to be small relative to $R_1^{ZZ}\langle I_{Z1}I_{Z2}\rangle$. Hence, the PHIP intensity as a function of the time can be described by a two-step reaction as indicated in Scheme 2. The time dependence of [S−HH*] (that is proportional to $\langle I_{Z1}I_{Z2}\rangle$) is given by eq 2, where $[H_2{}^*]^0$ is the concentration of parahydrogen at $t = 0$.

$$[S-HH^*](t) = \frac{k_{HYD}[H_2{}^*]^0}{R^{ZZ} - k_{HYD}}(\exp(-k_{HYD}t) - \exp(-R^{ZZ}t)) \quad (2)$$

In a related study, it was pointed out that eq 2 yields a first-order decay for [S−HH*] if $R^{ZZ} \gg k_{HYD}$.[21] However, this relation is not a necessary requirement for the experiment and the theory since R^{ZZ} is possibly of the same order of magnitude as k_{HYD} (e.g., 0.5 s^{-1}). Nevertheless, eq 2 can be applied to the ROCHESTER experiment if the main feature of the PHIP method is taken into account. During each FID, only the polarization is detected that has been formed just a few seconds before. Therefore, each detection pulse reads out the current "compromise" between formation and relaxation. Simultaneously, further polarization is generated independently during the nth cycle and is transformed into observable magnetization by the $(n+1)$th detection pulse. The "repetition time" t_{REP} (typically in the order of 10 s) is constant, whereas the concentration $[H_2{}^*]$ is not because parahydrogen is consumed by the chemical reaction independently of the NMR experiment. As explained above, the concentration $[H_2{}^*]$ follows a first-order exponential decay. Therefore, the expression $[H_2{}^*]^0$ in eq 2 is now a function of the time and has to be replaced by the expression $[H_2{}^*]^{00}\exp(-k_{HYD}t)$, whereas t is now represented by the constant t_{REP}. Thus, the time dependence of the

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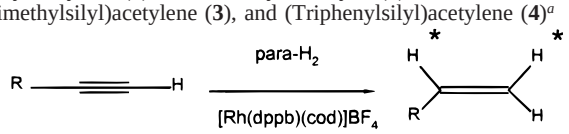
Table 1. Rates for the Hydrogenation of Different Acetylene Derivatives Determined Using the ROCHESTER Experiment: Phenylacetylene (**1**), 3,3-Dimethylbut-1-yne (**2**), (Trimethylsilyl)acetylene (**3**), and (Triphenylsilyl)acetylene (**4**)[a]



substrate	R−	k_{HYD} (s^{-1})
1	Ph−	0.140 ± 0.005
2	$(CH_3)_3C$−	0.085 ± 0.002
3	$(CH_3)Si$−	0.064 ± 0.004
4	$(Ph)_3Si$−	0.085 ± 0.003

[a] All measurements were performed using a total catalyst concentration ($[Cat]_{TOT} = [Cat] + [S-Cat]$, see Scheme 1) of $[Cat]_{TOT} = 14.16$ mM (catalyst precursor $[Rh(dppb)(cod)]BF_4$ in acetone-d_6). The values of k_{HYD} were determined by linear regression.

PHIP intensity (that is proportional to [S−HH*]) is obtained as

$$[S-HH^*](t) = \frac{k_{HYD}[H_2^*]^{00}}{R^{ZZ} - k_{HYD}}\exp(-k_{HYD}t)(\exp(-k_{HYD}t_{REP}) - \exp(-R^{ZZ}t_{REP})) \quad (3)$$

This expression is equivalent to

$$[S-HH^*](t) \propto \exp(-k_{HYD}t) \quad (4)$$

To investigate whether the experimental intensities as a function of $t = nt_{REP}$ can be described by eq 4, the following substrates were "tested": phenylacetylene (**1**), 3,3-dimethylbut-1-yne (**2**), (trimethylsilyl)acetylene (**3**), and (triphenylsilyl)-acetylene (**4**). $[Rh(dppb)(cod)]BF_4$[28] in acetone-d_6 was used as the catalyst precursor. The experimental results are summarized in Table 1. The small standard deviations indicate that the mechanistic model as well as the experiment are suited to describe and investigate the above reactions.

As an in situ method, PHIP NMR spectroscopy always yields the "true" rates associated with the formation of the product molecules that have actually been formed by a mechanism transferring the parahydrogen nuclei in pairs. Other competing reaction pathways are possible, but if those are "PHIP-silent", no perturbation results from these processes. To investigate whether the rate of product formation as determined by the PHIP method is actually associated with the dominant reaction pathway, the results can be compared to the turnover rate as measured by conventional NMR spectroscopy. On the other hand, the PHIP method yields in situ values, and therefore, any changes of the rates can be monitored as a function of the turnover.

We want to note that "conventional" in-phase NMR signals cannot be used to calibrate the integrals of the PHIP patterns, since the former are possibly subject to a saturation effect if t_{REP} is chosen so that they do not have enough time to recover completely before the next cycle begins. The PHIP patterns, of course, do not have to recover but are created freshly by the hydrogenation.

Application of the ROCHESTER Method to Other Mechanistic and Experimental Conditions. The method outlined in the preceding section, more precisely the way of data analysis used, is limited to cases in which the rate of production of the PHIP signals follows a pseudo-first-order kinetics. The polarization signals of interest can be caused either by the hydrogenation product or by an intermediate with a lifetime sufficient to observe NMR resonances. An example for the latter case is presented in the subsequent section, where the generation of catalyst-attached product molecules is shown to follow a pseudo-first-order kinetics. The use of cationic Rh^I complexes throughout this study does not mean that all systems must follow the "unsaturated route" [1,2] of olefin hydrogenation. The experimental conditions can, in principle, be varied so that complementary pseudo-first-order cases are reached. We want to mention briefly a few cases. (1) Systems that follow the "unsaturated route", whereby the substrate occurs in excess: This leads to eq 1 and a first-order decay of polarization, as discussed above. (2) Systems following the "unsaturated route", whereby hydrogen occurs in excess, and $K[S] \ll 1$: In this case, the rate law can be approximated by

$$\frac{d[S-HH]}{dt} = \frac{k_1K}{K[S]+1}[S][Cat]_{TOT}[H_2]_{excess} \approx k_1K[Cat]_{TOT}[H_2]_{excess}[S] = k_{HYD}^{H2-exc}[S] \quad (5)$$

We are currently working on implementing a method experimentally in which the polarization decay is substrate-controlled. If both complementary pseudo-first-order conditions can be achieved, the relation

$$\frac{k_{HYD}^{S-exc}}{k_{HYD}^{H2-exc}} = \frac{1}{K[H_2]_{excess}} \quad (6)$$

holds (if, of course, the same mechanism applies in both cases). This would provide for an interesting method to determine K in situ which, otherwise, is difficult to achieve using conventional kinetic methods. (3) Systems following the "hydride route": As a typical system, the catalytic properties of Wilkinsons's catalyst were investigated[29−31] and the decay of the observable dihydride concentration, $[RhH_2ClL_3]$ ($L = PPh_3$), was measured by a kinetic study in the presence of a large excess of cyclohexene. These experimental conditions lead to a pseudo-first-order rate law.[29] This example shows that it is possible to "implement" simple kinetic laws by a careful adjustment of the experimental conditions. Current work focuses on the implementation of accurate conditions to use PHIP for the determination of hydrogenation rates more universally by considering several different mechanisms.

The ortho/para equilibration in the static magnetic field during homogeneous hydrogenations can be regarded by a density matrix description of an intermediate state involving a Hamiltonian that does not commute with the density matrix of parahydrogen, i.e., causing a symmetry breakdown in the intermediate state.[11] If the hydrogenation yields a weakly coupled product spin system, all information about intermediate states gets lost and only the operator $I_{Z1}I_{Z2}$ remains. In contrast to the isotropic density matrix of parahydrogen, the expectation value of this operator decreases as a function of time due to dipolar relaxation. The relaxation of $I_{Z1}I_{Z2}$ in the product molecule is dominated by R^{ZZ}, whereas relaxation during the lifetime of the intermediate state leads to a competing "reaction

(28) dppb = diphenylphosphinobutane, cod = cycloocta-1,5-diene.

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(31) Halpern, J. *Inorg. Chim. Acta* **1981**, 50, 11−19.

$$I_{Z1}I_{Z2} \xrightarrow{n^{th}\ 45^\circ} \begin{aligned} &0.5\ I_{Z1}\ I_{Z2} \\ &0.5\ I_{Z1}\ I_{X2}\ \text{(SQ)} \\ &0.5\ I_{X1}\ I_{Z2}\ \text{(SQ)} \\ &0.5\ I_{X1}\ I_{X2} = 0.25\ (I_{X1}\ I_{X2} + I_{Y1}\ I_{Y2}) \\ &\qquad + 0.25\ (I_{X1}\ I_{X2} - I_{Y1}\ I_{Y2}) \\ &\qquad = 0.25\ ZQ_X + 0.25\ DQ_X \end{aligned}$$

$$\xrightarrow{\text{relaxation}} \xrightarrow{(n+1)^{th}\ 45^\circ} \text{observable magnetization}$$

Figure 3. Operators produced by a 45° detection pulse applied to $\sigma_{PHIP} = I_{Z1}I_{Z2}$. ZQ: zero quantum coherence, SQ: single quantum coherence, DQ: double quantum coherence.

pathway" and thereby to an effective hydrogenation rate that is diminished depending on the lifetime of the intermediate, or, if the intermediate state is passed through due to a fast equilibrium (nonproductive parahydrogen addition and elimination), depending on the fraction of the intermediate state. The effect thereof is expected to be negligible in most cases, since the lifetime and hence the population of an intermediate is usually small. Accordingly, the small conversion rates as determined by Brown et al.[32] (on the order of 10^{-4} s^{-1} in solution) are small relative to the duration of the experiment.

To finish the description of the ROCHESTER experiment, we want to discuss qualitatively the influence of relaxation. A necessary condition for this experiment is that all coherences produced by the *n*th detection pulse have actually decayed to zero such that they do not contribute to the magnetization produced by the $(n + 1)$th detection pulse. Figure 3 summarizes the different operators produced by a single 45° detection pulse. The 45° pulse transforms σ_{PHIP} into the coherences *ZQ*, *SQ*, and *DQ* corresponding to the coherence order $p = 0$, 1, and 2, respectively. These coherences are affected by relaxation during the *n*th FID and during a subsequent delay. The transversal relaxation of the coherences *SQ* and *DQ* is most likely dominated by the inhomogeneity of the external magnetic field. The operators $0.25ZQ_X = 0.25(I_{X1}I_{X2} + I_{Y1}I_{Y2})$ and $0.5I_{Z1}I_{Z2}$ possibly relax more slowly and may affect the $(n+1)$th FID if the subsequent delay is not long enough. The sum of both is isotropic except for a term $\alpha(t)0.25I_{Z1}I_{Z2}$, where $\alpha(t)$ defines the fraction that has not decayed to zero at the beginning of the $(n + 1)$th cycle. Only this fraction is transformed into further observable magnetization. Assuming that all operators decay with the same rates, the two subsequent 45° pulses can be combined to one 90° pulse which does not lead to any detectable magnetization. The influence of incomplete relaxation is expected to be negligible, however, if t_{REP} is on the order of $2-3\ T_1^{ZZ}$.

Determining the Rate of Product Detachment from the Catalyst Using the DYPAS Method. Recently, we reported the detection of a special type of intermediate that occurs during homogeneously catalyzed hydrogenations: freshly hydrogenated product molecules still being attached to a cationic Rh^I catalyst via an arene ring.[22] The rate of the detachment step turned out to be relatively low, and as a consequence thereof, these intermediates become visible in the PHIP NMR spectrum as resonances shifted to higher fields. This type of intermediate can be observed with a styrene derivative as the substrate and a cationic Rh^I complex containing a chelating diphosphine ligand. The rate of product formation may be strongly influenced by this "additional" reaction step that can be the rate limiting and, hence, the decisive one. This case has already been

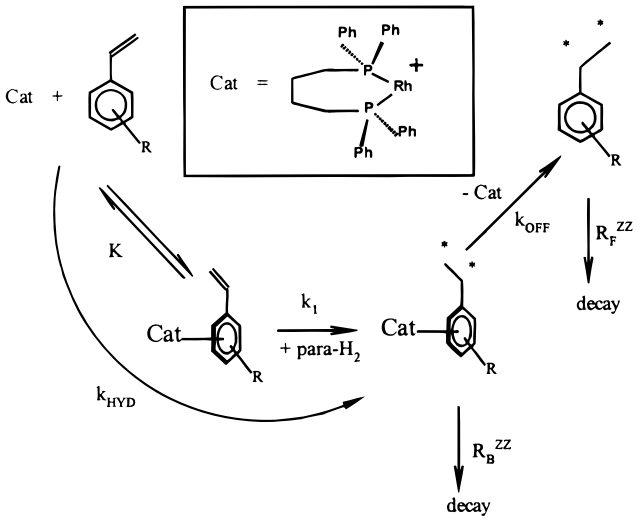


Figure 4. Reaction sequence for the formation and decomposition of catalyst-attached ethylbenzene derivatives. The asterisks mark the positions of the two former parahydrogen nuclei. Solvent molecules in the coordination sphere have been neglected.

investigated by R. H. Crabtree et al. to apply to hydrogenation reactions catalyzed by Ir complexes, where the analogous product−catalyst adducts turned out to be stable such that they can be isolated.[23]

When using a cationic Rh^I complex containing a *chiral* chelating diphosphine ligand, ethylbenzene derivatives without a C_2 axis in the molecular plane (the same holds for the corresponding styrene derivatives) form two diastereomeric product−catalyst complexes. Accordingly, two geometrically different adducts can be discriminated via separated resonances in their PHIP NMR spectrum. A measurement of the rates of their formation and decomposition should allow to monitor the effectiveness of the chiral catalyst and, therefore, yield information about the origin of enantioselection. Such studies are currently in progress.

As already mentioned, the distinct observation of these catalyst-attached product molecules is a consequence of a small detachment rate. To be visible as individual and nonbroadened signals in the NMR spectrum, the intermediate must be stable with respect to the time scale as defined by the amount of the shift of the corresponding resonances (typically on the order of 20−60 Hz at a proton resonance frequency of 200 MHz). The intermediate can hardly be detected by conventional NMR spectroscopy in the thermodynamic equilibrium because the corresponding concentration is very low. Accordingly, we take advantage of the unique ability of the PHIP NMR method: the accumulation of intermediate molecules during the transient chemical reaction and, simultaneously, the generation of a magnetic nonequilibrium state that yields a large signal enhancement. A few seconds after the hydrogen addition has stopped, the chemical reaction has accumulated "sufficient" intermediate molecules in the solution for detection by PHIP if their decomposition rate is not too high. Nevertheless, this concentration is frequently still much too low for the detection by conventional NMR methods. Therefore, it is possible to measure rates associated with the formation and decomposition of such intermediates only as a consequence of the PHIP signal enhancement.

Figure 4 explains the occurrence of the PHIP signals corresponding to free and attached ethylbenzene derivatives, and it defines the model used to quantitatively describe the expected and observed time dependence of the PHIP intensities. As shown

(32) Brown, J. M.; Canning, L. C. *J. Organomet. Chem.* **1983**, 255, 103−111.

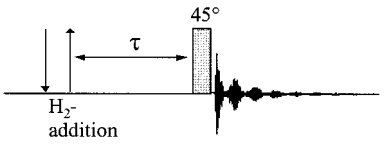


Figure 5. "Pulse sequence" of the DYPAS experiment to determine the rates of all processes leading to the formation and the decay of a PHIP NMR signal. The delay time τ is varied between 1 and approximately 30 s, depending on the rates of the involved processes.

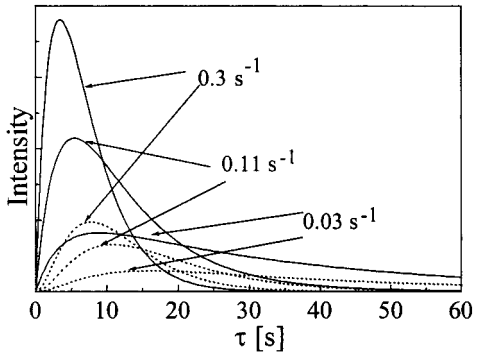


Figure 6. Theoretical course of the DYPAS intensities during the hydrogenation of styrene derivatives as a function of the delay time τ (according to the eqs 9 and 10). The parameters k_{OFF} and R^{ZZ} are fixed to $k_{OFF} = 0.15\ s^{-1}$ and $R^{ZZ} = 0.1\ s^{-1}$. Solid lines: attached product, dashed lines: free product. The numbers represent different values for k_{HYD}.

in Figure 5, DYPAS is proposed to determine the detachment rate (k_{OFF}) as well as the hydrogenation rate (k_{HYD}). According to Figure 4, the processes that take place during the delay τ can be described by the following system of coupled differential equations:

$$\frac{d}{dt}\begin{pmatrix}[H_2^*]\\ In_B\\ In_F\end{pmatrix} = \begin{pmatrix}-k_{HYD} & 0 & 0\\ k_{HYD} & -k_{OFF} + R_B^{ZZ} & 0\\ 0 & k_{OFF} & -R_F^{ZZ}\end{pmatrix}\begin{pmatrix}[H_2^*]\\ In_B\\ In_F\end{pmatrix} \quad (7)$$

In eq 7, In_B and In_F are the PHIP intensities of bound and free ethylbenzene, respectively, and R_B^{ZZ} and R_F^{ZZ} are the associated rates of longitudinal relaxation. For simplicity, any constant factor relating the concentration and the intensity has been disregarded. The solutions of eq 7 under the boundary conditions $[H_2](0) = [H_2]^0$ and $In_B(0) = In_F(0) = 0$ are

$$[H_2^*](t) = [H_2^*]^0 \exp(-k_{HYD}t) \quad (8)$$

$$In_B(t) = \frac{k_{HYD}[H_2^*]^0}{R_B^{ZZ} + k_{OFF} - k_{HYD}}(\exp(-k_{HYD}t) - \exp(-(R_B^{ZZ} + k_{OFF})t)) \quad (9)$$

$$In_F(t) = \frac{k_{OFF}}{R_F^{ZZ} - R_B^{ZZ} - k_{OFF}}\left(In_B(t) + \frac{k_{HYD}}{k_{HYD} - R_F^{ZZ}}[H_2^*](t) - [H_2^*]^0\frac{k_{HYD}}{k_{HYD} - R_F^{ZZ}}\exp(-R_F^{ZZ}t)\right) \quad (10)$$

The theoretical time dependence of the PHIP intensities is shown in Figure 6. The higher the value of k_{OFF} (or the smaller k_{HYD}), the later the intensity of the free product equals the intensity associated with the bound molecules. The overall intensity diminishes if the rate of relaxation increases. In the case of a low production rate, the overall intensity is low whereas the polarization can be observed during a longer period of time.

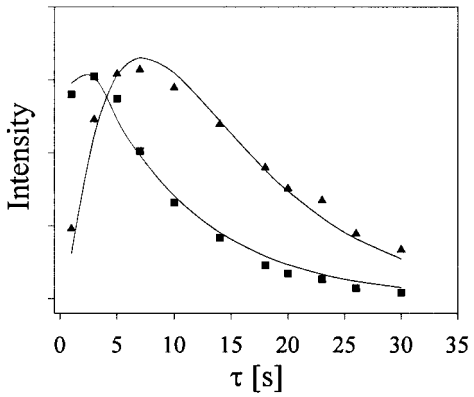
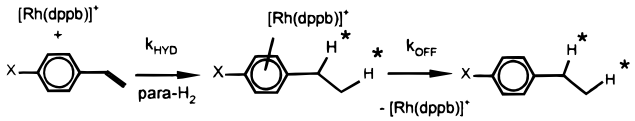


Figure 7. DYPAS intensities of attached (squares) and free (triangles) ethylbenzene during the hydrogenation with the catalyst precursor [Rh(dppb)(cod)]BF_4 in acetone-d_6. The symbols represent the experimental values, and the lines are the optimized fits according to the eqs 9 and 10. The best fit has been achieved with $k_{HYD} = 0.111 \pm 0.009\ s^{-1}$, $k_{OFF} = 0.351 \pm 0.003\ s^{-1}$, $R_F^{ZZ} = 0.20 \pm 0.02\ s^{-1}$, and $R_B^{ZZ} = 1.23 \pm 0.25\ s^{-1}$. The high value for R_B^{ZZ} (relative to R_F^{ZZ}) is in good agreement with the expectation of an increased correlation time in the bound state.

Table 2. Experimental Values for the Rates k_{HYD} and k_{OFF} Obtained during the Hydrogenation of Different Styrene Derivatives Performing the DYPAS Experiment Depicted in Figure 5[a]



X−	k_{HYD} (s^{-1})	k_{OFF} (s^{-1})
−H	0.111 ± 0.009	0.35 ± 0.03
−OMe	0.138 ± 0.010	0.45 ± 0.04
−OEt	(0.40)	0.273 ± 0.024
$-NH_2$	(0.84)	0.113 ± 0.036

[a] The total catalyst concentration was 5.52 mM in acetone-d_6. The errors are the standard errors of the least-squares optimization. The numbers in brackets indicate experimental values with a high uncertainty, even though the fits are very good.

To show that the model defined in Figure 4 is well-suited to describe the PHIP intensity as a function of time, several para-substituted styrenes have been investigated using the catalyst precursor [Rh(cod)(dppb)]BF_4 in acetone-d_6. As a characteristic example, the experimental intensities observed during the hydrogenation of *p*-methoxystyrene are shown in Figure 7 (together with the least-squares fit according to the eqs 9 and 10). The results of the least-squares optimizations are summarized in Table 2. Substitution of the para position of styrene by electron-density donating groups roughly causes two opposite effects: (i) the hydrogenation rate increases whereas (ii) the rate of product detachment decreases. We propose that both effects are a consequence of the increasing bonding strength between the arene ring (of the substrate and the product) and the cationic Rh^I catalyst. This effect possibly causes an increase of K (and, therefore, k_{HYD}; see eq 1) and most likely causes a decrease of k_{OFF}. The experimental data included in Table 2 suggest that the detachment process is also influenced by sterical effects. Possibly, the rate of detachment is diminished in the case of X = H because this substituent is sterically less pretentious than the other ones. To draw precise conclusions, it is necessary to determine more experimental data including activation parameters. It is important to realize that, in the case

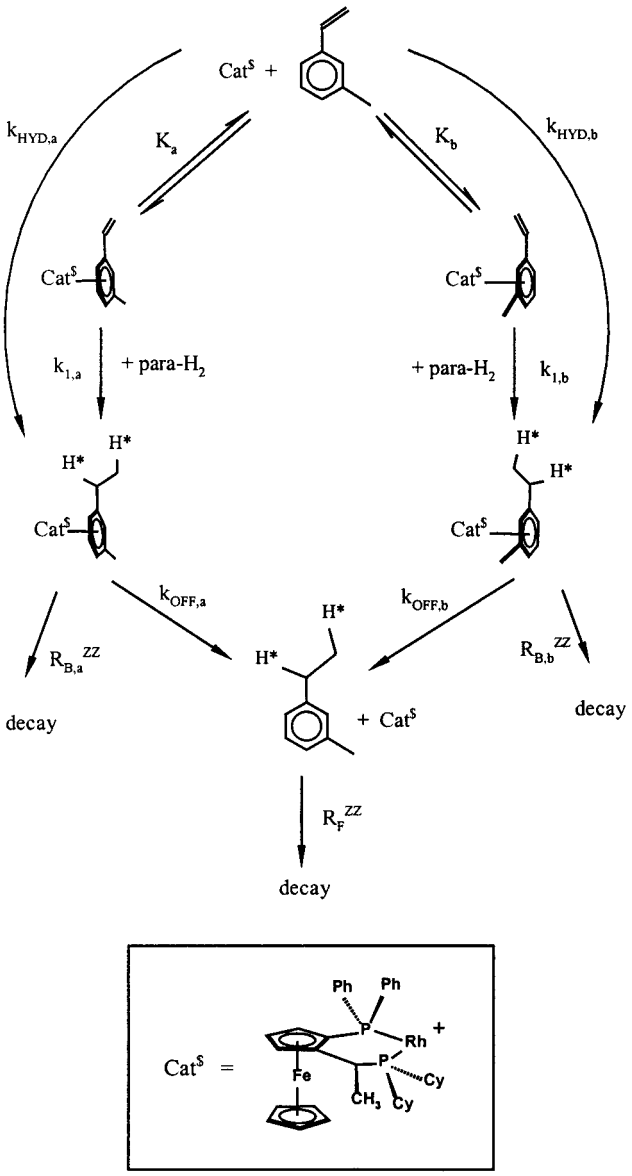


Figure 8. Reaction scheme to explain the occurrence of two diastereomeric product−catalyst complexes during the hydrogenation of certain styrene derivatives with chiral catalysts. Cat$ symbolizes the active chiral catalyst species, and the asterisks mark the positions of the two former parahydrogen nuclei. The indices *a* and *b* indicate the two different reaction pathways, whereas the indices *B* and *F* represent rates associated with bound and free product molecules, respectively. Solvent molecules in the coordination sphere have been neglected.

of strongly electron-donating substituents (e.g., NH_2), the detachment step becomes rate limiting for the catalytic cycle.

To establish a link between the ROCHESTER and the DYPAS experiment, k_{HYD} can also be determined independently of R^{ZZ} and k_{OFF} according to the ROCHESTER experiment depicted in Figure 1. In this case, $[S-HH]^*_{attached}$ (polarization stemming from attached product molecules) follows a first-order decay according to the rate k_{HYD} which does not change the validity of eqs 3 and 4 if R^{ZZ} is replaced by $k' = k_{OFF} + R^{ZZ}$. This has indeed been verified experimentally during the hydrogenation of styrene with $[Rh(cod)(dppb)]BF_4$ ($c = 3$ mM). Under these conditions, a value of $k_{HYD} = (0.058 \pm 0.001)\ s^{-1}$ was determined with the ROCHESTER experiment.

As pointed out before, two diastereomeric product−catalyst complexes are generated in the case of a *chiral* catalyst. They can easily be discriminated via PHIP NMR spectroscopy, e.g., while hydrogenating 3-methylstyrene with [Rh((*R*)-(*S*)-JOSIPHOS)(cod)]BF_4[33] as the catalyst precursor.[22] We propose the mechanism depicted in Figure 8 to quantitatively account for the occurrence of the two product−catalyst resonances. The time dependence of the PHIP intensity during the delay τ (according to the DYPAS experiment depicted in Figure 5) can be described by the following system of coupled differential equations:

$$\begin{pmatrix} -k_\Sigma & 0 & 0 & 0 \\ 0 & -R_F^{ZZ} & k_{OFF,a} & k_{OFF,b} \\ k_{HYD,a} & 0 & -k_{OFF,a} - R_B^{ZZ} & 0 \\ k_{HYD,b} & 0 & 0 & -k_{OFF,b} - R_B^{ZZ} \end{pmatrix} \begin{pmatrix} [H_2^*] \\ In_F \\ In_{B,a} \\ In_{B,b} \end{pmatrix} = \frac{d}{dt} \begin{pmatrix} [H_2^*] \\ In_F \\ In_{B,a} \\ In_{B,b} \end{pmatrix} \quad (11)$$

where $k_\Sigma = k_{HYD,a} + k_{HYD,b}$. $In_{B,a/b}$ is the PHIP intensity associated with the bound product molecules (i.e., the two diastereomeric catalyst−product complexes a and b). In_F is the PHIP intensity associated with the polarized free product molecules, and $R_{B/F}{}^{ZZ}$ represents the rate of longitudinal relaxation. The solutions of this system of coupled differential equations were derived by Mathematica under the boundary conditions $[H_2](0) = [H_2]^0$ and $In_F(0) = In_{B,a}(0) = In_{B,b}(0) = 0$:

$$In_F = [H_2^*]^0 \left(\frac{k_{HYD,a}k_{OFF,a}}{(k_{HYD,a} + k_{HYD,b} - k_{OFF,a} - R_B^{ZZ})(k_{HYD,a} + k_{HYD,b} - R_F^{ZZ})} (\exp(-(k_{HYD,a} + k_{HYD,b})t) - \exp(-R_F^{ZZ}t)) + \frac{k_{HYD,b}k_{OFF,b}}{(k_{HYD,a} + k_{HYD,b} - k_{OFF,b} - R_B^{ZZ})(k_{HYD,a} + k_{HYD,b} - R_F^{ZZ})} (\exp(-(k_{HYD,a} + k_{HYD,b})t) - \exp(-R_F^{ZZ}t)) - \frac{k_{HYD,a}k_{OFF,a}}{(k_{HYD,a} + k_{HYD,b} - k_{OFF,a} - R_B^{ZZ})(k_{OFF,a} + R_B^{ZZ} - R_F^{ZZ})} (\exp(-(k_{OFF,a} + R_B^{ZZ})t) - \exp(-R_F^{ZZ}t)) - \frac{k_{HYD,b}k_{OFF,b}}{(k_{HYD,a} + k_{HYD,b} - k_{OFF,b} - R_B^{ZZ})(k_{OFF,b} + R_B^{ZZ} - R_F^{ZZ})} (\exp(-(k_{OFF,b} + R_B^{ZZ})t) - \exp(-R_F^{ZZ}t)) \right) \quad (12)$$

$$In_{B,a/b} = [H_2^*]^0 \left(\frac{k_{HYD,a/b}}{(k_{HYD,a} + k_{HYD,b} - k_{OFF,a/b} - R_B^{ZZ})} (-\exp(-(k_{HYD,a} + k_{HYD,b})t) + \exp(-(R_B^{ZZ} + k_{OFF,a/b})t)) \right) \quad (13)$$

$$[H_2^*](t) = [H_2^*]^0 \exp(-(k_{HYD,a} + k_{HYD,b})t) \quad (14)$$

To verify the suitability of the mechanistic model as defined by Figure 8, we used [Rh((*R*)-(*S*)-JOSIPHOS)(cod)]BF_4 as the catalyst precursor that was generated in situ by stirring an

(33) (*R*)-(*S*)-JOSIPHOS = (*R*)-1-[(1*S*)-2(diphenylphosphino)ferrocenyl]-ethyldicyclohexylphosphine.

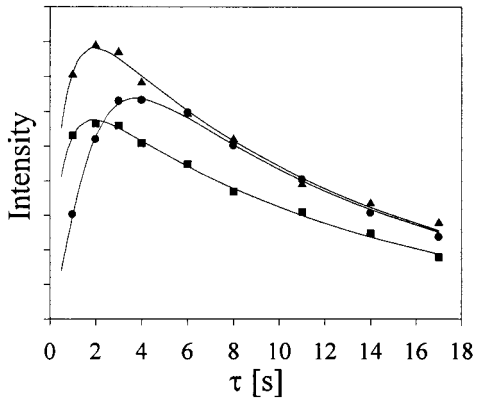


Figure 9. Experimental DYPAS intensities (symbols) vs delay time τ during the hydrogenation of 3-methylstyrene with [Rh((*R*)-(*S*)-JOSIPHOS)(cod)]BF_4 ($c = 0.0133$ M). The best fit has been achieved with the following parameters: $k_{HYD,a} = (0.034 \pm 0.002)$ s^{-1}, $k_{HYD,b} = (0.044 \pm 0.002)$ s^{-1}, $R_B^{ZZ} = (1.03 \pm 0.15)$ s^{-1}, $R_F^{ZZ} = (0.88 \pm 0.06)$ s^{-1}, $k_{OFF,a} = (0.48 \pm 0.08)$ s^{-1}, and $k_{OFF,b} = (0.44 \pm 0.06)$ s^{-1}. Circles represent the free product; triangles and squares represent the two different product−catalyst complexes.

equimolare mixture of $[Rh(cod)_2]BF_4$ and (*R*)-(*S*)-JOSIPHOS in acetone-d_6 without the presence of any substrate. Thereafter, 3-methylstyrene was added and hydrogenated. As a result of a DYPAS experiment, the PHIP intensities obtained as a function of τ and the optimized multiparameter fits are shown in Figure 9. The good agreement reveals that the model as defined by Figure 8 and eq 11 successfully fits the experimental PHIP intensities. This strongly indicates that Figure 8 is well-suited to describe the reactions governing the delay τ. The method thus allows to differentiate quantitatively between two possible diastereomeric reaction pathways. Further measurements with other catalysts are currently under way to investigate the differences between the rates corresponding to the two diastereomeric alternatives. The results might be significant for optimizing catalysts for the stereoselective hydrogenation of a prochiral substrate.

Conclusions

We propose two PHIP NMR methods to quantitatively investigate homogeneous hydrogenations. The first method, ROCHESTER, focuses on the rate of hydrogen transfer and, depending on the experimental conditions, is capable of providing detailed information about the background of the observed hydrogenation rate. The second method, DYPAS, provides a possibility to monitor all processes occurring during a variable delay time. It can be used to determine the rates of various relaxation processes as well as to measure the rates of the formation and the decomposition of all visible intermediates and product molecules. With this method, the occurrence of a special type of intermediate, product−catalyst adducts, in the PHIP NMR spectra recorded during the hydrogenation of styrene derivatives with cationic Rh^I catalysts can be investigated. The associated processes, namely the formation and decomposition of these intermediates, have been described by sets of coupled differential equations that have been solved and fitted to the experimental data. The production rates of the product−catalyst complexes as well as the kinetics of their detachment turned out to be strongly influenced by the electronic properties of substituents in the arene ring of ethylbenzene (the hydrogenation product): Electron-donating substitution in the para position increases the hydrogenation rate but decreases the detachment rate. In the case of *p*-aminoethylbenzene, the detachment step proved to be rate limiting for the turnover. We used DYPAS to visualize two diastereomerically different product−catalyst complexes in the case of a chiral catalyst and 3-methylstyrene as the substrate. These two complexes are formed by two "diastereomeric reaction pathways" that both yield the same product molecule. Due to its ability to yield kinetic parameters, this method should provide a possibility to screen and optimize chiral catalysts: Different chiral catalyst systems can be expected to cause more or less distinct differences between the corresponding reaction pathways. These differences reflect and indicate the potential and suitability of a catalyst complex for an asymmetric induction. In summary, the results demonstrate that PHIP NMR spectroscopy can be utilized as a powerful and extraordinary kinetic in situ method to investigate homogeneous hydrogenation reactions.

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