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BIFUNCTIONALLY CATALYZED 1,3-PROTON TRANSFER OF A PROPENE BY A sec-AMIDINE STUDIED BY DEUTERIUM ISOTOPE EFFECTS. A STEPWISE TWO-PROTON TRANSFER MECHANISM

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ABSTRACT

A two-hydron transfer mechanism involving hydron transfers from carbon to nitrogen and from nitrogen to carbon was studied. The rearrangement of 1,3,3-triphenylpropene (**1**) into 1,1,3-triphenylpropene (**2**) catalyzed by 2,10-diazabicyclo[4.4.0]dec-1-ene (**3**) in benzene at 25·00 °C was studied by ^{2}H-labeling experiments and kinetic ^{2}H-isotope effects. The synthesis and purification of [6,10-$^2H_2$]-2,10-diazabicyclo[4.4.0]dec-1-ene ([6,10-$^2H_2$]-**3**), [3-^{2}H]-1,3,3-triphenylpropene ([3-^{2}H]-**1**), [3-^{2}H]-1,1,3-triphenylpropene ([3-^{2}H]-**2**) and [3,3-$^2H_2$]-1,1,3-triphenylpropene ([3,3-$^2H_2$]-**2**) together with their precursors are reported. Partial reaction of [3-^{2}H]-**1** with [6,10-$^1H_2$]-**3** gave 42% conversion into product **2**, which was shown by ^{1}H NMR to be composed of 88% [3-^{1}H]-**2** and 12% [3-^{2}H]-**2**. Partial reaction of [3-^{1}H]-**1** with [6,10-$^2H_2$]-**3** gave 43% of **2**, composed of 73% [3-^{1}H]-**2** and 27% [3-^{2}H]-**2**.

These results clearly show that a substantial fraction of the reaction takes place in a bifunctional manner but isotope exchange and/or monofunctionally catalyzed reactions interfere. The following kinetic deuterium isotope effects on the rearrangement **1** → **2** were measured: $k^{HH}/k^{DH} = 6·56$; $k^{HH}/k^{HD} = 1·19$; $k^{HH}/k^{DD} = 7·08$; $k^{HD}/k^{DD} = 5·94$; and $k^{DH}/k^{DD} = 1·08$.

On the basis of these results, a concerted two-hydron transfer mechanism is excluded. Instead, a stepwise mechanism is favored, in which at first the 3-hydron of **1** is abstracted by **3** yielding an ion pair(s), the carbanion of which in a separate step is then hydronated to yield the product **2**.

The abstraction of the 3-hydron from **1** might be hydrogen bond assisted. The two hydron transfer transition states are together rate limiting, although they limit the rate to different extents. A detailed mechanistic analysis is presented together with the results of an investigation of the nature of the catalyst. The dimerization constant for **3** was determined by ^{1}H NMR to be 1·67 l mol^{-1} at 25·0 °C. Isotopomer composition was measured by ^{1}H NMR and GLC was used for the separation of the substrate and products. Computer-assisted capillary GLC was used for the kinetics.

INTRODUCTION

Bifunctional catalysis involving transfers of two hydrons is thought to be of great importance in enzyme action and many other organic reactions.[1] To obtain a deeper understanding of the nature of two-proton transfers in bifunctional catalysis, we are investigating a number of

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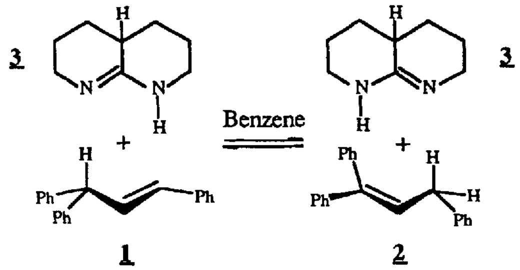
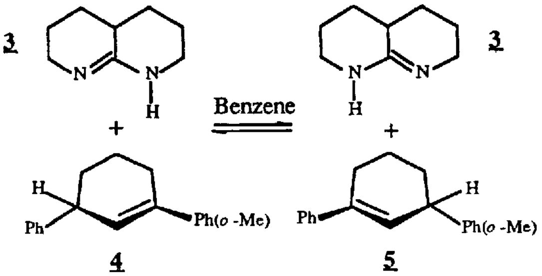


1 H = ^{1}H (3 - ^{1}H - **1**)
H = ^{2}H (3 - ^{2}H - **1**)

3 H = ^{1}H, ^{1}H (6,10 - ^{1}H$_2$ - **3**)
H = ^{2}H, ^{2}H (6,10 - ^{2}H$_2$ - **3**)

2 H = ^{1}H, ^{1}H (3 - ^{1}H - **2**)
H = ^{1}H, ^{2}H (3 - ^{2}H - **2**)
H = ^{2}H, ^{2}H (3,3 - ^{2}H$_2$ - **2**)

Scheme 1



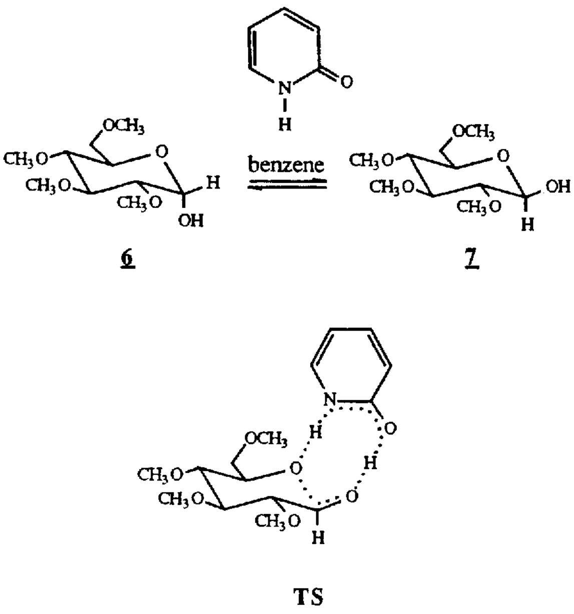
Scheme 2

reaction systems. For example, we are elucidating the detailed mechanisms of reactions which may involve two-proton transfers from and to carbon, nitrogen and oxygen.

In this paper a full report is provided on ^{2}H-labeling experiments and kinetic deuterium isotope effects for a bifunctional catalysis in which hydrons are transferred from and to *carbon* and *nitrogen*. The reversible rearrangement of 1,3,3-triphenylpropene (**1**) to 1,1,3-triphenylpropene (**2**) using 2,10-diazabicyclo[4.4.0]dec-1-ene (**3**) in benzene is the reaction system that has been studied in detail (Scheme 1).[2]

We have recently reported on the stereochemistry of the closely related reaction system shown in Scheme 2. The 1,3-hydron transfer of the cyclohexene **4** to **5** catalyzed by the *sec*-amidine **3** was shown to take place in a suprafacial manner.[3] The enantiospecificity of the reaction was measured to be >98·4% using a novel and convenient stereochemical method in which reversible reactions are regarded as a series of irreversible processes.[4] This method has also been used in chromatographic theory.[5]

We have recently also reported[6] on the classical 2-pyridinone-catalyzed mutarotation of 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranose (α-TMG) in benzene, discovered by Swain and Brown more than 30 years ago. In this reaction two hydrons are transferred from and to oxygen and nitrogen (Scheme 3).



Scheme 3

Using experimental primary and secondary and calculated primary deuterium isotope effects, detailed conclusions emerged about the transition state. The nature of this catalysis is different from that of the title reaction, as will be discussed below.

In this paper we try to answer questions about how the two hydron transfers depend on each other, e.g. do the transfers of the two hydrons from carbon to nitrogen and from nitrogen to carbon take place in one step, i.e. concertedly, or is the bifunctionally catalyzed rearrangement a stepwise reaction?

RESULTS AND DISCUSSION

According to Woodward and Hoffman,[7] suprafacial 1,3-sigmatropic shifts are symmetry forbidden. As a consequence, uncatalyzed 1,3-sigmatropic shifts are high barrier processes. This work was initiated by an idea about how to circumvent this symmetry forbiddenness, e.g. by using amidines as catalysts and 'open up' an allowed pseudo-pericyclic rearrangement route as illustrated in Figure 1.[8] For the purpose of elucidating this idea, the reaction system shown in Scheme 1 was developed. Below we report and discuss results of ^{2}H-labeling and kinetic deuterium isotope effect experiments that we have designed to clarify the nature of *sec*-amidine-catalyzed 1,3-hydron transfers.

^{2}H Labeling experiments and reaction mechanisms

Previously we reported that the bicyclic amidine **3** catalyzes the rearrangement of [3-^{2}H]-**1** into **2** in benzene at 75 °C.[2] A reaction mixture initially 0·99 M in the catalyst **3** and 0·05 M in the substrate [3-^{2}H]-**1** was reacted for 1 h and then quenched (Table 1). The mixture of the propene isomers was isolated and analyzed by GLC. This analysis showed that 40% of the

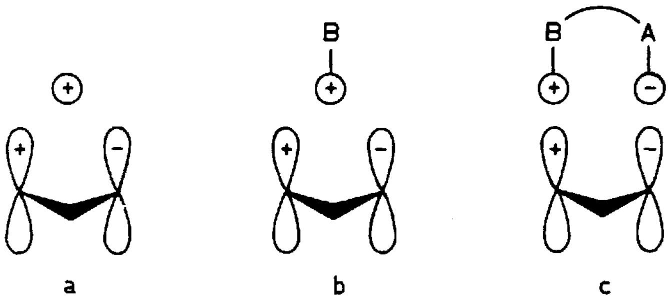


Figure 1. Illustration of interactions in important orbitals involved in (a) uncatalyzed, (b) monofunctionally catalyzed and (c) bifunctionally catalyzed 1,3-proton transfer reactions

mixture consisted of the rearrangement product **2**. The propenes were separated by preparative GLC and analyzed by ^{1}H NMR spectroscopy. The fraction of **1** was found to consist solely (within experimental error) of the ^{2}H-labeled starting material [3-^{2}H]-**1**. In contrast, the fraction of **2** was mainly (93%) composed of non-deuteriated compound.

In a separate experiment employing [3-^{2}H]-**2** and unlabeled **3**, it was shown that the exchange of the carbon-bonded deutron with the amidine proton was much slower than the rate of catalyzed isomerization of [3-^{2}H]-**1** to **2**. Hence these results indicated that the rearrangement could mainly involve activated complexes such as A in Scheme 4, i.e. that the rearrangement is bifunctionally rather than monofunctionally catalyzed. On the other hand, these limited results do not exclude the possibility of a multi-step reaction and that the observed isotope distribution in **2** is the consequence of deuterium–protium exchange within ion-pair intermediates.

To avoid misinterpretations caused by unexpected isotope effects, the following 'mirror' experiment was carried out. A mixture which initially was 0·49 M in the ^{2}H-labeled catalyst [6,10-^{2}H$_2$]-**3** and 0·06 M in the non-labeled substrate **1** in benzene as solvent was reacted at 75 °C and quenched and analyzed as above. The isolated product mixture consisted of 23% **1** and 77% **2**. The product **2** was composed of 42% of [3-^{2}H]-**2** and 58% of non-deuteriated **2**. No trace of [3,3-^{2}H$_2$]-**2** could be detected by ^{1}H NMR (Table 1).

The above labeling experiments show conclusively that at least a substantial fraction of this amidine-catalyzed rearrangement is bifunctional in nature. However, the results also clearly show considerable interference from isotope exchange and/or monofunctionally catalyzed rearrangements.

In the light of these results, a number of transition-state structures for the rearrangement and exchange reactions could be envisaged (Scheme 4). In addition to structure A mentioned above, in which there is a concerted transfer of the two hydrons from and to carbons and nitrogens, transition states B–E, involving non-concerted 1,3-hydron transfers, are possible representations. In structure B the 3-hydrogen of **1** is in transit but the NH binds only to the C-1 with an asymmetric hydrogen bond. In C, on the other hand, the 3-hydron is being transferred but no NH···C bond has developed in the transistion state. Structure D depicts a transition state in which the 3-hydron of **1** has been transferred completely to nitrogen and the other hydron bonded to N is in transit. In transition state E a hydrogen bond remains between the C-3 of **1** and the NH group, while the other N-hydron is in transit.

Any of the transition states A–E could be thought of as being possible rate-limiting transition states for the rearrangement. The transition states B–E may lead to ion-pair intermediates such

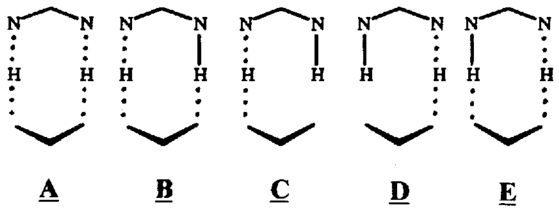
Table 1. Reaction mixture compositions, reaction conditions and results of labeling experiments with [3-^{1}H]-**1**, [3-^{2}H]-**1**, [6,10-$^{1}H_2$]-**3** and [6,10-$^{2}H_2$]-**3** in benzene at 25 and 75 °C

Substrate [**1**]	Concentration/ M	Catalyst [**3**]	Concentration/ M	Temperature/ °C	Reaction time/min	Isomer composition of reaction mixture[a]	Isotopomer composition or reaction mixture [b]
[3-^{2}H]-**1**	0·05	[6,10-$^{1}H_2$]-**3**	0·99	75	60	60% **1**	100% [3-^{2}H]-**1**
						40% **2**	93% [3-^{1}H]-**2**
							7% [3-^{2}H]-**2**
[3-^{2}H]-**1**	0·06	[6,10-$^{1}H_2$]-**3**	0·61	25	7060	58% **1**	91% [3-^{2}H]-**1**
							9% [3-^{1}H]-**1**
						42% **2**	88% [3-^{1}H]-**2**
							12% [3-^{2}H]-**2**
[3-^{1}H]-**1**	0·06	[6,10-$^{2}H_2$]-**3**[c]	0·49	75	99	23% **1**	100% [3-^{1}H]-**1**
						77% **2**	58% [3-^{1}H]-**2**
							42% [3-^{2}H]-**2**
							0% [3,3-$^{2}H_2$]-**2**
[3-^{1}H]-**1**	0·20	[6,10-$^{2}H_2$]-**3**[c]	1·80	75	42	20% **1**	100% [3-^{1}H]-**1**
						80% **2**	57% [3-^{1}H]-**2**
							43% [3-^{2}H]-**2**
							0% [3,3-$^{2}H_2$]-**2**
[3-^{1}H]-**1**	0·06	[6,10-$^{2}H_2$]-**3**[c]	0·59	25	1485	57% **1**	100% [3-^{1}H]-**1**
						43% **2**	73% [3-^{1}H]-**2**
							27% [3-^{2}H]-**2**
							0% [3,3-$^{2}H_2$]-**2**

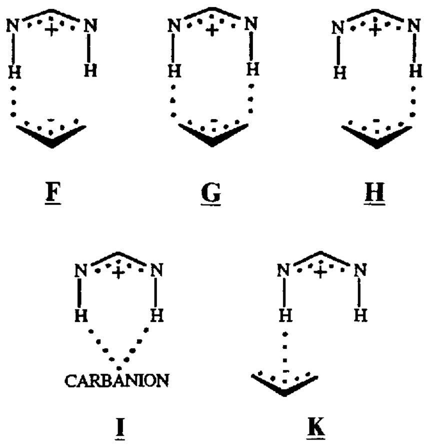
[a] Composition determined by GLC.

[b] Isotopomer composition determined by ^{1}H NMR.

[c] ^{1}H NMR showed that **3** contained 96 atom-% ^{2}H at the 10-position.



Scheme 4



Scheme 5

as F–H (Scheme 5). The observed exchange is possibly the consequence of exchange within such ion pairs via transition states of type I. Monofunctionally catalyzed rearrangement may also involve intermediates of the type F–G and a transition state such as K. Hence, in addition to the possibility that the exchange and rearrangement processes are independent reactions, they could be coupled, e.g. be stepwise processes employing common transition states and intermediates.

An obvious source of further mechanistic information is kinetic deuterium isotope effects. However, the knowledge of the relationships between transition-state structures and such isotope effects for concerted two-hydron transfer reactions is limited,[6b,9] We have now measured kinetic deuterium isotope effects for the reaction system shown in Scheme 1 at 25·00 °C. At this temperature the reactions proceed at convenient rates to allow the use of a quench-extraction GLC procedure for accurate kinetics. We have also analyzed in detail the outcome of labeling experiments at this lower temperature and the results are summarized in Table 1.

Kinetic deuterium isotope effects

In order to obtain detailed information on the rate-limiting transition state for the **3**-catalyzed rearrangement of **1** → **2**, experiments were designed for obtaining kinetic deuterium isotope effects. The reversibility of the rearrangement of **1** to **2**, which has $K \approx 14$, and the isotope exchange reactions mentioned above together complicate the reliable determination of isotope effects for the forward reaction. To avoid these problems we wished to make accurate measurements with the use of only a low percentage conversion of **1** → **2**. Such a low conversion demands an analytical procedure with very high accuracy. For the present purpose capillary chromatography was applied. Experimental and computational details of the procedure are given in the Experimental section below. In this way, rate constants for the reactions shown in equations (1)–(4) were determined. The rate constants and calculated isotope effects are shown in Tables 2 and 3, respectively. The interpretation of these isotope effects requires caution, as indicated below!

$$[3\text{-}^{1}\mathrm{H}]\text{-}\mathbf{1} + [6,10\text{-}^{1}\mathrm{H}_2]\text{-}\mathbf{3} \xrightarrow{k^{\mathrm{HH}}} \text{products} \tag{1}$$

$$[3\text{-}^{2}\mathrm{H}]\text{-}\mathbf{1} + [6,10\text{-}^{1}\mathrm{H}_2]\text{-}\mathbf{3} \xrightarrow{k^{\mathrm{DH}}} \text{products} \tag{2}$$

$$[3\text{-}^{1}\mathrm{H}]\text{-}\mathbf{1} + [6,10\text{-}^{2}\mathrm{H}_2]\text{-}\mathbf{3} \xrightarrow{k^{\mathrm{HD}}} \text{products} \tag{3}$$

$$[3\text{-}^{2}\mathrm{H}]\text{-}\mathbf{1} + [6,10\text{-}^{2}\mathrm{H}_2]\text{-}\mathbf{3} \xrightarrow{k^{\mathrm{DD}}} \text{products} \tag{4}$$

Nature of the catalyst **3**

Essentially the same amidine concentration was used in all experiments described in Table 2. One reason for this is that **3** was expected to be partially dimerized at the concentration used (Scheme 6). Of the three species in Scheme 6 only the monomer (M) and perhaps the linear dimer (Dl) are expected to be catalytically active. However, in Dl the steric crowding around

Table 2. Rate data for the **3**-catalysed rearrangement of **1** → **2** in benzene at 25·00 ± 0·03 °C[a]

Substrate	Catalyst	[3]/M	$k_{\mathrm{obsd}}/10^{-6}\,\mathrm{s}^{-1}$	$k^{b}/10^{-6}\,\mathrm{l\,mol^{-1}\,s^{-1}}$
$[3\text{-}^{1}\mathrm{H}]\text{-}\mathbf{1}$	$[6,10\text{-}^{1}\mathrm{H}_2]\text{-}\mathbf{3}$	0·580	9·57	16·5
		0·582	9·64	16·6
		0·579	9·45	16·3
$[3\text{-}^{2}\mathrm{H}]\text{-}\mathbf{1}$	$[6,10\text{-}^{1}\mathrm{H}_2]\text{-}\mathbf{3}$	0·579	1·46	2·52
		0·579	1·45	2·50
$[3\text{-}^{1}\mathrm{H}]\text{-}\mathbf{1}$	$[6,10\text{-}^{2}\mathrm{H}_2]\text{-}\mathbf{3}$	0·559	7·69	13·8
		0·559	7·75	13·9
$[3\text{-}^{2}\mathrm{H}]\text{-}\mathbf{1}$	$[6,10\text{-}^{2}\mathrm{H}_2]\text{-}\mathbf{3}$	0·568	1·33	2·34
		0·561	1·30	2·31

[a] The initial substrate concentration in all experiments was 0·06 M.
[b] k is defined as $k_{\mathrm{obsd}}/[3]$.

Table 3. Deuterium kinetic isotope effects at 25·00 °C based on calculated average k values in Table 2[a]

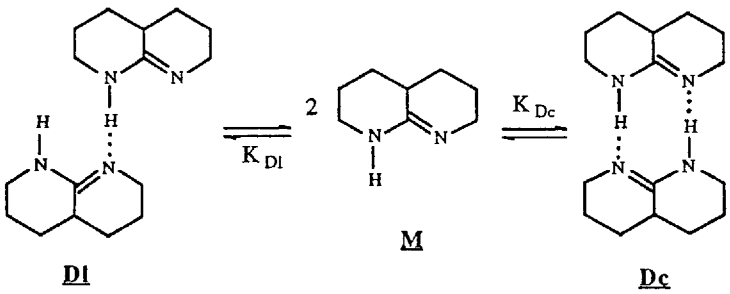
$k^{\mathrm{HH}}/k^{\mathrm{DH}}$	$k^{\mathrm{HH}}/k^{\mathrm{HD}}$	$k^{\mathrm{HH}}/k^{\mathrm{DD}}$	$k^{\mathrm{HD}}/k^{\mathrm{DD}}$	$k^{\mathrm{DH}}/k^{\mathrm{DD}}$
6·56	1·19	7·08	5·94	1·08

[a] The first superscript refers to the substrate and the second to the catalyst.

the lone pair not occupied by hydrogen bonding may inhibit significant catalytic activity. No catalytic activity is expected from Dc since all lone pairs are occupied in hydrogen bonds.

As part of the elucidation of the nature of the catalytic species, we determined the dimerization constant of [6,10-$^1H_2$]-**3** in benzene using ^1H NMR.[10] Only a single signal from the nitrogen-bonded protons of **3** is observed by ^1H NMR. A study of the NH chemical shift as a function of the amidine concentration revealed that it is strongly concentration dependent (Figure 2). The curve in Figure 2 was analyzed with several association models and the best fit was obtained with the simple dimerization model $2M \rightleftharpoons D$ and a dimerization constant $K_D = 1{\cdot}67\ l\,mol^{-1}$ at 25·0 °C. For further details we refer to the Experimental section. Thus in a 0·6 M solution of [6,10-$^1H_2$]-**3** only about 50% of the amidine is present in monomeric form. The other 50% is present as dimers, presumably mainly of the Dc type.

The next step in the elucidation of the nature of the catalytic species was to study the rate of rearrangement [3-^1H]-**1** → [3-^1H]-**2** as a function of [6,10-$^1H_2$]-**3** concentration, i.e. at various [D]/[M] ratios. In Figure 3 k_{obs} for this pseudo-first-order rearrangement is plotted



Scheme 6

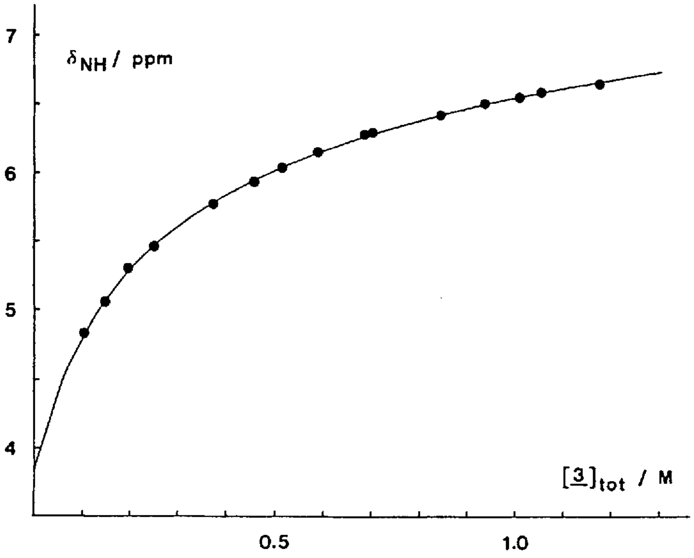


Figure 2. Plot of δ_{NH} vs $[[6,10\text{-}^1H_2]\text{-}3]_{tot}$ for dimerization of **3** in benzene at 25·0 °C. The solid line is a computer-simulated curve using $\delta_M = 3{\cdot}83$, $\delta_D = 8{\cdot}48$ and $K_D = 1{\cdot}67\ l\,mol^{-1}$

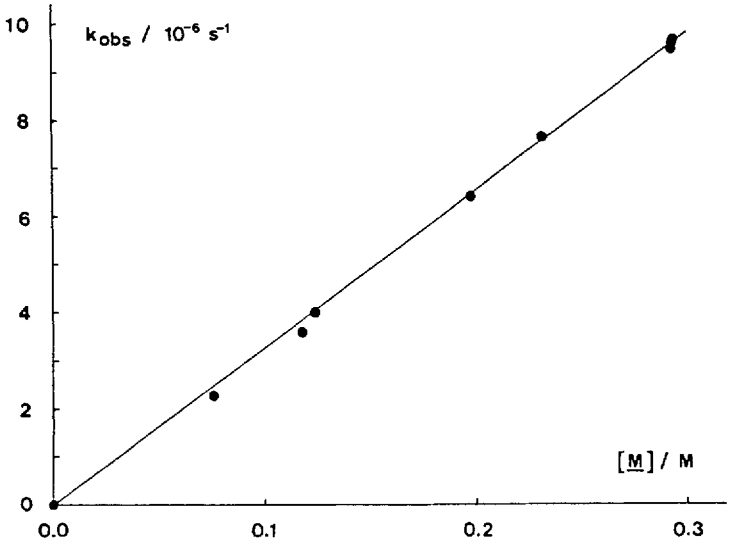


Figure 3. Dependence of k_{obs} on monomer concentration [M] of [6,10-$^1H_2$]-**3** at $K_D = 1 \cdot 67$ l mol^{-1} for the reaction of [3-^{1}H]-**1** → [3-^{1}H]-**2** in benzene at 25·00 °C

against the amidine monomer concentration obtained with $K_D = 1 \cdot 67$ l mol^{-1}. The linearity of this plot shows that no amidine dimers contribute significantly to the catalysis. Thus $k_{obs} = k_M[M]$ and k_M is estimated from the slope to be $32 \cdot 6 \times 10^{-6}$ l mol^{-1} s^{-1}.

Deuterium isotope effects

As mentioned above, the knowledge of what isotope effects to expect for two-hydron transfer reactions is limited.[9] However, in the present case the data in Table 3 exclude the possibility that we are dealing with a concerted two-hydron transfer mechanism. The main evidence against such a mechanism is the observed large difference between k^{HH}/k^{DH} (6·56) and k^{HH}/k^{HD} (1·19). A concerted transfer is expected to yield $k^{HH}/k^{DH} \approx k^{HH}/k^{HD}$ if the transition state is symmetric with respect to the hydron transfers (cf. A in Scheme 4).

Instead, we conclude, on the basis of the pronounced difference between these isotope effects, that the abstraction of the 3-hydron from **1** is rate limiting. However, the second hydron is presumably not transferred simultaneously but it could assist the abstraction of the 3-hydron from **1** by hydrogen bonding (cf. B in Scheme 4), thereby giving rise to a secondary isotope effect. Also, the other isotope effects in Table 2 are consistent with such a mechanistic picture and thus suggest a stepwise mechanism.

Hence a stepwise mechanism lends support from the similarity of pK_a values of **1** and **2** and the asymmetry of the two hydron transfers in combination with the accompanying hydron exchange reactions. It seems plausible that the rearrangement employs one or more ion-pair intermediates and that the transition state B or C is rate limiting and that D or E is populated in the hydronation of the intermediate preceding **2**. It seems likely that an ion pair with two hydrogen bonds (G) (Scheme 5) is on the reaction coordinate. The ion pairs are assumed to participate in the exchange reactions (cf. I).

However, we have to consider another mechanistic possibility, viz. that more than one reaction step may be rate limiting. The hydron abstraction from **1** and the hydronation of an intermediate to yield **2** may together be rate controlling, although in different amounts, i.e. the two transition states have similar free energies. Thus analysis using the mechanism in equation (5) shows that the two transition states contribute to the rate limitation to different extents in the experiments in Table 2, depending on the combination of labels. In equation (5) only the monomer is a catalyst, since the dimers have been proved not to take part significantly in the catalysis. Applying the steady-state approximation to equation (5) we obtain equation (6).

$$\mathrm{M} + \mathbf{1} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{I} \xrightarrow[k_{-2}]{} \mathbf{2} + \mathrm{M} \tag{5}$$

$$k_{\mathrm{M}} = k_1 \frac{k_{-2}}{k_{-1} + k_{-2}} \tag{6}$$

and for the observed isotope effects in Table 3 we derive the following expressions:

$$k^{\mathrm{HH}}/k^{\mathrm{DD}} = \frac{k_1^{\mathrm{HH}}}{k_1^{\mathrm{DD}}} \cdot \frac{k_{-2}^{\mathrm{HH}}}{k_{-2}^{\mathrm{DD}}} \cdot \frac{k_{-1}^{\mathrm{DD}} + k_{-2}^{\mathrm{DD}}}{k_{-1}^{\mathrm{HH}} + k_{-2}^{\mathrm{HH}}} \tag{7}$$

$$k^{\mathrm{HH}}/k^{\mathrm{DH}} = \frac{k_1^{\mathrm{HH}}}{k_1^{\mathrm{DH}}} \cdot \frac{k_{-2}^{\mathrm{HH}}}{k_{-2}^{\mathrm{DH}}} \cdot \frac{k_{-1}^{\mathrm{DH}} + k_{-2}^{\mathrm{DH}}}{k_{-1}^{\mathrm{HH}} + k_{-2}^{\mathrm{HH}}} \tag{8}$$

$$k^{\mathrm{HH}}/k^{\mathrm{HD}} = \frac{k_1^{\mathrm{HH}}}{k_1^{\mathrm{HD}}} \cdot \frac{k_{-2}^{\mathrm{HH}}}{k_{-2}^{\mathrm{HD}}} \cdot \frac{k_{-1}^{\mathrm{HD}} + k_{-2}^{\mathrm{HD}}}{k_{-1}^{\mathrm{HH}} + k_{-2}^{\mathrm{HH}}} \tag{9}$$

$$k^{\mathrm{HD}}/k^{\mathrm{DD}} = \frac{k_1^{\mathrm{HD}}}{k_1^{\mathrm{DD}}} \cdot \frac{k_{-2}^{\mathrm{HD}}}{k_{-2}^{\mathrm{DD}}} \cdot \frac{k_{-1}^{\mathrm{DD}} + k_{-2}^{\mathrm{DD}}}{k_{-1}^{\mathrm{HD}} + k_{-2}^{\mathrm{HD}}} \tag{10}$$

$$k^{\mathrm{DH}}/k^{\mathrm{DD}} = \frac{k_1^{\mathrm{DH}}}{k_1^{\mathrm{DD}}} \cdot \frac{k_{-2}^{\mathrm{DH}}}{k_{-2}^{\mathrm{DD}}} \cdot \frac{k_{-1}^{\mathrm{DD}} + k_{-2}^{\mathrm{DD}}}{k_{-1}^{\mathrm{DH}} + k_{-2}^{\mathrm{DH}}} \tag{11}$$

It we assume that

$$k_1^{\mathrm{HH}}/k_1^{\mathrm{DD}} = k_1^{\mathrm{HH}}/k_1^{\mathrm{DH}} = k_1^{\mathrm{HD}}/k_1^{\mathrm{DD}} = k_{-1}^{\mathrm{HH}}/k_{-1}^{\mathrm{DD}} = k_{-1}^{\mathrm{HH}}/k_{-1}^{\mathrm{DH}}$$
$$= k_{-1}^{\mathrm{HD}}/k_{-1}^{\mathrm{DD}} = k_{-2}^{\mathrm{HH}}/k_{-2}^{\mathrm{DD}} = k_{-2}^{\mathrm{HH}}/k_{-2}^{\mathrm{HD}} = k_{-2}^{\mathrm{DH}}/k_{-2}^{\mathrm{DD}} = 7$$

and that

$$k_1^{\mathrm{HH}}/k_1^{\mathrm{HD}} = k_1^{\mathrm{DH}}/k_1^{\mathrm{DD}} = k_{-1}^{\mathrm{HH}}/k_{-1}^{\mathrm{HD}} = k_{-1}^{\mathrm{DH}}/k_{-1}^{\mathrm{DD}} = k_{-2}^{\mathrm{HH}}/k_{-2}^{\mathrm{DH}} = k_{-2}^{\mathrm{HD}}/k_{-2}^{\mathrm{DD}} = 1$$

and, e.g., $k_{-2}^{\mathrm{HH}}/k_{-1}^{\mathrm{HH}} = 30$, we simulate the following isotope effects: $k^{\mathrm{HH}}/k^{\mathrm{DH}} = 6{\cdot}8$, $k^{\mathrm{HH}}/k^{\mathrm{HD}} = 1{\cdot}19$, $k^{\mathrm{HH}}/k^{\mathrm{DD}} = 7{\cdot}0$, $k^{\mathrm{HD}}/k^{\mathrm{DD}} = 5{\cdot}9$ and $k^{\mathrm{DH}}/k^{\mathrm{DD}} = 1{\cdot}03$.

The similarity of some of these values with those in Table 3 is striking, although significant differences are noticed and should be considered in the light of the following comments. In addition to the fact that the assumptions above do not take secondary isotope effects into account, we have made no corrections to the observed isotope effects from an isotope effect on the dimerization equilibrium of the amidine **3**. If $k^{\mathrm{HH}}/k^{\mathrm{DD}}$ is, e.g., 1·1, then correction of the isotope effects $k^{\mathrm{HH}}/k^{\mathrm{DD}}$, $k^{\mathrm{HH}}/k^{\mathrm{HD}}$ and $k^{\mathrm{DH}}/k^{\mathrm{DD}}$ in Table 3 should result in 3% larger values. Another correction originates from the fact that the substrate [3-^{2}H]-**1** contains about 0·5 atom-% of ^{1}H in the 3-position. We determine rate constants using only about 4% of conversion of substrate into product and, since the primary isotope effects are about 7, this small fraction of ^{1}H results in a correction of isotope effects $k^{\mathrm{HH}}/k^{\mathrm{DD}}$, $k^{\mathrm{HH}}/k^{\mathrm{DH}}$ and $k^{\mathrm{HD}}/k^{\mathrm{DD}}$. The correction increases the values by about 3·4%.

Further, some of the isotope effects in Table 3 should be increased slightly because the [6,10-$^{2}H_2$]-**3** used contained only 90 atom-% of ^{2}H in each of the labeled positions.

Even more important is the consideration that extensive $^{1}H/^{2}H$ exchange reactions are taking place within the reaction intermediates. If all corrections above were taken into account $k^{HH}/k^{DD} = 7{\cdot}7$ is predicted. Using this value and assuming that the rearrangement is occurring bifunctionally without any exchange and that $k_{-2}^{HH}/k_{-1}^{HH} = 10$, we predict the following isotope effects: $k^{HH}/k^{DH} = 7{\cdot}1$, $k^{HH}/k^{HD} = 1{\cdot}6$, $k^{HD}/k^{DD} = 4{\cdot}8$ and $k^{DH}/k^{DD} = 1{\cdot}09$. k_{-2}^{HH}/k_{-1}^{HH} was given the value 10 to reproduce the 'fixed point' k^{DH}/k^{DD}. The latter value is only slightly influenced by the correction and the exchange.

Hence the favored mechanism emerging is a stepwise one with two rate-limiting transition states (c.f. B–E in Scheme 4).

Why does the catalysis take place by a stepwise rather than a concerted mechanism?

We have concluded that the amidine **3**-catalyzed 1,3-proton transfer of **1** to **2** takes place by a stepwise and not by a concerted mechanism. In the first step a proton is transferred from carbon to nitrogen yielding a carbanion–amidinium ion pair. In a second step an amidinium proton is delivered to the carbanion yielding the rearrangement product **2**. Why is this stepwise process the low-energy pathway rather than the concerted mechanism in which the two protons are transferred simultaneously from carbon to nitrogen and from nitrogen to carbon?

It is known that in monofunctional catalysis by, e.g., amines there is a barrier towards protonation of the carbanion by the amidinium ion in the intermediate. Therefore, it seems reasonable to assume that there also should be a barrier for monofunctional protonation of the substitute allyl anion by an amidinium ion. In the rate-limiting transition state of the **3**-catalyzed rearrangement of **1** to **2**, neither the triphenyl-substituted allyl anion nor the amidinium ion is fully developed. As a consequence, we predict that a concerted two-proton transfer might have a considerably higher barrier than the stepwise process that we have elucidated experimentally.

EXPERIMENTAL

General

The NMR spectra were obtained with a JEOL JNM-FX100 Fourier transform spectrometer equipped with a 5 mm $^{1}H/^{13}C$ dual probe or with a Varian XL 400 Fourier transform spectrometer with a 5 mm switchable probe.

GLC analyses of substrate purity and the labeling experiments were performed with a Perkin-Elmer 990 gas chromatograph equipped with a 3 m × 3 mm i.d. column containing 3% Apiezon L on Varaport 30 (100–120 mesh). The carrier gas was nitrogen (172 kPa) and the oven was held at 185 °C. The injector and the detector temperatures were 210 and 235 °C, respectively.

Preparative GLC was performed with a Varian Aerograph 90P instrument equipped with a 0·6 m × 10 mm i.d. column containing 15% Apiezon L on Chromosorb W (60–80 mesh). The carrier gas was helium at a flow-rate of 60 ml min^{-1}. The oven temperature was 180 °C. The injector and the detector temperatures were held at 210 °C. The trapping equipment was cooled in liquid nitrogen.

The glove-box used was a Mecaplex GB 80, made of stainless steel and equipped with a gas-purification system which removed water and oxygen. The water content in the glove-box atmosphere was measured with a Shaw Model SHA-TR hygrometer. Typically, the content was

1–2 ppm at atmospheric pressure. Whenever possible, the preparations were performed in the glove-box.

The analytical equipment used in the kinetic studies is described under Kinetics.

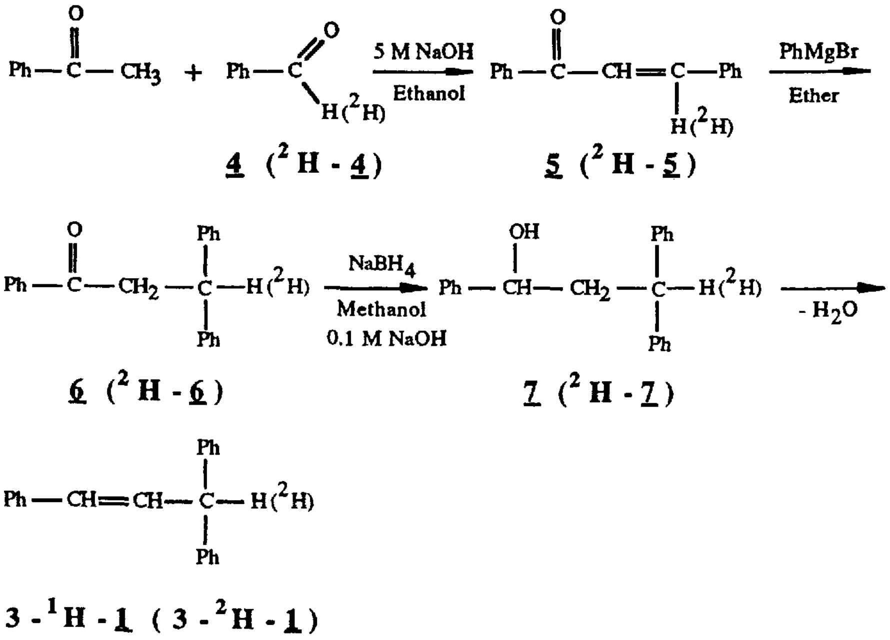
Synthesis and purification of substrates

1,3,3-Triphenylpropene ([3-^{1}H]-1). Prepared according to Scheme 7.

3,3-Diphenylpropiophenone (6)[11]. Prepared from benzylideneacetophenone (**5**)[12] by addition of phenylmagnesium bromide. Compound **5** was made by condensing acetophenone with benzaldehyde. The ketone **6** was reduced in the following way.

1,3,3-Triphenylpropan-1-ol (7). The ketone (**6**) (16·5 g, 0·06 mol), dissolved in 150 ml of methanol, was added to a mixture of 175 ml of methanol and $NaBH_4$ (3·0 g, 0·08 mol) in 41 ml 0·1 M NaOH. The reaction flask was kept at 45 °C during the whole addition and for a further 15 min. After evaporation of the methanol the residue was diluted with 250 ml of water and extracted with four portions (100 ml) of diethyl ether. The organic phase was dried over $MgSO_4$ and, after evaporation, the product was recrystallized from light petroleum. The yield of **7** was 14 g (85%), m.p. 73·5–74·5 °C (lit.[13] yield 95%, m.p. 72 °C).

1,3,3-Triphenylpropene ([3-^{1}H]-1). Prepared from **7** (13 g, 0·04 mol) by refluxing in 20% H_2SO_4. The product was purified by repeated recrystallization from ethanol. GLC analysis showed no impurities. Yield 9·8 g (80%), m.p. 98·5–99 °C (lit.[13] yield 85%, m.p. 98–99 °C). ^{1}H NMR (C^2HCl_3): δ 4·89 (d, 1H, C3-H), 6·35 (d, 1H, C1-H), 6·67 (q, 1H, C2-H) 7·3 (complex, 15H, aromatic).



Scheme 7

[3-^{2}H]-1,3,3-Triphenylpropene ([3-^{2}H]-1). Prepared according to Scheme 7 using [1-^{2}H] benzaldehyde ([^{2}H]-**4**), which was prepared from benzil, ^2H_2O and KCN.[14] After distillation the deuterium content was determined to be >99 atom-% (lit. 98 atom-%).

[3-^{2}H]Benzylideneacetophenone ([^{2}H]-5). Prepared in 76% yield from [1-^{2}H]benzaldehyde ([^{2}H]-**4**) and acetophenone using the method employed in the synthesis of **5**.[12] The deuterium content was not determined and the product, after recrystallization from ethanol, was used in the synthesis of [3-^{2}H]-*3,3-diphenylpropiophenone* ([^{2}H]-**6**).

[3-^{2}H]-3,3-Diphenylpropiophenone ([^{2}H]-6). Prepared from [^{2}H]-**5** by the procedure used for preparing **6**.[11] The yield of [^{2}H]-**6** was 66% and the product was used in the next step without an accurate determination of its deuterium content.

[3-^{2}H]-1,3,3,-Triphenylpropan-1-ol ([^{2}H]-7). Prepared from [^{2}H]-**6** (15·5 g, 0·054 mol) dissolved in 40 ml of diethyl ether and a mixture of 100 ml of methanol and $NaBH_4$ (3 g, 0·079 mol) dissolved in 40 ml of 0·1 M NaOH. The reaction mixture was kept at 45 °C during the addition of the solution of [^{2}H]-**6**. After completion of the addition, the solution was stirred at 45 °C for 15 min. The residue remaining after evaporation of the solvent was diluted with 230 ml of water and extracted with diethyl ether. The combined ether extracts (4 × 100 ml) were dried with $MgSO_4$ and evaporated to dryness. The residue was recrystallized from light petroleum, yielding 15·6 g (99·9%) of [^{2}H]-**7**. The deuterium content was not determined accurately.

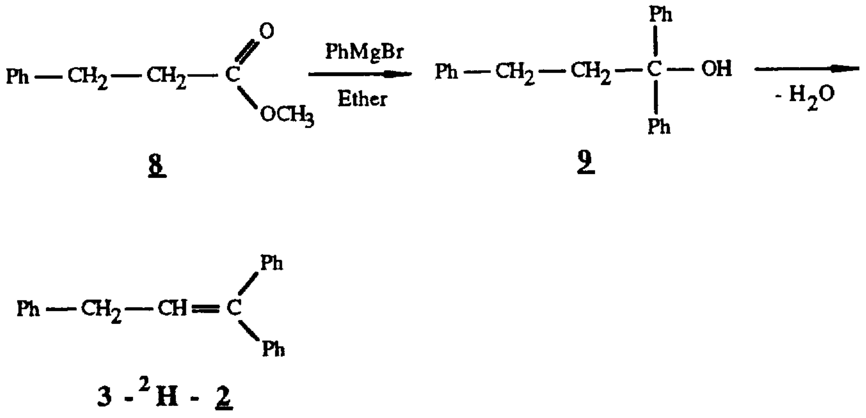
[3-^{2}H]-1,3,3-Triphenylpropene ([3-^{2}H]-1). Compound [^{2}H]-**7** (15·0 g, 0·052 mol) was dissolved in toluene (150 ml) and transferred to a water separator together with *p*-toluenesulphonic acid (ca 0·5 g). After 1·5 h of water elimination–separation the reaction mixture was cooled and washed with $NaHCO_3$ solution and finally with brine. After evaporation of the solvent some light petroleum was added to the viscous residue, whereupon it immediately crystallized. After two recrystallizations from ethanol a 72% yield (10·2 g) of [3-^{2}H]-**1** was obtained. Analysis by ^{1}H NMR using a ^{13}C satellite as reference showed that the product contained >99 atom-% of deuterium in the 3-position. GLC analysis showed no detectable impurities. ^{1}H NMR (C^2HCl_3): δ 6·35 (d, 1H, C1-H), 6·67 (d, 1H, C2-H), 7·3 (complex, 15H, aromatic).

1,1,3-Triphenylpropene ([3-^{1}H]-2). Prepared according to Scheme 8.

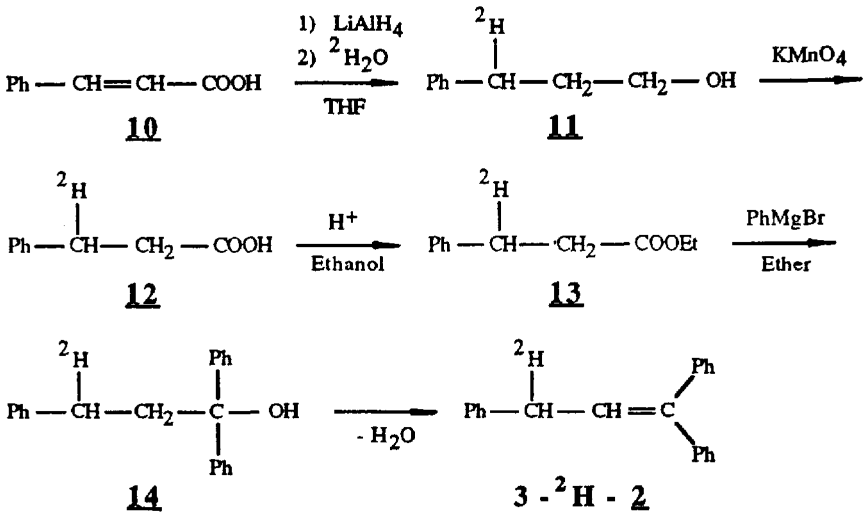
3-Phenylpropanoic acid methyl ester (8). Prepared from 3-phenylpropanoic acid and methanol in benzene. A Soxhlet extractor with molecular sieves (4 Å) trapped the eliminated water. The esterification was followed by TLC.

1,1,3-Triphenylpropan-1-ol (9)[15]. Prepared from **8** and a Grignard reagent made of bromobenzene and magnesium. The product was recrystallized twice from light petroleum, to which benzene had been added in small amounts until **8** dissolved in the boiling solvent.

1,1,3-Triphenylpropene ([3-^{1}H]-2). Prepared from **9** by *p*-toluenesulphonic acid-catalyzed elimination of water using the procedure described for the preparation of [3-^{2}H]-**1**. The product was distilled under reduced pressure, leaving a viscous liquid which crystallized when



Scheme 8



Scheme 9

stored at 5 °C. GLC analysis showed no trace of impurities. ^{1}H NMR (C^{2}HCl$_3$): δ 3·47 (d, 2H, C3-H), 6·26 (t, 1H, C2-H), 7·3 (complex, 15H, aromatic).

[3-^{2}H]-1,1,3-Triphenylpropene ([3-^{2}H]-2). Prepared according to Scheme 9.

[3-^{2}H]-3-Phenylpropan-1-ol (11). Prepared according to Almy and Cram.[16] The deuterium content of the product was not determined accurately.

[3-^{2}H]-3-Phenylpropanoic acid (12). Prepared from **11** by oxidation with KMnO$_4$ in KH$_2$PO$_4$–K$_2$HPO$_4$ buffer. After isolation, the acid was esterified with ethanol (cf. preparation of **8**).

[3-^{2}H]-1,1,3-Triphenylpropene ([3-^{2}H]-2). Prepared from **12** by the method described for [3-^{1}H]-**2**. The product was distilled under reduced pressure (145 °C, 0·1 mmHg) and purified by preparative GLC. ^{1}H NMR analysis showed that [3-^{2}H]-**2** contained >98 atom-% ^{1}H in one of the 3-positions. ^{1}H NMR (C^2HCl_3): δ 3·47 (d, 1H, C3-H), 6·26 (d, 1H, C2-H), 7·3 (complex, 15H, aromatic).

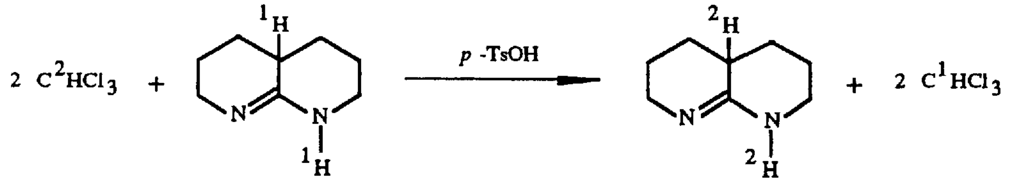
[3,3-^{2}H$_2$]-1,1,3-Triphenylpropene ([3,3-^{2}H$_2$]-2). Prepared from [3-^{2}H]-**1**. Sodium (5 g, 0·22 mol) was dissolved in 50 ml of CH_3O^2H in a nitrogen atmosphere. After completion of the reaction [3-^{2}H]-**1** (2 g, 0·007 mol) was added and the mixture was refluxed for 5 days. The reaction mixture was quenched with 1 M HCl (250 ml) and the solution was extracted with $CHCl_3$. The product was purified by repeated preparative GLC, yielding 1·5 g (73%) of [3,3-^{2}H$_2$]-**2**. No trace of impurities was detected by analytical GLC. Determination of the deuterium content by ^{1}H NMR using a ^{13}C satellite as reference showed [3, 3-^{2}H$_2$]-**2** to contain in the 3-positions more than 99 atom-% deuterium. ^{1}H NMR (C^2HCl_3): δ 6·26 (s, 1H, C2-H), 7·3 (complex, 15H, aromatic).

Synthesis and purification of catalysts

2,10-Diazabicyclo[4.4.0]dec-1-ene ([6,10-^{1}H$_2$]-3). Prepared according to the procedure developed by Löfås and Ahlberg.[17] Purification was performed by repeated sublimations (0·02 mmHg, 60–70 °C). All manipulations of the compound were performed in a glove-box.

[6,10-^{2}H$_2$]-2,10-Diazabicyclo[4.4.0]dec-1-ene ([6,10-^{2}H$_2$]-3). Prepared by acid-catalyzed ^{1}H/^{2}H exchange of [6,10-^{1}H$_2$]-**3** with C^2HCl_3 (Scheme 10). Thus not only the nitrogen-bonded hydrogen undergoes exchange but also the carbon-bonded hydrogen in the 6-position, presumably via a ketene aminal intermediate.[18] The apparatus shown in Figure 4 was designed to be able to perform repeated ^{1}H/^{2}H exchanges and sublimation without exposure to air. Non-deuteriated aminine was introduced into compartment 1 together with a stirrer bar and C^2HCl_3 was added through the Mininert® valve (4) using a syringe (5). The syringe was removed after addition of each portion of C^2HCl_3. The apparatus was connected to an oil-pump vacuum through the outlet 6 and to nitrogen through the inlet 7 to re-establish the pressure after each evaporation. During the sublimation the sublimate was collected in tube 2 and a mixture of product and impurities in compartment 3, which was held at ca −30 °C.

Into compartment 1 1·26 g (9·17 mmol) of [6,10-^{1}H$_2$]-**3**, 5 ml (0·06 mol) of dried C^2HCl_3 (>99·5 atom-%) and a small grain of *p*-toluenesulfonic acid were introduced. After 3 h of reaction the solvent was evaporated while stirring the solution. A further 5 ml of C^2HCl_3 were added and the procedure was repeated. Altogether the exchange reaction and evaporation were carried out four times. The residue was sublimed at 50–75 °C (0·49 mmHg) for about 2 h,



Scheme 10

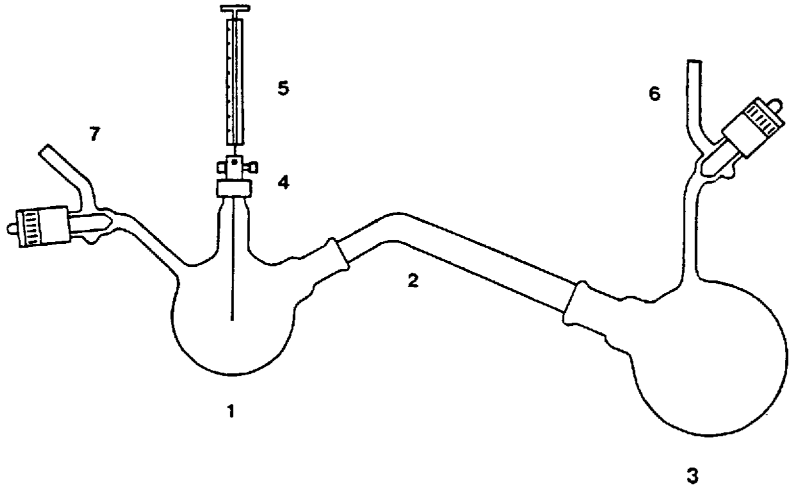


Figure 4. Apparatus used for repeated $^1H/^2H$ exchange and sublimation of 3

yielding 0·87 g (69%) of [6,10-$^2H_2$]-**3**. To achieve the required purity, further sublimation was performed with a Büchi block, avoiding exposure of the amidine to air. A 7 mm diameter glass tube equipped with a tap was used and the sublimation of 0·148 g lasted 5 h at 79–84 °C. The yield was 0·124 g (84%). ^1H NMR studies showed that in the product used in the kinetics 90% of the nitrogen-bonded hydrogen atoms were deuterium atoms. The amidine used for the labeling experiments was 96 atom-% deuteriated in the 10-nitrogen position. The analysis was carried out in [$^2H_6$]benzene as solvent.

Determination of the dimerization constant for the amidine ([6,10-$^1H_2$]-3)

There were reasons to believe that **3** is substantially dimerized in benzene and that cyclic dimers are strongly favored over linear dimers (D1) (Scheme 6). Instead of selecting microcalorimetry, which has been used previously to determine association constants,[6a,19] ^1H NMR was applied because of the expected large chemical shift difference of the nitrogen-bonded hydrogens of the monomer and those participating in hydrogen bonds. Only a single peak from the nitrogen-bonded hydrogens of [6,10-$^1H_2$]-**3** was observed, but its chemical shift (δ_{NH}) showed a considerable dependence on the concentration of the amidine. Figure 2 shows a plot of δ_{NH} vs the total concentration of [6,10-$^1H_2$]-**3**. The amidine solutions were prepared by successive dilution of a 'mother' solution of [6,10-$^1H_2$]-**3** using syringes. The data in Figure 2 were analyzed using equations (12) and (13), where δ_M and δ_D represent the chemical shifts of M and D, respectively.[10] Equation (12) is a corrected version of the corresponding equation in Ref. 10. Since cyclic dimers presumably dominate strongly over the linear dimers, the parameter δ_D is essentially equal to δ_{Dc} and [D] equals [Dc].

$$\delta_{NH} = (\delta_M[M] + 2\delta_D[D])/([M] + 2[D]) \tag{12}$$

$$K_D = [D]/[M]^2 \tag{13}$$

Computer simulation gave values of $K_D = 1{\cdot}67\ \mathrm{l\,mol^{-1}}$, $\delta_M = 3{\cdot}83$ and $\delta_D = 8{\cdot}48$ at 25·0 °C. Thus about 50% of [6,10-$^1H_2$]-**3** is present as dimers in a 0·6 M solution of [6,10-$^1H_2$]-**3**.

Kinetics

A closer analysis of the necessary conditions for the accurate experimental determination of isotope effects for the catalyzed rearrangement **1** → **2** showed the major pitfall to be caused by the back-reaction **1** ← **2** in combination with isotope exchange. Therefore, we decided to make use of only the beginning of the reaction, i.e. to base the rate constant determinations on only ca 4% rearrangement. This allows us to ignore the back-reaction, since $[\mathbf{2}] \ll [\mathbf{1}]$. Modern capillary GLC makes such an approach possible. The following derivation has been used:

$$\frac{\mathrm{d}[\mathbf{1}]}{\mathrm{d}t} = -k_{\mathrm{obsd}}[\mathbf{1}]; \; k_{\mathrm{obsd}} = k_1[\mathbf{3}]$$

$$\ln([\mathbf{1}]_t/[\mathbf{1}]_0) = -k_{\mathrm{obsd}}t; \; [\mathbf{1}]_t + [\mathbf{2}]_t = [\mathbf{1}]_0; \; [\mathbf{2}]_0 = 0$$

$$\ln\left(1 - \frac{[\mathbf{2}]_t}{[\mathbf{1}]_0}\right) = -k_{\mathrm{obsd}}t$$

Thus k_{obsd} was evaluated from plots of $-\ln(1 - [\mathbf{2}]_t/[\mathbf{1}]_0)$ vs t.

All glassware used in the kinetic studies was rinsed with 1 M HCl, distilled water, aqueous ammonia and finally with several portions of distilled water. The syringes and caps were treated with benzene and ethanol. All equipment was dried at 110 °C for at least 24 h, except for the syringes, caps and volumetric flasks, which were dried at 50 °C.

All kinetic runs were performed in a HETO 02 PT 623 thermostat at 25·00 °C. The temperature variation during the experiments was less than ±0·01 °C. The absolute accuracy in the temperature determinations was better than ±0·03 °C. The bath temperature was measured using a precalibrated thermometer with a relative accuracy of ±0·02 °C. Conical flasks with PTFE-coated septa were used as reaction vessels. The septa were found to be tight enough for the present purposes.

A benzene solution (2 ml) of the catalyst (0·64 M) was prepared in the glove-box, which also hosted a balance. Using a dried syringe 500 μl of the amidine solution were transferred into the reaction vessel within the glove-box, the vessel was placed in the thermostat, and after equilibration, 50 μl of a benzene solution of the substrate (0·60 M) were added to the vessel with a syringe. At intervals samples (30–50 μl) were removed from the reaction mixture with a syringe. The sample was immediately quenched in 2 ml of 1 M HCl and ca 150 μl of benzene were added. After extraction the benzene phase was washed with 2 ml of water and analyzed by capillary GLC as described below.

All reaction mixtures were analyzed using a Varian GC 3400 instrument equipped with a Varian 8000 autosampler. All data treatments were carried out using a Varian DC 604 computer. The column of choice for the separation of the two triphenylpropenes was a DB-5 fused-silica capillary column (corresponds to SE-54) with a film thickness of 0·25 μm. The column dimensions were 30 m × 0·32 mm i.d. and the carrier gas (nitrogen) flow-rate was 1·02 ml min^{-1}. The injector temperature (splitless injection) was 230 °C and the detector (flame ionization) temperature was 235 °C. The following oven temperature program was used: initial column temperature 60 °C with an initial hold time of 1 min, increased to 150 °C at 50 °C min^{-1}, to 200 °C at 40 °C min^{-1} and to 250 °C at 30 °C min^{-1} with a final hold time of 4 min. The total analysis time was 9·71 min. The autosampler sampled a volume of 0·7 μl and the injection time was 0·03 min.

Splitless injection was chosen because the split mode did not yield reproducible results. The splitless mode demands reproducible injection times and volumes. A 4 mm open glass insert packed with glass-wool was used to increase vaporization. The procedure was highly reproducible and gave the required accuracy. In the splitless mode, almost all of the sample is transferred on to the column. The split valve solenoid was closed for 1 min and then opened to flush out the remaining sample. In this way severe solvent peak tailing was avoided. Figure 5 shows a typical chromatogram and Figure 6 shows plots of $-\ln(1-[\mathbf{2}]/[\mathbf{1}]_0)$ vs time for the

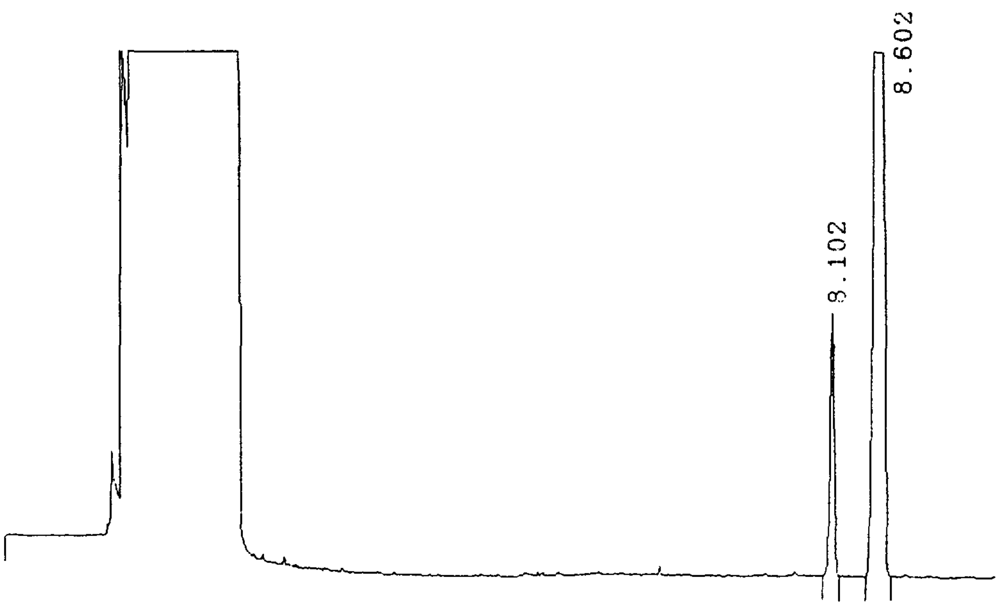


Figure 5. A typical chromatogram showed at 3% reaction. The left-hand (minor) peak refers to the product (**2**) and the right-hand peak to the substrate (**1**). The stepped peak lines are a consequence of the printer used. Integration was of course performed much more accurately. The resolution value was 6 or greater

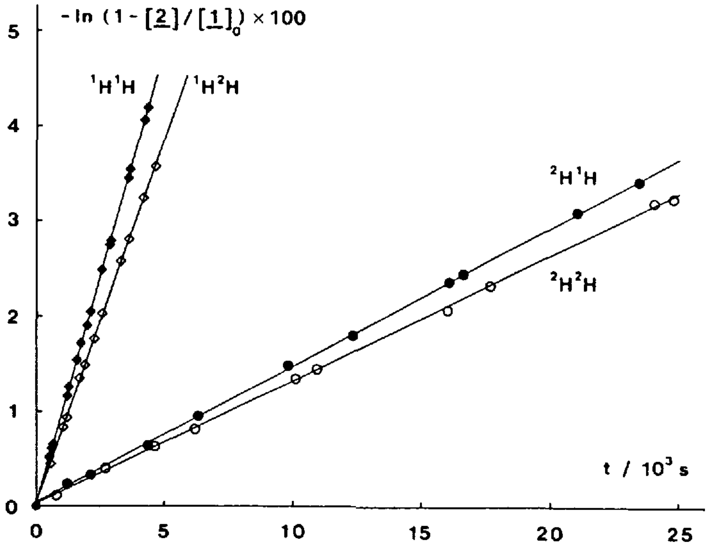


Figure 6. Plots of $-\ln(1-[\mathbf{2}]/[\mathbf{1}]_0)$ vs time for the runs in Table 2. The labels ^{1}H^{1}H, ^{1}H^{2}H, ^{2}H^{1}H and ^{2}H^{2}H refer to the substrate (first letter) and catalyst (second letter)

runs collected in Table 2. The ratio $[\mathbf{2}]_t/[\mathbf{1}]_0$ has been shown by calibration to be equal to the peak area of **2** divided by the sum of the peak areas of **1** and **2** at reaction time *t*.

ACKNOWLEDGEMENTS

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