Uncatalyzed Meerwein−Ponndorf−Oppenauer−Verley Reduction of Aldehydes and Ketones under Supercritical Conditions

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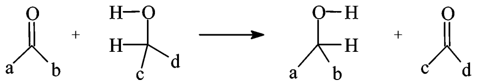
When a solution of a carbonyl compound in alcohol (primary or secondary) is heated to ca. 300 °C, a disproportionation reaction, in which a carbonyl compound is reduced to the corresponding alcohol and the alcohol is oxidized to the corresponding ketone, takes place. This uncatalyzed variation of the Meerwein−Ponndorf−Oppenauer−Verley reaction gives, in certain cases, e.g., reduction of acetophenone or benzaldehyde by *i*-PrOH, almost quantitative yields. Yields are higher with secondary alcohols such as *i*-PrOH than with a primary alcohol such as EtOH. The reactions were also performed in a flow system by passing at a slow rate the same solutions through a glass or a metal coil heated to elevated temperatures. Ab initio calculations performed at the B3LYP/6-31G* level show that thermodynamically *i*-PrOH is a more potent reducing agent than EtOH by ca. 4 kcal/mol. The computations also show that in cases of aromatic carbonyl compounds, part of the deriving force is obtained from the entropy change of the reaction. The major contributor to the high yield, however, is the excess alcohol used, which shifts the equilibrium to the right. Calculated entropy of activation as well as isotopic H/D labeling suggest a cyclic transition state.

Introduction

The disproportionation reaction between carbonyls and alcohols involving hydrogen transfer between the two (eq 1) was discovered about 70 years ago by Meerwein, Ponndorf, and Verley in the context of the reduction of the carbonyl compound (aldehyde or ketone) to the corresponding alcohol.[1−3] About 10 years later the reversible nature of the reaction was realized by Oppenauer, who illuminated the oxidation capability of the reaction.[4] This reaction is usually catalyzed by trivalent aluminum in an assumed cyclic transition state (eq 2).



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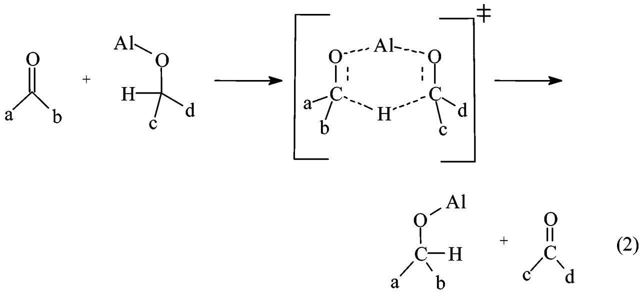

(2)

Despite its seniority in chemistry, a literature survey of recent years shows that this reaction does not cease to attract the attention of the chemical community. New uses and improvements are continually suggested,[5−8] as well as new catalysts such as borinic acid derivatives,[9] magnesium phosphates,[10] Ir, Rh complexes,[11,12] and chromium derivatives.[13]

In the course of our studies of reactions under supercritical conditions we have discovered that mixing a carbonyl compound (aldehyde or ketone) with alcohol at elevated temperatures induces the disproportionation typical of the Meerwein−Ponndorf−Oppenauer−Verley reaction. We report here the results of a study regarding the scope and limitation of this variation of the H transfer reaction with a brief examination of the mechanistic options. In light of the world's need for industrial green chemistry, we have also explored the feasibility of a continuous flow method. However, no attempt was made to optimize the method with respect to time, temperature,

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TABLE 1. Yields of Corresponding Alcohols in the Reduction of Various Carbonyl Compounds by *i*-PrOH and EtOH under Standard Conditions

substrate	yield (%) EtOH	yield (%) *i*-PrOH
PhCOMe	14	93
m-$MeOC_6H_4CHO$	52	85
m-$PhOC_6H_4CHO$	67	>98

TABLE 2. Effect of Added Base on the Reduction Yield under the Standard Conditions

ROH	NaOH	yield (%)
	PhCOMe	
EtOH	−	14
EtOH	+	42
i-PrOH	−	93
i-PrOH	+	78
	Cyclohexanone	
EtOH	−	36
EtOH	+	41
i-PrOH	−	50
i-PrOH	+	100

or yield. We were rather interested in exploring the boundaries and possibilities provided by this new approach.

Results and Discussion

Not unexpectedly, the alcohol giving the best results among the simple aliphatic alcohols was *i*-PrOH. Given in Table 1 are the results of a comparative study of the reduction of three carbonyl substrates by *i*-PrOH and EtOH. All of the reactions were performed under the same conditions, namely, $T = 300$ °C, $t = 1.5$ h, with substrate concentration ca. 10 wt % in the appropriate alcohol (standard conditions).

As can be seen from the results depicted in Table 1, *i*-PrOH is by far superior to EtOH. It should be emphasized that the high yields obtained with *i*-PrOH imply that after 1.5 h, the reaction has essentially reached complete, or nearly complete, equilibration. The gap between the effectiveness of the two alcohols is therefore much larger than the simple yields ratio and would have been better manifested at shorter reaction times. Of course, to obtain quantitative comparison, initial rates or initial yields have to be determined. However, as stated above, this was not the objective of this scope study.

Another conclusion that can be derived from the data in Table 1 is that although in our standard conditions we have used a reaction time of 1.5 h, for practical purposes, reaction times should be tailored to the specific reactant. Thus, for example, acetophenone, which yielded 93% after 1.5 h, yielded 85% of the corresponding alcohol already after only 0.5 h.

It is common, well-established knowledge that the Meerwein−Ponndorf−Oppenauer−Verley reaction is catalyzed by base. We have examined the sensitivity of our reaction to base by adding a small amount of NaOH (0.025 M in the *i*-PrOH solution) to the reaction mixture. Table 2 shows that although the addition of base improved the results in the case of EtOH reducing acetophenone, it slightly lowered the yield with *i*-PrOH as the reducing agent. On the other hand, whereas cyclohexanone benefited only marginally from the addition of the base in EtOH, the yield in *i*-PrOH jumped from 50% to 100% as a result of added base.

TABLE 3. Yields in Reduction of *m*-Methoxy Benzaldehyde by *i*-PrOH as a Function of Reaction Temperature (Standard Conditions Except for Temperature)

	T (°C) 240	260	280	300
yield (%)	32	61	89	99

Because of the ambiguity of the results it was suspected that catalytic sites on the metallic surface of the reaction container enhance the reaction. We have therefore conducted a series of experiments using three different cells. Two of them were cells fabricated from Swagelock parts made of either stainless steel or copper (see Experimental Section). In addition the reaction was also carried out in a glass ampule. We have found no differential effect of the surface material on the reaction yield.

Another important factor in this reaction is the temperature. Table 3 displays the effect of the reaction temperature on the yield of the alcohol in the reduction of *m*-methoxy benzaldehyde in the range 240−300 °C under the standard reaction conditions.

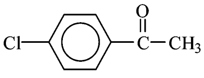
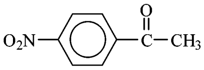
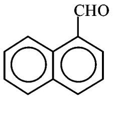
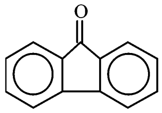
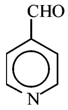
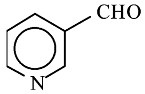
Clearly, the reaction is enhanced by the temperature. Assuming that the reverse reaction, namely, oxidation of the benzyl alcohol by the acetone, produced in the first step, is negligible and that the reaction is pseudo-first-order in the substrate, we can calculate the reaction rate constants at each temperature and derive from these the activation energy. Rate constants of 0.0007, 0.0017, and 0.0041 s^{-1} were obtained for the temperatures 240, 260, and 280 °C (the value at 300 °C was too close to equilibrium). These values lead to an activation energy of 24.5 kcal/mol. These values should be considered as rough estimates since the reaction time of 1.5 h is measured from the moment the reaction vessel is placed in the oven and does not reflect the actual time the reaction mixtures were incubated at the said temperatures.

Table 4 lists the results for a variety of additional carbonyl compounds.

All of the above reactions were done in batch. This is a major drawback of the method for industrial uses. Hence, we have explored the applicability of this reaction to a continuous flow system. The system consists of a syringe pump that pushes the reaction mixture into a spiral column placed in an oven and then through an orifice to a receiver where the mixture is collected and cooled. The results are given in Table 5. The temperature recorded was measured at the center of the oven, and the flow rate of the liquid reaction mixture at the exit of the pump was set to 2 mL/h.

Obviously, the yield in this case depends on the flow rate. This was demonstrated in the following experiments. 2-Butanone was dissolved in *i*-PrOH to a concentration of 15 wt %. The temperature at the center of the oven was maintained at 350 °C. In the first experiment the flow rate was 2 mL/h, yielding 81% of the starting material and 19% of 2-BuOH. When the flow rate was

TABLE 4. Yields of Corresponding Alcohols in the Reduction of Various Carbonyl Compounds by *i*-PrOH at Standard Concentration and Temperature

Substrate	Reaction Time	Yield %
	1.5	32
	1.5	19
	1.5	62
	1.5	66
PhCH=CH-CHO	1.0	46
	3.0	>95
	3.0	>98
$CH_3CH_2CH_2CHO$	3.0	>98

increased to 14 mL/h, the yield dropped drastically to only 2% of the desired alcohol and 98% of the starting material.

Mechanistic Aspects. Because one of the major factors determining the yield of these reactions is the thermodynamic deriving force, we have performed an ab initio calculation at the B3LYP/ 6-31G* level[14] for the isodesmic reaction[15] shown for the case of benzaldehyde and EtOH in eq 3.

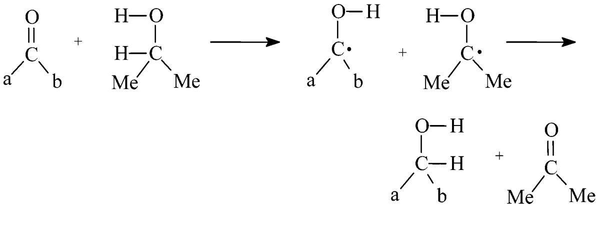
$$PhCHO + EtOH \rightleftharpoons PhCH_2OH + CH_3CHO \qquad (3)$$

The results are given in Table 6.

A clear outcome of the computational data is that *i*-PrOH is a better reducing agent than EtOH, probably stemming from the additional stabilizing Me−C=O interaction present in acetone in comparison with acetaldehyde. This is reflected in the exothermicity of the reaction of acetaldehyde with *i*-PrOH (4.1 kcal/mol) and is manifested, although to a lower extent, in the reaction of PhCHO compared to PhCOMe. These two reactions are endothermic probably because the conjugative interaction between the carbonyl group and the ring is lost in the product. However, the reaction of PhCOMe is more endothermic (by ca. 2 kcal/mol) as a result of the additional Me group. The endothermicity of the reaction suggests that the reaction energy will tilt the equilibrium constant (8.8 at 573 K) in favor of the reactants. This, however, can be balanced by a change in entropy that will render the reaction favoring the products in terms of free energy. Using the ab initio calculated thermodynamic data we indeed obtain that at 300 °C the overall $\Delta G = -0.6$ kcal/mol. This value translates at $T = 573$ K to $K = 1.7$. Thus, the entropy factor shifts the equilibrium to the right and hence there is a small preference in terms of free energy to the products. The major "push" in the product direction comes from the mass effect. Having a large excess of the reducing alcohol over the substrate is the main cause for having such a high yield in the reaction.

In the classical mechanism of the Meerwein−Ponndorf−Oppenauer−Verley reaction, the transition state encompasses aluminum alkoxide in which a hydride is transferred to the carbonyl carbon in a cyclic array. Clearly, this is only a descriptive presentation of the mechanism and the degree of ionicity at the transition state is rather small. The major ionic component is introduced in the ground state in the Al−O bond. However, the gas phase tolerates much less ionicity than the condensed phase, and therefore we should expect either a radical mechanism or a neutral cyclic transition state. The latter could be envisioned as the traditional transition state in which an H atom assumes the position of the Al atom.

A neutral noncyclic transition state will most probably involve two consecutive H radical transfer steps. The first H transfer will be from the central C−H unit of *i*-PrOH to the oxygen of the carbonyl group and the second from the OH of *i*-PrOH to the carbonyl carbon (eq 4).



(4)

This differs from the traditional cyclic transition state in which the hydrogen is exchanged between two carbons. A convenient way to resolve the two options is to use *i*-PrOD instead of *i*-PrOH. Since in the cyclic transition state hydrogen is transferred between two carbon atoms, such a transition state will produce no deuterium labeling at the benzylic position of a substrate such as benzaldehyde. On the other hand, as was pointed out above, a sequence of H transfers will produce PhCHDOH from the same substrate.

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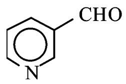
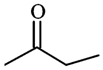
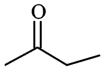
[15] An isodesmic equation is one in which there are equal numbers of each type of bond on each side. Clark, T. *A Handbook of Computational Chemistry*; Wiley: New York, 1985; p 97.

TABLE 5. Results of Reduction Experiments Using *i*-PrOH in the Flow System[a]

Substrate	Conc. %	T^{0}C	Alcohol	RCH_3	Impurities
PhCHO	13.9	350	62	19	2
$PhCOCH_3$	14.1	350	18	16	3
$PhCOCH_3$	10	400	-	20	-
	11.8	350	15	34	20
	10.4	400	24	-	-
	13.4	300	12	-	-

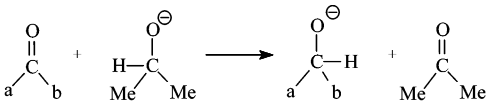
[a] Yields are given as percents of the starting material.

TABLE 6. Ab Initio (B3LYP/6-31G*) Computed Energies for Model Compounds Used in the Isodesmic Reaction and Their Reaction Energies (ΔE) with *i*-PrOH and EtOH

		ΔE (kcal/mol)	
compound	HF (au)	*i*-PrOH	EtOH
i-PrOH	−194.3533105		
acetone	−193.1556937		
EtOH	−155.0342889		
MeCHO	−153.8301224	−4.1	0.0
$PhCH_2OH$	−346.7705987		
PhCHO	−345.5734556	0.3	4.4
cyclohexanol	−311.0902461		
cyclohexanone	−309.8912915	−0.8	3.3
$PhCH(OH)CH_3$	−386.089635		
$PhCOCH_3$	−384.8959876	2.5	6.6

Heating benzaldehyde with *i*-PrOD for 1 h under standard conditions gave 87% of benzyl alcohol where no D atoms were incorporated into the benzylic position. This implies that in the reduction the carbonyl carbon obtains the hydrogen from the central carbon of *i*-PrOH as in the classical mechanism and therefore strongly suggests that the reaction takes place in a single step via a cyclic transition state rather than through a two consecutive H transfer steps. The large negative entropy of activation calculated for the reaction points also to a highly ordered transition state.

The mechanism of the base-catalyzed reaction has not been explored and may either take place via a single-step cyclic transition state taking place at the surface of the reaction vessel or involve either a hydride transfer from the alkoxide to the carbonyl carbon (eq 5) or H radical transfer to the carbonyl oxygen (eq 6). The latter produces a radical anion of acetone, which may be involved in a multitude of other elementary processes.



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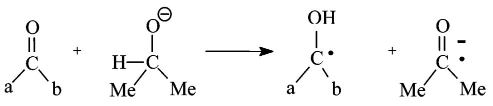
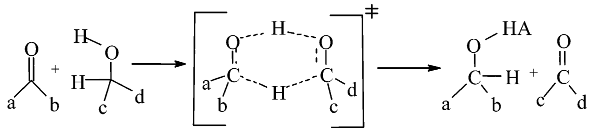


(6)

Summary and Conclusions

We have shown that at elevated temperatures the normally catalyzed Meerwein−Ponndorf−Oppenauer−Verley reaction takes place in a noncatalytic fashion. It may be driven nearly to completion, even in cases of endothermic reactions by using a large excess of the alcohol. The reaction is usually clean and does not yield wastes to be desposed of; the product carbonyl compound derived from the sacrificial alcohol can be easily separated and used in a different reaction. On the basis of isotopic labeling results we conclude that the transition state of the rate-determining step is cyclic.



The role of the metal catalyst is, most probably, to bridge the two reacting parties in the conformation, which will enable the transfer of hydride. The increased number of collisions at high temperature and the higher energy content of the molecules compensates for the absence of the bridging metal in our case. The alcoholic proton most likely functions as the metallic catalyst by forming a hydrogen bond between the alcohol and the carbonyl function. An indication of such a bonding can be found in Table 4 where electron-withdrawing substituents on the aromatic nucleus drastically reduce the yield.

Experimental Section

The static reaction was carried out in a 2-mL closed cell, which was assembled from stainless steel Swagelok parts. A 3/8 in. union part was capped from one side by a standard plug. The reaction mixture was introduced into the union and plugged from the other side. The cell was filled with 0.8−0.9 mL of liquid. At the end of the reaction the cell was cooled in the air. All manipulations with the reactants or products in the deuterated 2-propanol experiments were conducted inside a glovebox under nitrogen.

In the flow experiments we have used either copper, stainless steel, or glass tubings. The stretched length of the metallic coils was about 2 m, whereas the glass coil was about 150 cm. The tubings were coiled and placed in an oven. The diameter of the tubings was 1/4 in.

Reaction mixtures were analyzed using a 300-MHz NMR spectrometer. The accuracy of the integration is better than 5%.

Supporting Information Available: Gaussian archive files for structures appearing in Table 6. This material is available free of charge vi the Internet at http://pubs.acs.org.

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