Transfer Hydrogenation

Insight into and Practical Application of pH-Controlled Asymmetric Transfer Hydrogenation of Aromatic Ketones in Water**

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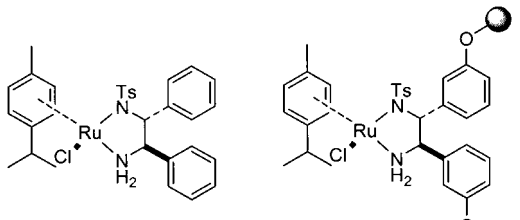
Dedicated to Professor Ryoji Noyori

Catalysis in water represents a major area of intense research in modern chemistry.[1] Water is inexpensive, readily available, and environmentally benign, and is thus an ideal solvent for chemical reactions. We recently reported that asymmetric transfer hydrogenation of aromatic ketones with the Ru–(*R*,*R*)-Ts-dpen catalyst (Ts-dpen = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) or its polymer-supported analogue



Ru–(*R*,*R*)-Ts-dpen Ru–(*R*,*R*)-PTs-dpen

Ru–(*R*,*R*)-PTs-dpen (PTs-dpen = poly(ethylene glycol)-supported Ts-dpen) can be considerably accelerated by using water as solvent and in the case of Ru–(*R*,*R*)-PTs-dpen, the catalyst was recycled more than 10 times without loss of enantioselectivity.[2,3] The reducing agent used in those studies was HCOONa. To our surprise, when the often-used HCOOH–NEt_3 azeotrope was adopted as reductant for the same reaction in water, a much slower reaction was observed. This prompted us to investigate whether the reaction was affected by the pH value of the solution. Although Benyei and Joó reported that the rate of transfer hydrogenation of benzaldehyde by aqueous HCOONa with a water-soluble

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Ru^{II}–phosphine catalyst is independent of the pH value of the solution under basic conditions,[4] recent work from Ogo et al. revealed a strong pH dependence in the rate of the reduction of ketones by HCOONa with $[(\eta^6\text{-}C_6M_6)Ru(bpy)(H_2O)]^{2+}$ (bpy = bipyridyl) in water.[5] However, there appear to be no reported studies on how the pH values may affect asymmetric transfer hydrogenation in aqueous media.

Asymmetric transfer hydrogenation of ketones is a powerful alternative to asymmetric hydrogenation for the production of chiral alcohols.[6] Among the various chiral catalysts reported, the most notable is the Ru–Ts-dpen catalyst developed by Noyori, Ikariya, Hashiguchi, and co-workers.[7] This catalyst and the related variants have been successfully applied by Noyori, Ikariya, and others to a wide range of prochiral ketones and imines.[3,7–9] The reaction is most often performed in 2-propanol or the HCOOH–NEt_3 azeotropic mixture; they act as both solvents and hydrogen sources. However, the transfer hydrogenation under such conditions tends to be sluggish, accompanied with low productivity. We herein report that asymmetric transfer hydrogenation with the Noyori–Ikariya catalyst is pH dependent and can be effected in faster rates, with little compromise on enantioselectivities, by a smaller amount of HCOOH–NEt_3 in water. Our preliminary observations concerning why the reduction is pH dependent are also presented.

Following on from our finding that aromatic ketones can be reduced more rapidly by HCOONa in water than in HCOOH–NEt_3 with the Ru–Ts-dpen catalyst,[2] we wondered whether similar acceleration in rates could be achieved with the azeotrope in water as solvent. We set out by examining the asymmetric transfer hydrogenation of acetophenone to 1-phenylethanol. As before,[2a] the precatalyst was generated by treating (*R*,*R*)-Ts-dpen (0.012 mmol) with $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.005 mmol) in water (1 mL) at 40 °C for 1 h, and the reduction started by introducing the HCOOH–NEt_3 azeotrope (1.0 mL; molar ratio HCOOH/NEt_3 = 2.5:1) and acetophenone with a substrate/catalyst (S/C) ratio of 100:1. Surprisingly, less than 2% conversion was observed after reduction at 40 °C for 1 h; the conversion rose to 98% after a prolonged time of 12 h. This is in stark contrast to the observation made with HCOONa in water, under which the ketone was fully converted into (*R*)-1-phenylethanol in 1 h albeit with a lower enantioselectivity (94 vs. 97% *ee*). The most discernable difference between the two systems was the pH value of the solution. The pH value of the azeotrope–water system was 3 at the beginning of the reaction; the aqueous HCOONa solution was far more basic (pH 7). Thus the question arose: Was the reaction rate affected by pH values, and if so, could the reduction be accelerated by adjusting the pH value?

To address this issue, we measured the initial rates of the reduction of acetophenone (1.0 mmol) in water (0.5 mL) at various initial solution pH values by adjusting the HCOOH/NEt_3 molar ratios; the total solution volume remained constant at 1.0 mL, however. Figure 1 shows the initial turnover frequency (TOF) as a function of the starting pH values. Our speculations were confirmed as the reaction barely took place at low pH values; it accelerated at pH 3.9, with the acceleration slowing down at approximately pH 4.8.

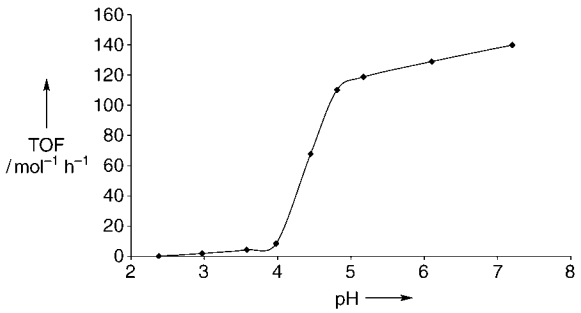


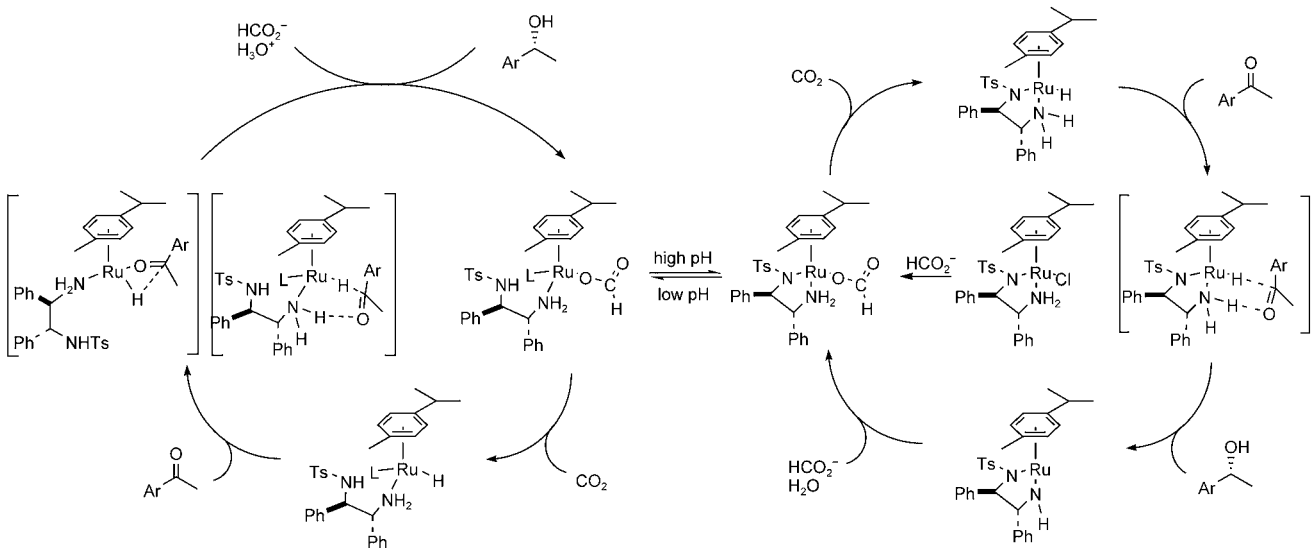
Figure 1. Initial TOF against initial solution pH values for the reduction of acetophenone (1 M, assuming the solution is homogeneous) by HCOOH–NEt_3 in water (1 mL total volume) with Ru–(*R*,*R*)-Ts-dpen at 40 °C. The initial pH values were determined by varying the HCOOH/NEt_3 molar ratios from 4.6:1.0 to 0.37:1.0.

The rate appeared to level off at pH > 7. However, examination of the effect of a further pH increase on the rate was difficult under the chosen conditions. The aforementioned $[(\eta^6\text{-}C_6M_6)Ru(bpy)(H_2O)]^{2+}$ resulted in a decreased rate at pH > 6 in the reduction of ketones.[5] This was attributed to the formation of a Ru^{II}–OH complex by deprotonation of a coordinated H_2O. The less significant effect of higher pH on the reduction in this case may stem from the higher basicity of Ts-dpen than that of bipyridine.[10]

The higher rates at pH values greater than 4 could be due to the increased concentration of $HCOO^-$. At pH > 4, HCOOH ($pK_a = 3.6$) exists predominately as $HCOO^-$, which is needed to form the ruthenium formato complex (Scheme 1, see below). This would be in line with our previous report that the rate of the reduction of acetophenone by HCOONa increases with the formate concentration in water when [formate] < 5 M.[2a] However, there appears to be no correlation of TOF with $[HCOO^-]$ in this study. Thus, for example, the initial TOF increased 8 times when the initial pH value changed from 4.0 to 4.5; the corresponding change in the calculated initial $[HCOO^-]$ was only from 3.1 to 2.9 M, suggesting that the observed TOF–pH correlation cannot simply be ascribed to the variation in formate concentration.

To address the issue raised above further, we followed the reduction of acetophenone starting at pH 2.3. As can be seen from Figure 2, the reduction barely occurred before the pH value increased to approximately 3.5, which seems to support the notion that the reduction is governed by the concentration of formate. The observed increase in solution pH with time is a consequence of the decomposition of HCOOH by Ru–Ts-dpen and its consumption in the reduction of the ketone. The decomposition gave rise to CO_2 and H_2, as shown by MS in the absence of ketone. However, the most surprising observation is that the enantioselectivity varied with the pH value as well (Figure 2). This observation suggests that there might be a competing pathway in operation under acidic conditions, which is less selective than that at higher pH values and becomes insignificant under basic conditions. A similar change in *ee* values with time was noticed by Carmona, Oro, Joó, and co-workers, but the cause was less clear.[11]

The observed change in reaction rates with solution pH values suggests that the rates can be modulated by the pH.



Scheme 1. Proposed catalytic cycles for the reduction of ketones under acidic and basic conditions. L may be a water molecule.

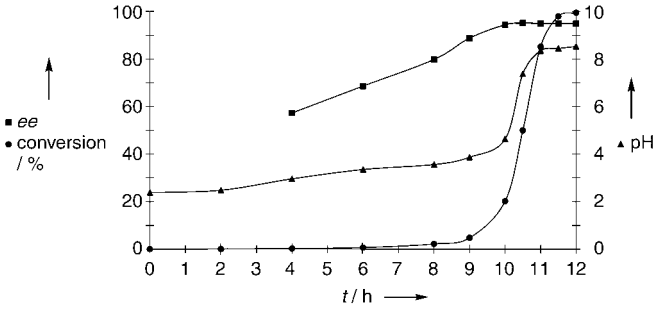


Figure 2. Graph of conversion (●), enantioselectivity (■), and pH (▲) versus time for the reduction of acetophenone (1 M) by HCOOH–NEt_3 (initial molar ratio: 4.6:1.0; 0.5 mL) in water (0.5 mL) with Ru–(*R*,*R*)-Ts-dpen at 40 °C.

This is indeed the case. Thus, as illustrated in Figure 3, the reduction of acetophenone could be rapidly initiated by raising the pH value by simple adding NEt_3 and suppressed by adding HCOOH. The reversible rise and fall in rates against pH may partly result from the fluctuation of formate concentration; but there could be another explanation, that is, there may exist two interchangeable catalytic pathways, with their proportion determined by solution pH. Consistent with this, the aqueous solution changed color reversibly; the solution was yellow under acidic conditions and orange under basic conditions (Figure 3).

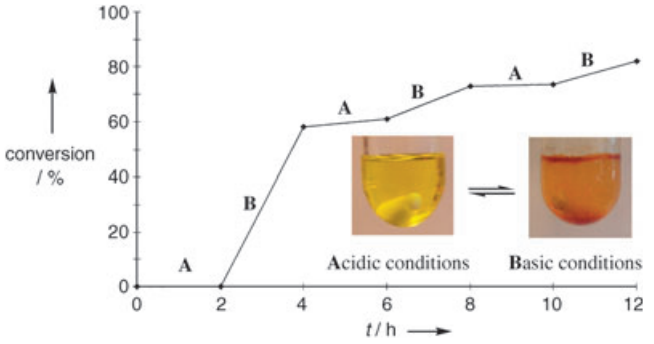
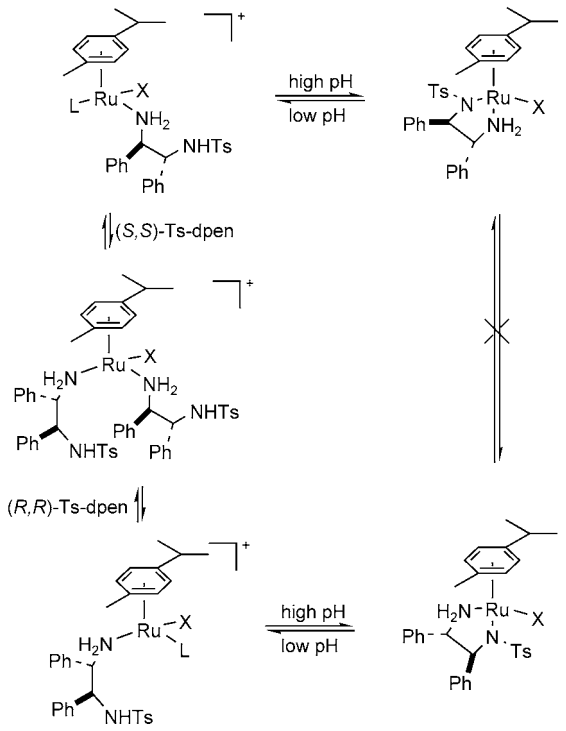


Figure 3. Graph of conversion versus time for the reduction of acetophenone (1 M) by HCOOH–NEt_3 in water (1:1 initial volume ratio, 0.5 mL water) with Ru–(*R*,*R*)-Ts-dpen at 40 °C. In regions A the initial HCOOH/NEt_3 molar ratio was maintained at 4.6:1.0 (pH 2.8), whereas in regions B HCOOH/NEt_3 = 2.3:1.0 (pH 3.7).

Taken the above observations together, we propose that the Ru–Ts-dpen catalyst operates through two catalytic cycles (Scheme 1). The cycle under basic conditions follows the concerted mechanism proposed by Noyori et al.,[12,13] whereas that at low pH values starts with the protonation of the coordinated Ts-dpen. The low rates and low *ee* values in the latter case can be interpreted as resulting from the conventional, stepwise reduction of ketones[12b,14] and/or from a similar concerted mechanism with a less-well-organized transition state. The Ru^{II}–Cl precatalyst is probably hydrolyzed with displacement of the chloride by water,[15] thus explaining its solubility in water. The question concerning which nitrogen atom is protonated is not yet clear but may be addressed from the following observations. The pK_a value of the amido nitrogen group in Ts-dpen has been measured to be 7.4,[10] and a lanthanide complex that contains a related NTs unit (pK_a = 6.4) has been shown to undergo a pH-dependent on-and-off process.[16] It is also known that the amino chelate rings in Ru^{II}–en (en = ethylenediamine) complexes are stable under conditions that are far more acidic than those used in this study.[17] Furthermore, the Ru^{II}–NTs bond is longer than the Ru^{II}–NH_2 bond in the precatalyst.[18] These observations suggest that the amido rather than the amino nitrogen atom is protonated.

If the (*R*,*R*)-Ts-dpen ligand is protonated under acidic conditions, introduction of the opposite enantiomer, (*S*,*S*)-Ts-dpen, to the solution could be expected to generate a mixture of Ru–(*R*,*R*)-Ts-dpen and Ru–(*S*,*S*)-Ts-dpen and lead to a racemic product. Furthermore, the ligand substitution process should be pH dependent, as the chelating effect of (*R*,*R*)-Ts-dpen would come into play at higher pH values (Scheme 2).



Scheme 2. Proposed ligand substitution as a function of pH. X may be a hydride or formate.

This is indeed the case, as shown in Figure 4 for the reduction of acetophenone. Thus, the addition of (*S*,*S*)-Ts-dpen (1 equiv) into an aqueous solution containing Ru–(*R*,*R*)-Ts-dpen (pH 4.6) lowered the enantioselectivity dramatically from the initial value of 98% *ee* at 5% conversion to 5% *ee* when the reaction was complete (Figure 4a). This corresponds to an *ee* value of 5% for the reduction upon the introduction of (*S*,*S*)-Ts-dpen and indicates that the subsequent reduction was virtually non-enantioselective. In sharp contrast, no significant effects on either the rate or *ee* values were noticed when the same ligand was introduced at a higher pH value of 7.7 (Figure 4b). These kinetic profiles are similar to those observed without the additional ligand, suggesting that the active catalytic species in the presence of additional (*S*,*S*)-Ts-dpen are the same Ru–(*R*,*R*)- or (*S*,*S*)-Ts-dpen complex. Further evidence in support of the mechanism is seen in the reaction by adding bipyridine, which inhibited the reduction of acetophenone only under acidic conditions.

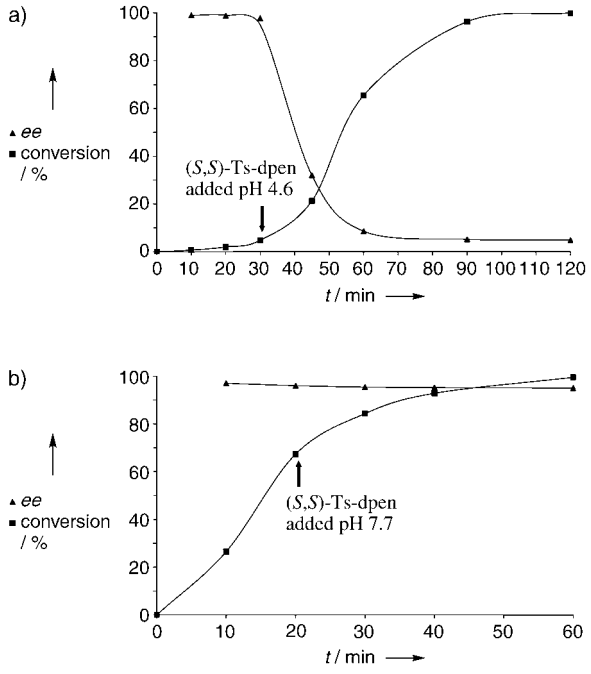


Figure 4. Effect of (*S*,*S*)-Ts-dpen (1 equiv added at the pH indicated) on the conversion (■) and enantioselectivity (▲) of the reduction of acetophenone (1 M) by HCOOH–NEt_3 in water (1:1 volume ratio) with Ru–(*R*,*R*)-Ts-dpen at 40 °C. The initial HCOOH/NEt_3 molar ratio was 2.3:1.0 (a) and 0.7:1.0 (b).

With these findings in hand, it was then easy to address the issue of slow reaction rates faced when combining the HCOOH–NEt_3 azeotrope with water.[19] Thus, instead of simply adding the azeotrope mixture to water, we used an aqueous solution of HCOOH and NEt_3, in which the amine acted as a pH modulator, thus ensuring that the pH value of the solution was maintained between 5 and 8 during any reduction. Under such conditions, aromatic ketones could be reduced with Ru–(*R*,*R*)-Ts-dpen to secondary alcohols in water at much faster rates and with little loss in enantioselectivities; some examples are given in Table 1. In comparison with the original conditions described by Noyori and coworkers,[7a] the current method affords similar conversions and *ee* values in much shorter times by using much smaller amounts of HCOOH and NEt_3.

Table 1: Asymmetric transfer hydrogenation of ketones by HCOOH–Et_3N with Ru–(*R*,*R*)-Ts-dpen in water.[a]

Ketones	*t* [h]	Conversion [%][b]	*ee* [%][b]
acetophenone	1.5	100	97
4′-fluoroacetophenone	1.5	100	92
4′-trifluoromethylacetophenone	1.3	100	95
4-acetylbenzonitrile	1.5	99	89
4′-nitroacetophenone	2	>99	85
4′-methoxyacetophenone	5	>99	97
3′-methoxyacetophenone	2.5	99	95
4-acetylpyridine	2	>99	96
2-acetylthiophene	2	>99	96
4′-methylpropiophenone	3	99	92

[a] The reactions were carried out in a mixture of H_2O (0.5 mL) and HCOOH–Et_3N (0.5 mL; molar ratio 1.2:1.0; initial pH 5) at 40 °C, with ketone (1 mmol) at a S/C ratio of 100:1. [b] Determined by GC. The configuration of the alcohol was *R*.

One of the limitations of the Ru–Ts-dpen catalyst and related variants was their low productivity, with most applications having S/C ratios of ≈200:1.[7–9] This limitation can now be effectively circumvented by employing the current method. As is seen from Table 2, by controlling the pH to a range of 5–8 by simply adjusting the HCOOH/NEt_3 ratios, aromatic ketones can be readily reduced at S/C ratios of 1000:1–10000:1 in water to afford the chiral alcohols with little compromise in enantioselectivities.

Table 2: Asymmetric transfer hydrogenation of ketones in water at higher S/C ratios.[a]

Ketones	S/C	*t* [h]	Conversion [%][b]	*ee* [%][b]
Acetophenone	1000	9	>99	96
4′-chloroacetophenone	1000	11	>99	93
4′-methoxyacetophenone	1000	32	99	95
2-acetylfuran	1000	8	>99	96
2′-acetonaphthone	1000	11	>99	95
acetophenone	5000[c]	57	98	96
acetophenone	10000[d]	110	98	94

[a] The reactions were carried out in a mixture of H_2O (2.5 mL) and HCOOH–Et_3N (2.5 mL; 1.2:1.0) at 40 °C with 10 mmol of ketone at pH 5–8. [b] Determined by GC analysis. The configuration of the alcohol was *R*. [c] The volume of the mixture of water and HCOOH–Et_3N was 10 mL (1:1 volume ratio); ketone: 50 mmol. [d] Water (10 mL), HCOOH (initially 5 mL), Et_3N (20 mL), and ketone (0.1 mol) were used.

In summary, the results presented herein demonstrate that aqueous-phase asymmetric transfer hydrogenation of aromatic ketones by formic acid with the Noyori–Ikariya Ru–Ts-dpen catalyst is modulated by the solution pH. By controlling the pH value, much faster rates and higher turnover numbers in conjunction with excellent *ee* values can be delivered. Evidence is presented that suggests that there may be two competing catalytic cycles, and hence the reaction rates and enantioselectivities are a function of solution pH values.

Experimental Section

$[\{RuCl_2(p\text{-cymene})\}_2]$ (3.1 mg, 0.005 mmol) and (*R,R*)-Ts-dpen (4.4 mg, 0.012 mmol) were dissolved in degassed water (0.5 mL). After stirring at 40 °C for 1 h, HCOOH (0.13 mL, 3.3 mmol), Et_3N (0.37 mL, 2.7 mmol), and acetophenone (120 mg, 1.0 mmol) were added to the solution. Following degassing three times, the mixture was allowed to react at 40 °C for a certain period of time. The workup was the same as before[2] and the product was analyzed by GC (Chrompack Chirasil-Dex CB column).

The reduction at S/C = 10000:1 was carried out as follows: After preparation of the precatalyst in water (10 mL), HCOOH (5 mL, 0.13 mol), Et_3N (20 mL, 0.14 mol), and acetophenone (12 g, 0.10 mol) were introduced. The reaction was conducted in a way similar to that above, except that during the reduction HCOOH was periodically added to keep the pH value between 5 and 8.

The reduction could also be performed in the absence of water. An example under comparable conditions is given here. The catalyst was prepared in a similar way in degassed HCOOH–NEt_3 (1 mL; molar ratio = 0.9:1). The reduction started with the introduction of acetophenone (120 mg, 1 mmol; S/C = 100:1) and resulted in a complete reaction at 40 °C in 7 h with 97 % *ee*.

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[19] In neat HCOOH–NEt_3, the reduction was faster when the HCOOH/NEt_3 ratio decreased, but slower than that in the aqueous solution (see Experimental Section).

