A mechanistic study of the reduction of quinones by ascorbic acid

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Rates of the redox reaction between ascorbic acid, 1, and *p*-benzoquinone, 2, which forms dehydroascorbic acid and hydroquinone, are highly pH-dependent, increasing by a factor of around 60-fold between pH 2 and 4.5. This is evidently due to the increased reactivity of ascorbate relative to the undissociated acid. The reaction shows a maximum primary kinetic isotope effect, $k_H/k_D = 7.8$ and volumes of activation which are appreciably negative in the acidic range (-12 to -16 $cm^3\ mol^{-1}$) but around only -4 at higher pH while the volume of reaction is -12 $cm^3\ mol^{-1}$. Protic solvents are mandatory, water and methanol being the only practical solvents in which the reaction occurs at all. Rates in water–methanol mixtures show a non-linear correlation with *Y*-values, $m_s \approx 0.27$, suggesting charge dispersion in the transition state. Rates of reduction of several other quinones show similar behaviour. Hydrogen atom transfer following a one-electron transfer is proposed as the rate-determining step.

Introduction

Ascorbic acid, **1**, is a chiral reducing agent, albeit not a very powerful one, but it could become a valuable synthetic reagent if the scope of compounds capable of being reduced could be increased to include, for example, carbonyl compounds. A possible technique for widening the scope of the reaction would be the use of high pressure supposing the reductions were accompanied by a sufficiently large and negative volume of activation, information which hitherto was not available. This work reports the volume profile and other characteristics of the reaction. Ascorbic acid is readily converted to the ascorbate radical, **3**, which has been characterised by EPR spectroscopy[1] and, in general, acts as a one-electron reducing agent. Metals such as iron(III) are readily reduced[2] but few organic acceptors are known. Quinones are a class known to be reduced to the corresponding hydroquinones and the ascorbate radical has been shown to be formed intermediately.[3] Significantly, quinones are able to undergo one-electron reduction to the semiquinone *en route* to the quinol. At the outset therefore, a radical mechanism appears feasible.

Rates are sufficiently fast to require the use of stopped-flow techniques both for reactions at atmospheric pressure and at elevated pressures. Reactions are clean and accurately of first order in each reagent. Water was used as solvent both for reasons of solubility and since the reaction takes place in almost no other; methanol, the only other feasible medium, comes a poor second in terms of rates and was studied as water–methanol mixtures.

Experimental

Quinones were purified by sublimation under reduced pressure and samples used for kinetic measurements had melting points in agreement with published values.[4] Ascorbic acid monohydrate was of analytical grade. Deuterium-labelled ascorbic acid was prepared by three exchanges with D_2O of 99.9% atom purity and was finally dissolved in D_2O). All reactions studied had half lives of the order 1 s and rate constants were measured by stopped flow methods; either by a Rapid Kinetics Accessory (Applied Photophysics RX.1000) or by the high pressure equipment previously described.[5] Absorbance was monitored at 420 nm and reactions were run at 25 °C in deaerated water or water–methanol mixtures as solvent under pseudo-first order conditions with ascorbic acid in 10-fold excess over that of the quinone. At least three measurements were made under each of the conditions. Buffers used were HEPES and 'Hydrion' (phosphate).

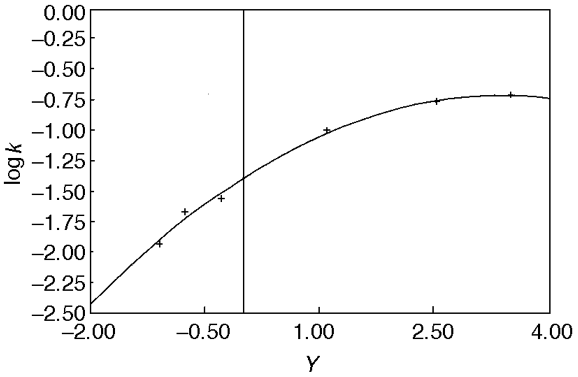


Fig. 1 Plot of log *k* *vs.* *Y* for reactions of benzoquinone with ascorbic acid in aqueous methanol

Rates were not found to be sensitive to the extent of degassing or to being measured under argon. Pseudo-first order rate constants were obtained from the kinetic data using the KINFIT program (supplied by Olis Kinfit, On Line Instrument Systems, Olis, Ga., USA). Molar volumes were measured using a vibrating fork densitometer (Paar Instruments, Model DMA 60).

Results

Pseudo-first order rate constants for various reactions are given in Tables 1–3. Partial molar volumes of reagents and products are given in Table 4.

Results and discussion

Under the conditions used, reactions gave accurate first order plots (Fig.1). The identity and purity of the products, hydroquinone, **4**, and dehydrascorbic acid, **3**, were confirmed by separation using HPLC calibrated against standard solutions of the authentic compounds whose retention times and UV

Table 1 Pseudo-first order rate constants for reactions of quinones with ascorbic acid. Temperature 25 °C; solvent, water; ascorbic acid concentration 0.252 M, initial [quinone] 0.027 M; uncertainty ±4%.[a]

	A	B	C	D	E	F	G
pH	Unbuffered	2.00	2.65	3.00	4.87	Unbuffered	Unbuffered
Pressure/bar	k_1/s^{-1}	k_1/s^{-1}	k_1/s^{-1}	k_1/s^{-1}	k_1/s^{-1}	k_1/s^{-1}	k_1/s^{-1}
1	0.79			1.73	38.0	0.099	1.92
100	0.81	0.76	1.14	1.87	39.7	0.085	1.98
250		0.79					
300	1.04			2.03		0.121	2.34
400			1.38		41.3		
500	1.24	0.93		2.40		0.138	2.59
700	1.43		1.57	2.66	43.3	0.160	2.94
750		1.08					
900	1.62			3.05		0.180	3.23
1000		1.14	1.93				
$\Delta V^‡$/cm^3 mol^{-1}	−20	−15	−16	−13	−4	−16	−14

[a] A–E, *p*-benzoquinone; F, 1,2-dichloro-4,5-dicyano-1,4-benzoquinone; G, 1,2-naphthoquinone.

Table 2 Pseudo-first order rate constants (±3%) for reactions between *p*-benzoquinone with ascorbic acid and [$^2H_2$]ascorbic acid; H_2O or D_2O

	k_1/s^{-1}
Ascorbic acid/H_2O	0.79
[$^2H_2$]Ascorbic acid/D_2O	0.101
k_H/k_D	7.8

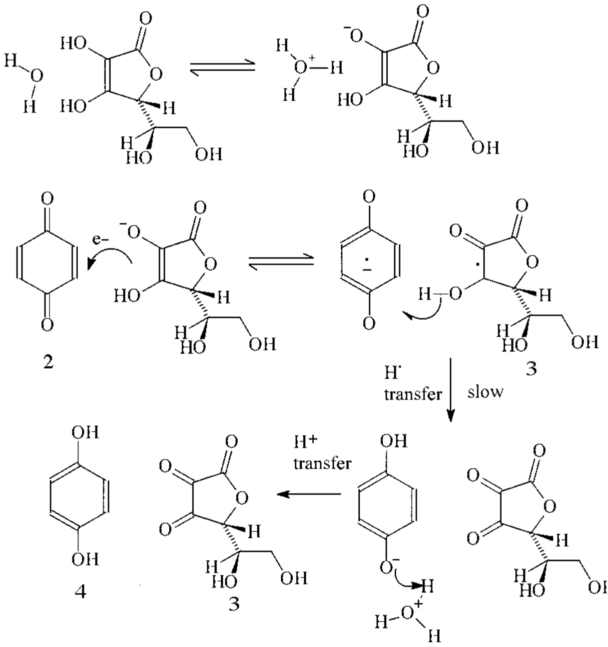
Table 3 Pseudo-first order rate constants (±2%) for the reaction between benzoquinone and ascorbic acid in methanol–water mixtures; T = 20 °C; ascorbic acid concentration 0.050 M

Mole fraction water	Y	k_1/10^{-2} s^{-1}
0	−1.09	1.16
0.10	−0.77	2.13
0.20	−0.29	2.72
0.50	1.11	10.1
0.80	2.53	17.3
1.00	3.49	19.8

Table 4 Partial molar volumes of reagents and products, water, 25 °C

Solute	Molar volume, V/cm^3 mol^{-1}
Benzoquinone (A)	85.41
Hydroquinone	87.96
Ascorbic acid (B)	106.31
Hydroquinone + dehydroascorbic acid (equimolar) (C)	179.49
Volume of reaction [C − (A + B)]	−12.2

spectra agreed with those of the reaction products. In the absence of a buffer, the initial pH of the solution was 2.7 due to the dissociation of the ascorbic acid. This rose to around 3.2 at the end of the reaction as some ascorbic acid was consumed but this caused only a minor perturbation in the kinetics. Rate constants were computed from data over 50–60% of the reaction. Rates in all cases were quite fast necessitating measurement by a stopped-flow method. Volumes of activation were recorded using solutions buffered by HEPES whose dissociation is only slightly affected by pressure.[6] A series of measurements were made at pH values between 2 and 4.87, the highest which could be used on account of the instability of the quinone. At the extremes, the species present are almost entirely ascorbic acid and ascorbate ion, respectively, and a very large change in activation volume was observed from highly negative −16 cm^3 mol^{-1} for the acid to only −4 cm^3 mol^{-1} for the ascorbate ion as well as a 50-fold increase in rate. The moderate reduction in volume for the overall reaction, ΔV = −12 cm^3 mol^{-1}, can be explained by the conversion of two very acidic protons of ascorbic acid to the less acidic and less hydrogen bonded phenolic ones. A proposed mechanism which fits the experimental evidence is shown in Scheme 1. It is suggested that ascorbate ion is the reactive species and that this is formed by dissociation of ascorbic acid assisted by high pressure conditions (for the dissociation of ascorbic acid, ΔV = −9.2 cm^3 mol^{-1})[7] which accounts for the negative volume of activation at low pH. The reaction commences by a one-electron transfer from ascorbate to the quinone. This is in accordance with the second order nature of the reaction. The products would be the radical ions and this step would be charge conserving so that little volume change should result. Added to this is the observation of radical species by EPR spectroscopy during the reaction[3] which makes such intermediates plausible and the redox potential for the (two-electron) process, 0.287 V, is also favourable.[10,11] It may be noted that *o*-naphthoquinone ($E°$ = 0.547 V) which has a lower reduction potential than does benzoquinone ($E°$ = 0.699 V) is the more rapidly reduced.



Scheme 1

The electron transfer must be reversible and the rate-determining step a hydrogen atom transfer which is consistent with the maximum kinetic isotope effect, k_H/k_D = 7.8, which is observed. This must be a primary effect although a solvent effect, expected to be small, is also incorporated. A similar observation has been made in the reduction of quinones by 9,10-dihydro-10-methylacridine, acting as an NADH analogue.[12] Hydrogen atom transfer is also charge-conserving and typically is accompanied by a very small volume change[8] which is observed for the reaction at the highest pH. Finally, the reaction is completed by a proton transfer. This would be the step which is particularly demanding of a protic solvent. Water is by far the best solvent for this reaction and the addition of even methanol causes a considerable reduction in rate. Rates in the mixed medium show a curved relationship with the solvation parameter, *Y*,[9] possibly indicating the requirement for specific hydrogen bonding in addition to solvent polarity. The slope, m_s is low, of the order 0.27, comparable to that for a charge-dispersive S_N2-reaction. No reaction was observed in other solvents although, in part, this is due to lack of solubility of the ascorbic acid. The requirement for an aqueous medium obviously limits the usefulness of ascorbic acid as a reducing agent for organic compounds. An attempt was made to investigate whether the diol sidechain of ascorbic acid was in any way responsible for reactivity. The isopropylidine derivative was prepared and reaction rates with benzoquinone measured as before. Rates were identical with those of ascorbic acid but this was found to be due to rapid hydrolysis of the derivative to ascorbic acid. Furthermore, enones which might have been considered substrates for reduction by ascorbic acid typically add ascorbate in a Michael fashion.[13] The conclusion is that ascorbate is likely to be a reducing agent of only limited application in organic chemistry.

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