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Reviews

Mixing and the Selectivity of Chemical Reactions

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Abstract:

Many desirable organic reactions are accompanied by side reactions and undesired by-products, which waste raw materials and complicate product work-up and isolation. By enhancing the competition between reactions to obtain more selective syntheses, ecological and economic benefits may be expected. The most effective way to do this is usually catalysis. Recently, however, more has been learned about the role of "reactive mixing", which refers here to bringing reagents together on the molecular scale. When chemical knowledge (especially reaction kinetics and physical organic chemistry) is combined with that of mixing, significant improvements to the selectivity of some syntheses can be achieved. This review offers an introduction to understanding how mixing influences those single-phase and two-phase reactions which are sufficiently fast that mixing cannot fully homogenize their reactants. It includes theoretical principles, typical experimental results, worked examples, and literature references for further study. Reactive mixing is treated in very few textbooks (refer to section 1), is unknown to many chemists, and is unfamiliar to many chemical engineers. It is hoped that its wider recognition will lead others to become intellectually fascinated by its structure and to value its practical applications.

1. Introduction

Probably the simplest reaction whose rate is strongly influenced by the way in which the reagents are mixed is acid−base neutralisation ($H^+ + OH^- \rightarrow H_2O$). The second-order kinetic rate constant is approximately 10^8 $m^3/mol{\cdot}s$, and the time scale of neutralisation is often on the order of nanoseconds (10^{-9} s) or even shorter. However, the time required to mix the two aqueous reagent solutions is hardly ever less than 1 ms and, on the technical scale of operation, might be on the order of 1−10 s. A measured neutralisation rate is therefore much slower than the true (or inherent) reaction rate and depends entirely on the rate of mixing. Combustion of either a liquid or a gaseous fuel is another common example where mixing-controlled chemical reactions take place.

By contrast, the alkaline hydrolysis of the ester ethyl ethanoate ($CH_3COOC_2H_5$) exhibits a smaller rate constant (ca. 10^{-4} $m^3/mol{\cdot}s$) with a typical time scale of several minutes. This is sufficiently long to allow the reagents to mix completely before hydrolysis can proceed to any significant extent. Mixing has no effect on the measured reaction rate, which is determined by the chemical kinetics. Many esterifications are also slow enough to be kinetically controlled.

A framework for classifying mixing-sensitive reactions consists of comparing time constants (or characteristic times) for mixing and reaction. A neutralisation's time constant is orders of magnitude shorter than that for mixing; mixing is rate-determining, and neutralisation is instantaneous relative to mixing. Ester hydrolysis is the opposite case: reaction kinetics determines its rate, and hydrolysis is slow relative to mixing. Most reactions in this text are intermediate, having time constants for mixing and reaction of similar magnitudes; they may be termed fast, and both kinetics and mixing determine their progress. This key classification applies to single and multiple one- and two-phase reactions.

The observed rates of single mixing-controlled reactions can be significantly increased by faster mixing, thus saving time and reducing reactor volume. With multiple reactions, mixing can influence not only reaction rates but also the distribution of reaction products. In some cases mixing can raise product yields, suppress by-product formation, simplify product isolation and purification, and improve conversion of raw materials to products. Such practical considerations dictate that this text treats the influence of mixing on the product distribution of multiple liquid-phase reactions, typically taking place in a solvent and in a semibatch reactor. The product distributions of sufficiently fast reactions respond similarly to inadequate mixing rates irrespective of whether the reagents are fully miscible (single-phase reactions) or partially miscible (two-phase reactions). Both types are included here, and although their behaviours with respect to mixing are similar, their modelling and practical realisation (e.g., reactor types) differ.

The influence of mixing on product distribution can be regarded from three, partly overlapping, points of view (a) qualitative, (b) semiquantitative, and (c) quantitative. In (a) some experimental results and observations can be qualitatively interpreted with the help of general chemical and physical principles. In (b) the emphasis shifts from phenomena to mechanisms, which must be understood in sufficient detail to permit time constants for various mixing mechanisms to be formulated and applied to identifying the controlling steps, for example, in the context of a particular multiple reaction it can often be decided from time constants whether certain variables (diffusivity, viscosity, etc.) and

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operating parameters (power input, feed rate, etc.) will influence product distribution. In (c) a fully quantitative treatment calls for much information about the reactions (thermodynamics, reaction kinetics, and possibly reaction mechanism) and about the flow field (velocity distribution, turbulence parameters). This level of detail has been attained in only a few cases but has allowed the development and quantitative validation of some theories and models to describe the interactions between mixing and reaction. For many reactions and technically oriented problems full quantitative treatment is unattainable, but a combination of (a) and (b) should be possible. The text therefore offers mainly well-established general principles and time constants; these provide guidance to interpreting experimental results, planning experiments and scale-up. More detailed information including level (c) is available in reference 1 for single-phase reactions and in refs 2−4 for two-phase reactions.

"Mixing" is a broad, generic term, which obviously includes reducing the variability of concentration, temperature, and so forth. In addition to considering this homogenisation, it is helpful to regard the scale at which variability exists and at which various mixing mechanisms reduce variability. For example in a stirred vessel macromixing refers to attaining homogeneity at the scale of the vessel. At the opposite extreme, chemical reaction and its precursor molecular diffusion are molecular-scale phenomena. Between these limits two further scales (micro- and meso-) have been identified and will subsequently be explained. In the context of a particular problem it is usually necessary to decide which scale with its associated mixing mechanism is relevant to the final product distribution. For instance some mixing rates in large reaction vessels are lower than at laboratory scale, and the most relevant mixing mechanism can be scale-dependent, making such reactions more difficult to scale up and to secure constant product yield and quality.

Unless otherwise stated the reactions to be considered here have second-order kinetics and partial orders of one in each reagent. The rate of a first- and also a pseudo-first-order reaction is unaffected by a nonuniform concentration distribution—the regions where concentration and rate are above average compensate those where these values are below average. This averaging does not apply to second-order reactions. When reactants (A, B, etc.) are initially separated and need to be mixed to promote reaction, the asymptotic states are (a) no mixing (total segregation of reactants), therefore no reaction, and (b) complete mixing (no segregation) and maximum reaction rate. In the subsequent text the intermediate state—incomplete mixing (partial segregation) and a rate lower than that when completely mixed—often occurs, promoting unexpected product distributions. This forms the central theme here.

An understanding of mixing is essential when considering the product distribution of many fast multiple reactions whether single- or multiphase. The ability to influence the yield of a reaction product not only by chemical means (catalysis, solvent, reagent stoichiometry, temperature, etc.) but also by physical means (agitation intensity, reactor type, viscosity of solvent, rate and location of adding reagents, etc.) is economically and ecologically significant.

The subsequent text is structured as follows. Sections 2 and 3 present evidence that yields and product distributions can be influenced by the ways in which reagents are mixed. Section 4 outlines mixing mechanisms and gives time constants for single-phase mixing at various scales. Section 5 describes four sets of well-characterised fast chemical reactions having mixing-sensitive yields. Section 6 summarises experimental results obtained with the section 5 reactions, which validate the theories and time constants for single-phase mixing in section 4. Section 7 shows how the time constants may be applied to securing the same product composition when scaling up fast mixing-sensitive reactions. A laboratory protocol to identify the relevant mixing time constant for scale-up by running small-scale experiments is included. Sections 8 and 9 deal with two-phase reactions. Section 8 develops time constants for diffusive mass transfer and reaction, showing how a classification of "fast", "slow", etc. reactions also exists when reagents are initially present in separate phases. A laboratory protocol for two-phase reactions is also included. Section 9 applies the fundamentals developed for single reactions in section 8 to multiple reactions, showing how their selectivities can be affected by mass transfer. Worked examples, typical experimental results, and extensive literature references feature in all sections.

2. Examples of Mixing-Sensitive Single-Phase Reactions

Reactions such as neutralisation, taking place on time scales much shorter than 1 ms, are effectively instantaneous relative to the time scale characteristic of any mixer. If only one reaction can occur, the practical consequence is that orders of magnitude more time is needed for reaction than would be predicted by chemical kinetics. This also applies to fast and instantaneous multiple reactions, but a further consequence is that often the product distribution is mixing-sensitive. As stated in section 1, this characteristic can be so practically important (e.g. when manufacturing high-value-added chemicals) that it is central to this text.

2.1. Competitive−Consecutive Reactions. The following scheme represents two reagents, A and B, which initially form an intermediate R. This in turn forms a final product S by reacting with further B.

$$\mathrm{A} + \mathrm{B} \xrightarrow{k_1} \mathrm{R} \tag{2.1}$$

$$\mathrm{R} + \mathrm{B} \xrightarrow{k_2} \mathrm{S} \tag{2.2}$$

When in a batch or semibatch operation n_{B0} mol of B are added to n_{A0} mol of A, such that $n_{B0} < 2n_{A0}$, the yields of the primary (R) and secondary (S) products can be shown

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from straightforward kinetic calculation[5,6] to depend only on the ratio of rate constants (k_1/k_2) and the initial stoichiometric ratio ($b = n_{B0}/n_{A0}$), when both reactions have stopped and therefore all B has been consumed. For example in the special case that $k_1 = 2k_2$, the final composition is given by

$$n_A/n_{A0} = (1 - 0.5b)^2 \tag{2.3}$$

$$n_R/n_{A0} = b - 0.5b^2 \tag{2.4}$$

$$n_S/n_{A0} = (0.5b)^2 \tag{2.5}$$

provided that $b < 2$. These results (and analogous derivations when $k_1 \neq 2k_2$) assume complete mixing of the reagents. It will be shown here that, when the reacting mixture is not homogeneous, the yields of R and S are lower and higher, respectively, than those predicted from kinetics. However, when reactions are slow enough relative to mixing that a uniform mixture is formed before significant reaction occurs, eqs 2.3−2.5 (and analogous equations for the cases $k_1 \neq 2k_2$) apply. From eq 2.4 it follows that the maximum yield of R is 50% whilst 25% of A is unconverted and the S-yield is 25% when using $b = 1$ (i.e., $n_{B0} = n_{A0}$) and both reactions have stopped.

2.1.1. Some Reactions of Symmetrical Diamines. In symmetrical diamines, having the general formula $H_2N(CH_2)_nNH_2$ and denoted by A, the reactivities of the two nitrogen atoms are often mutually independent when n is approximately 2 or greater. In this situation one expects $k_1 = 2k_2$ and a product distribution given by eqs 2.3−2.5.

The expected distribution was found when making amides from dodecanoic acid ($C_{11}H_{23}COOH$) (B) and 1,6-diaminohexane ($n = 6$)(A). Changing A to 1,2-diaminoethane ($n = 2$) the yield of R decreased from 50 to 37%, whilst that of S rose from 25 to 30% and less A reacted (unreacted 30%).[7]

By using the same two diamines, faster reacting isocyanates (B) (RNCO with various R groups) were employed. With both amines and every isocyanate, substantially more S was formed than predicted from eq 2.5. By changing from isocyanates to slower-reacting isothiocyanates (RNCS), S-yields decreased and agreed well with eq 2.5 when 1,6-diaminohexane ($n = 6$) was employed.[8]

The acylation of 1,2-diaminoethane (DAE) ($n = 2$) and of 1,4-diaminobutane (DAB) ($n = 4$) with either benzoyl chloride (C_6H_5COCl) or the less reactive benzoic anhydride ($(C_6H_5CO)_2O$) was studied to find conditions favouring a high yield of the monoamide (R). Despite a low reaction temperature (195 K), slow addition of the acylating solution (30 min), vigorous agitation of the diamine solution, and a 5-fold excess of diamine ($b = 0.2$), the expected product distribution (18% R, 1% S, and 81% unreacted diamine) was generally not found. The calculated "worst case" yield of S, when no R was finally present, was 10%. Measured yields of S were in the expected range (1−10%) and are given in Table 1.[9]

Table 1. **Measured yields of diamide (S) {% based on initial diamine}**

diamine (A)	acylating agent (B)	standard process (yield, %)	dilute process (yield, %)
DAE	chloride	9.9	2.2
DAE	anhydride	2.4	1.4
DAB	chloride	7.9	3.5
DAB	anhydride	2.7	0.9

Table 2. **Measured and expected yields of dinitro product (S)**

DPE (mol/m^3)	200	125	50	250	625
NO_2BF_4 (mol/m^3)	200	125	50	125	125
b	1	1	1	0.5	0.2
measured yield (%)	83	80	73	78	71
expected yield (%)	33	33	33	14	5

The slower-reacting anhydride produced less S and therefore more R than the acyl chloride. This was also seen when both reagents were diluted by a factor of 20, the stoichiometric ratio being unchanged ($b = 0.2$).

2.1.2. Nitration of 1,2-Diphenylethane (DPE). The two aromatic rings in this hydrocarbon ($H_5C_6(CH_2)_2C_6H_5$) (A) should have a similar reactivity to that of methylbenzene, and their separation by two methylene groups implies only a weak transmission of any substituent effects between the rings. Denoting the rate of attack of an electrophile (B) (e.g., NO_2^+) on a suitable position in *either* ring by k_1, whilst k_2 denotes the analogous rate for *one* ring, it may be expected that $k_1 = 2k_2$. The formation of the mono-(R) and di-(S) substituents of DPE should follow eqs 2.3−2.5. Using a polar, nonaqueous solvent ("sulpholane" $C_4H_8O_2S$) various initial concentrations of DPE and NO_2^+ (obtained from a nitronium salt, e.g., tetrafluoroborate) produced the yields of S given in Table 2. Here yield is expressed as $S/(R + S)$, that is, dinitro product relative to all nitro products, which is different from eq 2.5.[10,11]

Dilution reduced the formation of S (see also Table 1), as did a large excess of A relative to B. Five methods of adding the nitronium salt solution were also investigated. Raising the mixing intensity caused an increase in the R-yield from 22 to 46% whilst simultaneously reducing the S-yield from 78 to 54%.

In this study more S and therefore less R were formed than were expected based on the ratio of rate constants (k_1/k_2) and the initial stoichiometric ratio (b). This was attributed to insufficiently fast mixing on the molecular scale.[10,11]

2.1.3. Bromination of 1,3,5-Trimethoxybenzene. 1,3,5-Trimethoxybenzene (A) offers three equally reactive sites where a halogen (B) can substitute one hydrogen atom. Following this monosubstitution, there are two equivalent sites for the formation of dihalogenated product (S). The rate

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Table 3. **Product distributions from bromination of 1,3,5-trimethoxybenzene**

	N (rpm)				stopped flow
	0	213	425	1063	
A (%)	22.2	19.9	18.3	13.5	4
R (%)	57.9	61.3	64.5	73.4	87
S (%)	19.9	18.8	17.2	13.1	9

constants k_1, k_2, and k_3 for successive substitution at the first, second, and third sites are *not* in the ratio 3:2:1, because of the strong deactivation of subsequent electrophilic substitutions by halogens. Because $k_1 \gg k_2 \gg k_3$, much more R than S should finally be present, starting from approximately equimolar quantities of A and B ($b \approx 1$). The products (R and S) do not exhibit isomerism.

The methoxy group (H_3CO) strongly activates bromination,[12] and measured product distributions show substantially more S than would be expected, knowing that $k_1 \gg k_2$. Equal concentrations before mixing of 50 mol/m^3 of bromine as well as 1,3,5-trimethoxybenzene, each dissolved in equal volumes of methanol, were employed. Product distributions were measured after reaction and various stirrer speeds (*N*) were used. Table 3 gives typical results.[13]

The general trend was that, as the agitation intensity increased (due either to faster stirring or by use of a stopped-flow apparatus of the type used to measure the kinetics of fast reactions[5] whose mixing time (~1 ms) was shorter than in the stirred vessel), more substrate (A) reacted, forming more monobromo (R) and less dibromo (S) products. It is probable that $k_1 > 10^3\ k_2$, so that even in a stopped-flow apparatus the mixing rate was too low to prevent the formation of 9% S, i.e., reaction was faster than mixing in all cases. Quantitative treatment of these reactions is complicated by the following equilibrium between free bromine and the liberated bromide ion, which reduces the rate.

$$Br^- + Br_2 \leftrightarrow Br_3^- \qquad (2.6)$$

{A similar equilibrium arises in the mixing-sensitive iodination of the amino acid l-tyrosine.[14]}

2.1.4. Nitration of 1,2,4,5-Tetramethylbenzene (TMB). Single-phase nitration is considered, using a polar organic solvent (e.g., CH_3NO_2) for both TMB (A) and a nitronium salt (B) (e.g., $NO_2^+\ PF_6^-$). This and similar nitrations of aromatic hydrocarbons have been widely studied.[15,16] TMB is highly reactive, and its product mixture often contains high levels of unreacted TMB and dinitro product (*S*), which is not expected because $k_1 \approx 20\ k_2$,[17] indicating high yields of *R* when $b \approx 1$.

Table 4 gives experimental results[18] when equal volumes of reagent solutions (solvent nitromethane) were mixed.

The first three columns report initial concentrations, the next few give the product compositions, whereby the column marked "?" was unknown materials, S/R is the ratio of secondary to primary nitro products. SV and SF refer to a stirred vessel and a stopped-flow apparatus, respectively.

With no added water, changing from the stirred vessel to the more intensely mixed stopped-flow apparatus shifted the S/R ratio in the general direction of kinetically controlled reactions. However, because $k_1 \gg k_2$, roughly equal yields of R and S in SF still represent a wide deviation from the composition which is characteristic of perfect mixing.

A striking increase in the yield of R (with correspondingly less S) is seen when adding some two moles of water per mole of TMB, even in the weakly agitated vessel. The reduction in unidentified products is also significant. Water reversibly withdraws nitronium ions from the reacting mixture to form the nitroacidium ion according to the following equilibrium[18,19]

$$NO_2^+ + H_2O \leftrightarrow H_2NO_3^+ \qquad (2.7)$$

Subsequently this equilibrium returns to the left, releasing NO_2^+ at a low concentration level and nitrating TMB on a time scale of many minutes, rather than fractions of a second.[19]

Similar effects (analogous to slow drug release) on reaction rate and product distribution have been realised in (a) brominations, where addition of a bromide reduces the bromine concentration reversibly through eq 2.6, and (b) diazo-couplings, where pH influences the ionic preequilibria of the reactive species.[20,21]

2.1.5. Conclusions about Competitive−Consecutive Reactions. The experimental studies outlined in 2.1.1−2.1.4 as well as similar cases reviewed elsewhere[1] lead to the following conclusions.

The yield of the intermediate product (R) in eqs 2.1−2.2 can sometimes be increased by faster stirring, less reactive reagents, higher dilution, and an excess of reagent A relative to B. These trends, as well as others reported elsewhere,[1] have been observed with widely different reactions and may be attributed to insufficiently rapid mixing, rather than, for example, to chemical artefacts.

2.2. Competitive Reactions. Two reagents (A and C) competing for a common reagent (B) and forming different products (P and Q respectively) can be represented by

$$A + B \xrightarrow{k_1} P \qquad (2.8)$$

$$C + B \xrightarrow{k_2} Q \qquad (2.9)$$

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Table 4. **Product distributions from nitration of 1,2,4,5-tetramethylbenzene**

TMB (mol/m^3)	NO_2^+ (mol/m^3)	H_2O (mol/m^3)	A (mol %)	R (mol %)	S (mol %)	? (mol %)	S/R	apparatus
34	34	0	36.2	6.7	42.1	15.0	6.3	SV
39	39	70	10.6	81.0	2.0	6.4	0.025	SV
41	41	0					1.1	SF

For example B can be added gradually to a premixture of A and C.

These equations are the basis of the so-called competitive method to determine the ratio of rate constants (k_1/k_2). The initial concentrations of A and C must be known and insufficient B added so that reactions 2.8 and 2.9 do not go to completion. Usually the partial reaction orders of A and C should be one, and that of B should be the same in both reactions, for example one, giving second-order kinetics overall. The competitive method is then simple.[5]

Measurement of either the final product (P and Q) or reagent (A and C) concentrations when no B remains then allows the rate constant ratio to be calculated. (Texts on Reaction Kinetics and Physical Organic Chemistry give details.)

This competitive method assumes that both reaction rates are determined solely by classical kinetics so that mixing is irrelevant.[5] As early as 1926 competitive brominations were found to be fast relative to mixing, thus restricting the competitive method to slow reactions.[5,22]

2.2.1. Competitive Nitration of Benzene and Methylbenzene. Under kinetically controlled conditions (low concentration, fast mixing) methylbenzene (A) nitrates some 18−26 times faster than benzene (C).[15,23] Employing a nitronium salt and a polar organic solvent, the ratio of the mononitrated products P/Q ranged from 1.3 to 27.[24] The higher values were favoured by low NO_2^+ concentrations, large excesses of the hydrocarbons, and more intense agitation. Table 5, section a, refers to a magnetic stirrer, whilst Table 5, section b, refers to more intensive mixing with a Vibromixer.[24] In both cases a large excess of the hydrocarbons was employed. (e.g. initial concentrations were 2300 mol/m^3 of each).

With the magnetic stirrer the high power input was about 2.8 times that at low power. The Vibromixer applied generally more power for mixing and the high value was about 4 times the low one. It was concluded that only at low concentration and high power input were these competitive reactions taking place under kinetically controlled conditions.

Table 5. **Product ratio (P/Q) with different mixing conditions**

(a) Magnetic Stirrer

	initial NO_2^+ (mol/m^3)		
stirrer power	740	410	150
low	1.3	1.7	2.6
high	2.2	2.9	5.1

(b) Vibromixer

	initial NO_2^+ (mol/m^3)				
stirrer power	740	410	180	70	40
low	2.9	4.9	7[a]	17[a]	21.7
high	7.6	13.2	19.4	26.5	27.1

[a] Interpolated.

Table 6. **Degree of acid-catalysed hydrolysis of 2,2-dimethoxypropane in alkaline solution**

stirred speed (rpm)	concentration of added HCl (mol/m^3)			
	700	2000	5000	5000[a]
240	34%	41%	53%	57%
360	24%	31%	45%	50%
480	21%	29%	42%	49%

[a] Adiabatic (see text).

2.2.2. Competitive Hydrolysis and Neutralisation. The acetal 2,2-dimethoxypropane is stable in alkaline (NaOH) solution. During the addition of acid (HCl) to this solution, no measurable acid-catalysed hydrolysis of the acetal would be expected until all the alkali had been neutralised. This is based on the much higher rate constant for neutralisation compared to that for hydrolysis. However, significant hydrolysis of 2,2-dimethoxypropane has been observed when one part by volume of HCl solution (concentrations 700−5000 mol/m^3) was gradually added to 10 parts by volume of an alkaline acetal solution, containing more than sufficient NaOH to neutralise all the added acid. As the added HCl concentration varied, the initial concentrations of NaOH and acetal were changed to keep the stoichiometric ratios constant.[25] A Mettler RC1 heat flow calorimeter was employed as reactor. Table 6 gives some typical results.

The HCl was neutralised faster, causing less acetal hydrolysis, when its concentration was lower and stirring was faster. Under adiabatic conditions in the RC1 the exothermic neutralisation, which was stronger than the endothermic hydrolysis, caused a temperature rise of approximately 6 K, promoting faster hydrolysis.

Similar hydrolyses have been observed when concentrated alkali was added to a relatively stable, acidic ester solution, due to fast alkaline hydrolysis whilst mixing is taking place. Examples include the methyl and ethyl esters of monochlo-

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Table 7. **Fraction of dibromo isomers in the 2,4-form**

mode of Br_2 addition	rapid	rapid	slow	slow	
stirring	no	yes	no	yes	SF[a]
% 2,4-	13	24	17	40	70

[a] SF = stopped-flow apparatus.

roethanoic acid ($ClCH_2COOH$)[26] and a methanoate, which was an antibiotic precursor.[27]

2.2.3. Conclusions about Competitive Reactions. When, in eqs 2.8 and 2.9, $k_1 > k_2$, a much higher yield of product P than of product Q is expected on the basis of chemical kinetics. The ratio P/Q is reduced, however, when mixing is insufficiently fast relative to reaction rates. This can be seen in the two examples included here when stirring was weak and reagents were more concentrated. These and other effects are reported elsewhere.[1]

2.3. Local Transitory pH Gradients. Variations in acidity or alkalinity promoted hydrolyses in the examples in part 2.2.2. With fast reactions the local transient pH value near or at a reaction site can differ from the value in the bulk of the solution [as measured by a pH electrode] and can influence the preequilibria of the reagents and the product distributions.

2.3.1. Bromination of 1,3-Dihydroxybenzene (DHB). The formation of mono-, di-, and tribrominated products forms a set of competitive–consecutive reactions. The influence of mixing on the degree of substitution and the yields of R and S in eqs 2.1 and 2.2 is, however, not as significant in this example as its influence on the distribution of the dibromo (S) isomers substituted at positions 2- and 4- in one isomer and 4- and 6- in the other, i.e., product S can consist of two isomers.

A solution containing 50 mol Br_2/m^3 in methanol was added to an equal volume of a solution of 50 mol DHB/m^3. Reactions were complete when the limiting reagent (Br_2) was fully consumed. Table 7 reports the fraction of the 2,4-isomer relative to both dibromo isomers.[28]

The full product analysis (%) from the stopped-flow apparatus was the following:

DHB	38
2-mono-	2
4-mono-	33
2,4-di-	12
4,6-di-	5
2,4,6-tri-	10

The deactivating influence of bromine ($k_1 \gg k_2$ etc.) should have resulted in more monobromo products (R) than dibromo products (S). Even with the higher agitation levels in the stopped-flow device relative to the stirred tank, substantial quantities of di- and tribrominated DHB were formed, indicating that the kinetically controlled regime was not attained.

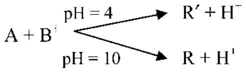

Figure 1. **Simplified scheme for azo-coupling of an aminonaphthol.**

Table 8. **Distribution of product dyes**

pH	initial A and B concentrations (mol/m^3)	R′ (%)	R (%)	S (%)
4	ca. 1–500	>97	<1	<1
10	<10	<3	>97	0
10	50–500	36	28	36

Table 7 shows that formation of the 2,4-dibromo isomer was favoured by agitation and slow bromine addition. For these electrophilic substitutions the phenolate form of DHB and its derivatives, stable at high pH, was more reactive than the phenol form, stable at low pH. The protons liberated during bromination would be removed to the bulk of the solution in a well-mixed system, but could accumulate near the reaction site when stirring was weak. The following sequence can be postulated. Initial bromination at position 2- and then at 4- provided that the HBr formed is removed by effective mixing, leading to 2,4-dibromo DHB. With weak mixing, DHB and its derivatives are in the protonated, less reactive form, whereby 4-monobromo DHB is formed followed by 4,6-dibromo DHB. Mixing helps to determine the pH near reaction sites, which influences product distribution.

2.3.2. Azo-Coupling of an Aminonaphthol. The aminonaphthol, 6-amino-4-hydroxy-2-naphthalenesulphonic acid (A) was coupled with the highly reactive 3-trifluoromethylbenzenediazonium ion (B^+) in aqueous solutions at pH values of either 4 or 10.[29] Figure 1 gives a simplified scheme, assuming no effect of mixing.

At pH = 4 coupling was at position 5 (see Figure 2) to give an aminoazo dye R′ and acidity which was neutralised by a suitable buffer.

At pH = 10 coupling was at position 3- (see Figure 2) to give a hydroxyazo dye R and again acidity, provided that reagent concentrations were below 10 mol/m^3. Thus, the ring substituted by B is (a) the one bearing the NH_2 group when pH = 4, and (b) the one bearing the OH group when pH = 10, provided that the reactions are kinetically controlled.

Table 8 reports product distributions at the two pH levels as a function of reagent concentrations and thus at various reaction rates. S is the bis-azo dye formed by further coupling (at position 1-) of the monoazo dye (R) with B, analogous to eqs 2.1 and 2.2.[29]

Two striking changes in product distribution took place when reagent concentrations were greatly increased at pH = 10, namely (a) R′, characteristic of pH = 4, now formed at pH = 10, and (b) the bis-azo dye (S), absent at low reaction rates, was now a large fraction of the products. The first change suggests that the protons were liberated so

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(26) Bourne, J. R.; Yu, S. Investigation of Micromixing in Stirred Tank Reactors Using Parallel Reactions. *Ind. Eng. Chem. Res.* **1994**, *33*, 41.

(27) Paul, E. L.; Mahadevan, H.; Foster, T.; Kennedy, M.; Midler, M. Effect of Mixing on Scale-Up of a Parallel Reaction System. *Chem. Eng. Sci.* **1992**, *47*, 2837.

(28) Bourne, J. R.; Rys, P.; Suter, K. Mixing Effects in the Bromination of Resorcin. *Chem. Eng. Sci.* **1977**, *32*, 711.

(29) Kaminski, R.; Lauk, U.; Skrabal, P.; Zollinger, H. pH-Dependence and Micromixing Effects on the Product Distribution of Couplings with 6-Amino-4-hydroxy-2-naphthalenesulphonic Acid. *Helv. Chim. Acta* **1983**, *66*, 2002.

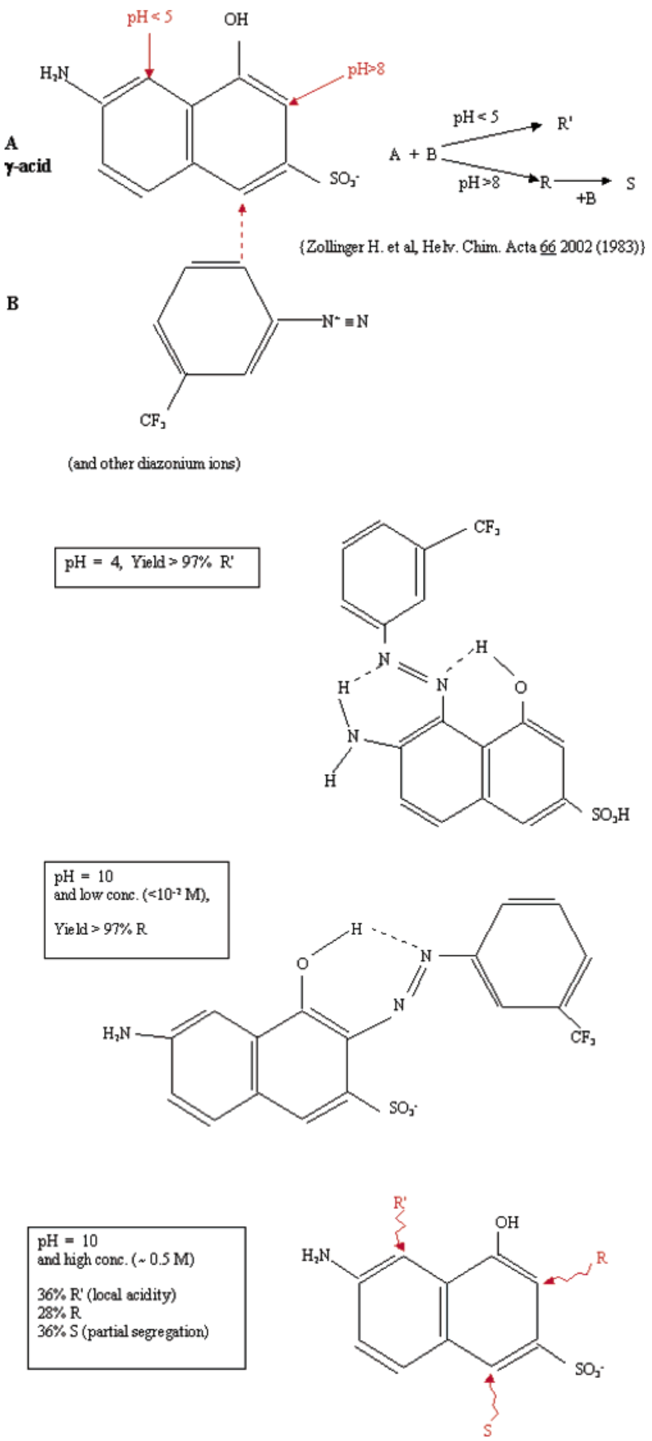

Figure 2. **Azo-coupling of an aminonaphthol and influence of molecular-scale pH gradients.**

rapidly, relative to their removal rate by mixing, that the pH at the reaction site sank well below 10, allowing also R′ to form. The second change is compatible with the characteristics of competitive−consecutive reactions (refer to part 2.1) whereby more S and less R form when the mixing rate is too low. Two measures raised the yield of R, whilst reducing those of R′ and S, namely (i) pre-neutralising the acidic diazonium salt solution and (ii) accelerating the mixing of the reagents.[29] Further information on the formation and influence of pH gradients is available.[21]

2.4. Conclusions: Single-Phase Reactions. Sufficiently fast, single-phase multiple reactions, involving, for example, competitive and consecutive steps, exhibit product distributions that depend on the methods used to mix the reagents. This behaviour is not restricted to particular reactions or classes of reactions nor can it be attributed to chemical artefacts.

Experiments show that the influence on selectivity of "mixing"—and this term needs to be more precisely understood—is more important when:

(a) Reagents exhibit high reactivities, so that reactions are fast.

(b) Concentrated reagent solutions are employed.

(c) Stirring is weak (low stirrer speed, poor stirrer design).

(d) Reagents are added to weakly agitated regions in a reaction vessel.

(e) Viscosities are high.

(f) Reagents are added at a rate faster than that at which they can mix completely.

Increasing the mixing rate can (i) increase the yield of the intermediate product (*R*) in competitive−consecutive reactions and can (ii) increase the difference between the yields of the products (P and Q) in competitive reactions.

3. Examples of Mixing-Sensitive Two-Phase Reactions

3.1. Introduction. Changes in the mixing intensity influence the rates of single two-phase reactions and the product distributions of competitive−consecutive as well as competitive two-phase reactions in qualitatively the same ways as for single-phase reactions (refer to section 2). The presence of a second phase introduces however more complexity.

For a reaction to occur between two reagents A and B, initially present in different phases, B must be transferred to and dissolve in the A-rich phase, before it can react there. Factors needing consideration include:

The phase (A-rich or B-rich) within which reaction takes place must be known. Sometimes this is obvious (e.g. pure gas or solid dissolving in a liquid) but in other cases (e.g. two partially miscible solutions) it is not.

The solubility, which can be a complex function of composition, sets an upper limit on the concentration of B-in the A-rich phase.

The dissolution rate of B can depend on the stirring intensity in either or both of the phases and can determine reaction rate and selectivity.

The reaction can be located (i) at the interface, (ii) near the interface but within the diffusion layer (or film) of the A-phase, or (iii) in the bulk of the A-rich solution far removed from the interface. This location also influences reaction rate and selectivity.

The concept of a diffusion layer or film was introduced by W. Nernst (1904) and developed by W. G. Whitman (1923). By postulating a stagnant layer at an electrode Nernst offered a model of why the observed rate of an inherently rapid electrode reaction was low and was also influenced by the flow conditions, despite a highly turbulent environment. In the present context, a stagnant film of thickness δ in the A-rich phase is supposed to exist so that the rate of

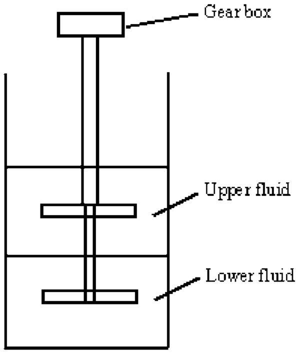

Figure 3. **Constant interfacial area cell (Lewis cell).**

diffusive mass transfer of B into the bulk of the A-rich phase (in the absence of reaction) is proportional to (D/δ), where D is the molecular diffusivity of solute B. This proportionality is often termed the liquid film mass transfer coefficient, k_L, giving the following definition.

$$k_L = D/\delta \tag{3.1}$$

The rate of mass transfer between phases is proportional to k_L but also to the interfacial area. In some equipment this area is well defined and easily measurable.

A common example is the stirred cell (sometimes termed the Lewis cell) Figure 3, which consists of a cylinder containing the A-rich solution[31] with above (or below) it the second, B-rich phase (gas or liquid).[2,30] Usually, each phase is weakly stirred so as not to disturb the interface, e.g. by causing ripples, and not to disperse the one phase in the other. Modest changes in stirrer speed influence δ and k_L, but not the interfacial area. Another example is the rotating disk electrode used to measure the effect of mass transfer on electrochemical and other reactions.[32] The stirred cell and the rotating disk are used at laboratory scale.

In other equipment, however, the one phase is dispersed as small particles, bubbles, or drops in the other phase to greatly increase the interfacial area relative to the Lewis-type cell. Sparging a gas into a turbulent liquid is a common example. Denoting the volume fraction of the dispersed phase in the dispersion by H, the so-called hold-up, and the average diameter of the particles, drops, etc., by d_{32}, the interfacial area per unit volume of dispersion (a, m^2/m^3) is given by

$$a = 6\,H/d_{32} \tag{3.2}$$

In the absence of reaction, the rate of mass transfer between phases is proportional to k_La. When two-phase reaction occurs, this proportionality is not always valid, and k_L and a can influence the rate of mass transfer and reaction (mol/m^3·s) in other ways. The influence of mechanical agitation is (a) relatively weak on k_L and (b) stronger on d_{32}, where often $d_{32} \approx N^{-1.2}$ or $d_{32} \approx N^{-1}$ is found for bubbles and drops, N being the rotational speed of the stirrer. With constant dispersed phase hold-up, $a \approx N$ is a useful approximation over a small range of stirrer speeds, when dispersing a liquid.

3.2. Competitive−Consecutive Reactions. The reaction scheme, used in part 2.1, is

$$\mathrm{A} + \mathrm{B} \xrightarrow{k_1} \mathrm{R} \tag{2.1}$$

$$\mathrm{R} + \mathrm{B} \xrightarrow{k_2} \mathrm{S} \tag{2.2}$$

As with single-phase reactions faster mixing or slower reaction can increase the yield of the primary product R at the cost of less S.

3.2.1. Substitution by Chlorine in 4-Hydroxytoluene. Various proportions of the monochlorinated (R, Cl at 3-) and dichlorinated (S, Cl at 3- and 5-) products have been observed in these substitutions for which $k_1 \gg k_2$.[2,33−35]

In a stirred cell with a flat interface the R-yield increased with rising stirrer speed. The film thickness (δ) decreased from 195 to 114 μm as the stirrer speed (N) rose from 140 to 300 rpm and, although the accuracy of such determinations is uncertain, the values are consistent with similar studies.[30] {These film thicknesses are larger than in turbulent, dispersed systems because with a stirred cell gentle agitation is essential to preserve a horizontal gas−liquid interface and therefore a known interfacial area}. The rising R-yield when stirring was increased implies that part of the second reaction (forming S) moved from the film to the bulk, whilst the first reaction (forming R) remained predominantly in the film.[33] In some further runs the Cl_2 stream was diluted with air, thereby reducing the Cl_2 (B) solubility. The higher A/B ratio resulted in higher R-yields.[33]

This A/B ratio was also increased by raising the A-concentration in the range 1250−4660 mol/m^3, but the yield of R then *decreased*. This contradictory trend was probably caused by the rising viscosity of the 4-hydroxytoluene (A) solutions, thereby increasing the film thickness (δ)[33] and decreasing k_L from 2.2×10^{-5} to 7.1×10^{-6} m/s. These changes allowed more S to form in the film, where the local Cl_2 concentration was high.

In related experiments Cl_2 was sparged into a bubble column and also into a stirred vessel: both were made of glass allowing the bubbles to be observed. Using gas distributors having differently sized holes, bubbles of Cl_2 (subsequently Cl_2 + HCl) having mean sizes between 0.34 and 6.1 mm were generated. In both reactors the R-yield increased with increasing bubble size.[34] From independent studies it is known that, when bubbles are significantly smaller than 1 mm they behave as rigid spheres. Bubbles larger than about 1 mm have however a mobile interface and can oscillate. The liquid film mass-transfer coefficient around "small" bubbles is significantly smaller than around "large" ones, so that δ for "large" bubbles is smaller and diffusive mass transfer is faster. This seems to

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(31) Hanna, G. J.; Noble, R. D. Measurement of Liquid−Liquid Interfacial Kinetics. *Chem. Rev.* **1985**, *85*, 583.

(32) Riddiford, A. C. *Adv. Electrochem. Electrochem. Eng.* **1966**, *4*, 47.

(33) Teramoto, M.; Nagayasu, T.; Matsui, T.; Hashimoto, K.; Nagata, S. Selectivity of Consecutive Gas−Liquid Reactions. *J. Chem. Eng. Jpn.* **1969**, *2*, 186.

(34) Teramoto, M.; Fujita, S.; Kataoka, M.; Hashimoto, K.; Nagata, S. Effect of Bubble Size on the Selectivity of Consecutive Gas−Liquid Reactions. *J. Chem. Eng. Japan* **1970**, *3*, 79.

(35) Pangarkar, V. G.; Sharma, M. M. Consecutive Reactions: Role of Mass Transfer Factors. *Chem. Eng. Sci.* **1974**, *29*, 561.

be the reason higher R-yields were measured when sparging "large" bubbles.

These chlorinations are further discussed in section 9.2.4.

3.2.2. Addition of Chlorine to 1,5-Cyclooctadiene. Measurements of product distribution and conversion at 293 K, employing Cl_2 (B) and cyclooctadiene (C_8H_{12}) (A) each dissolved in CCl_4 prior to single-phase mixing, gave $k_1/k_2 \approx 2$ as expected.[36]

A first set of two-phase chlorinations used a Lewis cell with a stirrer in the liquid. The yield of the monochloro product R decreased, in some cases almost to zero, as the temperature (303−310 K) and the initial reagent ratio B/A were increased. When the solubility of Cl_2 exceeded the concentration of A, R-yields were particularly low indicating over-chlorination in the Cl_2-rich film. The two trends are consistent with inadequate mixing and an excessive film thickness.

In a second set Cl_2 was sparged into a vigorously stirred solution. The yield of R increased and reached the levels expected in the kinetically controlled regime.

3.3. Competitive Reactions. The reaction scheme used in section 2.2 is

$$A + B \xrightarrow{k_1} P \tag{2.8}$$

$$C + B \xrightarrow{k_2} Q \tag{2.9}$$

Faster mixing, leading to a smaller effect of interphase mass transfer, enhances the difference between the yields of the two products (P and Q).

3.3.1. Competitive Nitrations of Aromatic Compounds. A mixed acid, typical of that used for industrial mononitration[15] and containing 15 mol % HNO_3, 30 mol % H_2SO_4, and 55 mol % H_2O was employed to nitrate toluene (A_t), benzene (A_b) and chlorobenzene (A_{cb}) in two-phase mixtures.[37−39] Single-phase kinetic measurements at low HNO_3 concentrations gave $k_{CB}/k_B \approx 0.065$ and $k_T/k_B \approx 20$.[15] Measured product distributions from two-phase competitive nitrations, using the higher acid concentration given above, were evaluated to give the following ratios $k_{CB}/k_B \approx 0.24$[38] and $k_T/k_B \approx 1.5-2.0$.[37] This evaluation assumed that the ratio of the concentrations of the aromatic substrates in the aqueous phase, where nitration took place, was the same as in the organic phase. This is incorrect. Introducing a correction for the differing solubilities of benzene and toluene and assuming no mass-transfer limitation gave $k_T/k_B \approx 12$.[39] Clearly the ratios of 1.5−2.0 derived from two-phase nitrations do indicate that transfer of the aromatics to the aqueous phase was partly limiting. Experiments varying the stirring intensity would have changed the mass-transfer limitation.

Section 9.3.3 provides more information on these nitrations.

3.3.2. Hydrolyses of Isomeric Esters. The esters 1,2-dimethylphthalate (A) and 1,3-dimethylphthalate (C) (C_6H_4-$(COOCH_3)_2$) were hydrolyzed with NaOH (B) under single-phase and two-phase conditions. An excess of alkali was employed and neither acid nor half-ester were found in the hydrolysis products.[40]

Using 0.186 N NaOH and a single phase, the measured pseudofirst-order rate constants were for A 2.3×10^{-3} s^{-1} and for C 9.3×10^{-3} s^{-1}, indicating that 1,3-DMP hydrolyses four times faster than 1,2-DMP.

With toluene as solvent for the esters, analogous rate constants from two-phase experiments were for A 1.8×10^{-6} s^{-1} (unstirred) and 62×10^{-6} s^{-1} (dispersed) as well as for C 0.85×10^{-6} s^{-1} (unstirred) and 30×10^{-6} s^{-1} (dispersed), indicating that 1,2-DMP hydrolyses twice as fast as 1,3-DMP, i.e., the relative rates were reversed compared to single-phase hydrolysis.

With no hydrolysis, 1,2-DMP (A) dissolved in water 3 times as fast as 1,3-DMP(C) indicating its higher solubility (the distribution coefficient of A was 4 times that of C).[40] The hydrolysis rate of each ester was proportional to a (interfacial area per unit volume).

These results show that solubility and mass-transfer rates influenced relative hydrolysis rates in the two-phase case.

3.3.3. Esterification of Cephalosporic Acid. In this example a solution of cephalosporic acid and 4-nitrobenzylbromide in a mixture of polar organic solvents was prepared. Upon addition of potassium carbonate particles this solid and the acid rapidly formed the carboxylate, which in turn was slowly esterified by the alkyl bromide. The ester was then, however, partially decomposed in the solution surrounding the dissolving K_2CO_3 particles.[41] Formation and decomposition of the required ester competed. When the stirrer speed was increased, the particles dissolved somewhat faster and the surrounding film became thinner, which raised the yield of the ester, e.g. by about 10% when the speed was raised by a factor of 4.

3.4. Other Mixing-Sensitive Two-Phase Multiple Reactions. Many further examples may be found in the book by Doraiswamy and Sharma[2] and in subsequent papers by M. M. Sharma and co-workers. The product distribution formed during the sulphonation of benzene has been studied in detail.[42]

3.5. Conclusions. Agitation intensity can influence the product distribution of sufficiently fast two-phase multiple reactions. In competitive−consecutive reactions the yield of the intermediate product (R) is usually increased by more intensive mixing. When competitive reactions take place, faster mixing can enhance the difference between the yields of the various products (P and Q). Later (sections 8 and 9) it will be shown that an influence of mixing is likely when

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(36) Kondelik, P.; Pasek, J. Effect of Mass Transfer on the Selectivity of Consecutive Reactions in a Gas−Liquid System. *Collect. Czech. Chem. Commun.* **1981**, *46*, 1635.

(37) Hanson, C.; Marsland, J. G. Macrokinetics of Toluene Nitration. *Chem. Eng. Sci.* **1971**, *26*, 1513.

(38) Hanson, C.; Marsland, J. G.; Naz, M. A. Macrokinetics of Chlorobenzene Nitration. *Chem. Eng. Sci.* **1974**, *29*, 297.

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(40) Tomita, A.; Ebina, N.; Tamai, Y. Base-Catalysed Ester Hydrolysis in a Toluene−Water System. *J. Am. Chem. Soc.* **1977**, *99*, 5725.

(41) Yamazaki, H.; Yazawa, H.; Miyanami, K. Effect of Mixing on Esterification of Cephalosporic Acid in a Solid−Liquid System. *Chem. Eng. Sci.* **1989**, *44*, 109.

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the half-life of the limiting reagent in a two-phase reaction is shorter than a few seconds.

4. Time Constants of Single-Phase Mixing

4.1. Introduction. A deeper understanding of the experimental results summarised in section 2 and an ability to make some predictions (e.g. the likely influence of operating variables on product distribution) require a transfer from level a) qualitative to level b) semiquantitative (refer to section 1). An outline is given here of the mixing mechanisms operating at various scales and their time constants—for further details, refer to ref 1. The slowest step, having the longest time constant, is then likely to determine the outcome of chemical reactions.

4.2. Time Constant of Chemical Reaction. For a second-order reaction using equimolar concentrations (c_o) of the two reagents, the half-life (t_R), which is the time required for reaction to reduce the reagent concentration to half its initial value, is given by

$$t_R = (kc_o)^{-1} \tag{4.1}$$

where k is the second-order rate constant. Equation 4.1 refers to batch reaction conditions. For semibatch operation suppose a volume V_B of a solution having an initial concentration of B equal to c_{B0} is gradually added to a solution whose volume is V_A. To calculate the half-life, the concentration of B *after* mixing the two solutions, but before reaction is employed, giving

$$t_R = [kc_{B0}\, V_B/\,(V_A + V_B)]^{-1} \tag{4.1′}$$

The half-lives of other reactions are similarly determined from the reaction kinetics.

4.3. Time Constant of Micromixing by Molecular Diffusion. Chemical reaction is a molecular-scale phenomenon, and reagents, initially present in separate solutions, can only encounter each other through the action of molecular diffusion. During mixing, thin fluid laminae are formed (Figure 4) as outlined in section 4.4.

When adjacent layers differ in composition, molecular diffusion takes place between them (e.g. A into a B-rich lamina and vice versa) and progressively homogenises the mixture on the molecular scale. Micromixing denotes mixing at or near the molecular scale and includes molecular diffusion as its ultimate mechanism. During diffusion the laminae are being deformed, and the half-life of molecular diffusion within progressively thinning laminae (t_{DS}) is given by

$$t_{DS} = 2(\nu/\epsilon)^{0.5} \operatorname{arc\,sinh}(0.05\nu/D) \tag{4.2}$$

where D is the diffusivity, ν, the kinematic viscosity, and ϵ, the rate of dissipation to heat of the kinetic energy contained in the turbulent velocity fluctuations. In a well stirred aqueous solution, for example, $\nu = 10^{-6}$ m^2/s, $D = 10^{-9}$ m^2/s and $\epsilon = 1$ W/kg. This is a typical power input to a stirrer, and its dissipation results in a temperature rise of ca. 0.9 K/h. Equation 4.2 then gives $t_{DS} = 9$ ms. The influence of the diffusivity on this time constant is rather weak.

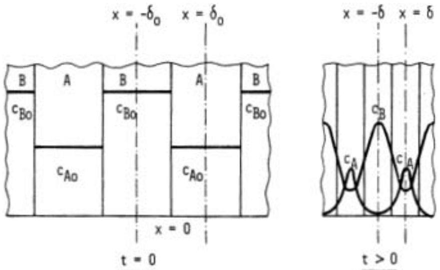

Figure 4. **Concentration profiles due to molecular diffusion in thinning laminae.**[1]

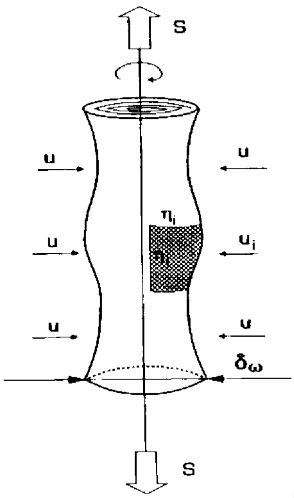

Figure 5. **Vortex tube engulfing surrounding fluid to form laminated structure.**[1]

4.4. Time Constant of Micromixing by Engulfment. Vorticity and transitory vortex tubes are characteristic of turbulent flow (Figure 5). It is supposed that small, energetic vortices acting near the Kolmogorov scale (see below) draw in (or engulf) surrounding fluid forming a short-lived laminated structure within the vortex tube. When a small amount of initially B-rich solution engulfs A-rich surroundings, the rate of growth of the engulfed volume (V_E) is given by

$$dV_E/dt = EV_E \tag{4.3}$$

where the engulfment rate coefficient (E) can be found from

$$E = 0.058\,(\epsilon/\nu)^{1/2} \tag{4.4}$$

The time constant for micromixing by engulfment is E^{-1}, giving

$$t_E = 17\,(\nu/\epsilon)^{1/2} \tag{4.5}$$

When $\epsilon = 1$ W/kg and $\nu = 10^{-6}$ m^2/s, $E = 58$ Hz and $t_E = 17$ ms. For solutions of low-to-medium molecular mass solutes in common, low-viscosity solvents, t_E usually exceeds t_{DS}, and engulfment, rather than molecular diffusion, determines the micromixing rate.

The prefix "micro" can be given a more precise meaning. Even in a highly turbulent fluid, exhibiting, for example, three-dimensional velocity fluctuations and a wide spectrum of vortex sizes, the flow at sufficiently small scales is no

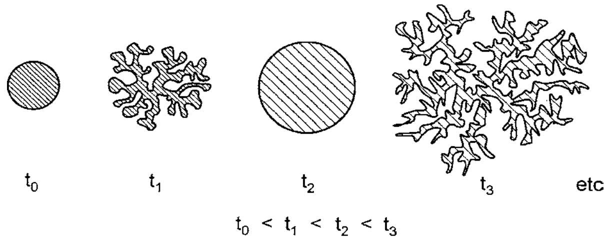

Figure 6. **Disintegration of fluid element to scale where micromixing occurs.**[1]

longer turbulent, but laminar. This applies below the Kolmogorov scale (λ_K) given by

$$\lambda_K = (\nu^3/\epsilon)^{1/4} \tag{4.6}$$

For the conditions given above $\lambda_K = 31\ \mu$m. The engulfment, deformation, and diffusion already referred to take place near or below λ_K, and it should be noted that their time constants (t_{DS} and t_E) include a dependence on viscosity. Rapid micromixing is promoted by fast stirring (high ϵ) and low-viscosity solvents (low ν).

The engulfment mechanism provides the basis for a relatively simple micromixing model, which is on the level (c) "quantitative" mentioned in section 1. When $t_E > t_{DS}$, deformation and diffusion rapidly homogenise the growing vortex at the molecular scale: c_i denotes the concentration of any substance i within the vortex. The concentration of this substance in the surroundings is $\langle c_i \rangle$. A mass balance on substance i in the vortex is therefore

$$\begin{aligned} \text{accumulation} &= \text{inflow} + \text{formation through reaction} \\ d(V_E\, c_i)/dt &= E V_E \langle c_i \rangle + r_i V_E \end{aligned} \tag{4.7}$$

where r_i is the chemical reaction rate which is given by classical kinetics. Equations 4.3 and 4.7 give

$$dc_i/dt = E(\langle c_i \rangle - c_i) + r_i \tag{4.8}$$

This basic form of the *E*-model of micromixing consists of eqs 4.3 and 4.8 with eq 4.4 for parameter estimation. Reaction kinetics relate r_i and c_i, c_j, c_k, etc. For fast reactions eq 4.8 is usually integrated for sufficient time to consume all the limiting reagent. The set of all concentrations then represents the required product composition when all the reactions have stopped.

4.5. Time Constant of Mesomixing by Eddy Disintegration. When a feed stream has entered a turbulent environment (e.g., in a stirred tank), it gradually disintegrates from an initial scale (Λ_C) towards the Kolmogorov scale (λ_K) where micromixing can occur. Figure 6 represents this break up schematically. Its time constant is given by

$$t_S \approx 2(\Lambda_C{}^2/\epsilon)^{1/3} \tag{4.9}$$

Some estimates of the initial scale of unmixedness include:

(a) Suppose that the feed is introduced through a small pipe into a larger turbulent environment, so that the momentum of the feed stream is negligible relative to that of the surrounding flow (velocity *u*). The feed stream rapidly adopts this velocity, so that by continuity

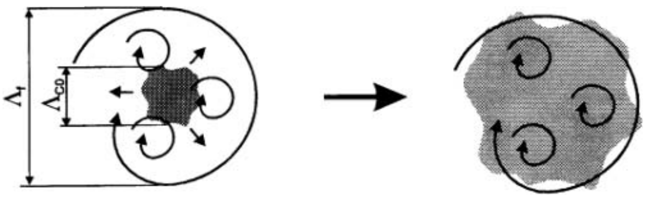

Figure 7. **Growth of concentration eddy from feed stream (Λ_{C0}) to size of eddy in ambient turbulence (Λ_f).**[1]

$$\Lambda_C = (Q_B/\pi u)^{0.5} \tag{4.10}$$

where Q_B is the flow rate of the feed. For example when 1 mL/s of B-rich feed enters a bulk stream moving at $u = 1$ m/s and $\epsilon = 1$ W/kg, eqs 4.9 and 4.10 give $t_S = 7$ ms and $\Lambda_C = 0.56$ mm. These equations predict slower mesomixing when the feed rate is increased, whilst the stirring rate is unchanged.

(b) In contrast to case (a), suppose now that the feed enters with a much higher velocity than *u* and forms a strong jet. Λ_C is then approximately equal to the radius of the feed pipe, and ϵ is enhanced by the action of the jet.

(c) Returning to case (a), suppose now that the feed is much more concentrated than its environment, so that engulfment needs a long time to incorporate sufficient of the surroundings to cause reaction. During this time eddies of unmixed feed can grow to reach the integral scale of the bulk flow (Λ_f), and so $\Lambda_C \approx \Lambda_f$. Figure 7 represents the relaxation of Λ_C towards Λ_f. In a stirred tank Λ_f might be 10−20% of the tank diameter at positions well-removed from the impeller. The turbulence is, however, inhomogeneous, and close to the impeller Λ_f will be smaller.

The prefix "meso" refers to a scale which is intermediate between that of the vessel (macro) and that below which the flow is no longer turbulent (micro). It particularly refers to the scale of the fresh feed stream.[1]

4.6. Time Constant of Mesomixing by Turbulent Diffusion/Dispersion. Turbulent diffusion and turbulent dispersion are both used to denote the spreading of a stream as it flows, the important point being that the mechanism is turbulent, not molecular. It operates, for example, during bulk blending (section 4.7). Figure 8 shows the initial spreading of a feed stream (flow rate Q_B) in the direction normal to its flow, where $X^0(r,x)$ is the local volume fraction of feed material. When the local velocity (*u*) and the turbulent diffusivity (D_T) are constant during the dispersion of the feed, a Gaussian concentration distribution forms with a time constant (t_D) given by

$$t_D = Q_B/uD_T \tag{4.11}$$

Adding, for example, 1 mL/s of B-rich solution to a bulk stream moving at $u = 1$m/s when D_T is 2×10^{-4} m^2/s gives $t_D = 5$ ms. More generally t_D depends on the feed rate and the turbulence characteristics near the feed pipe's outlet.[1]

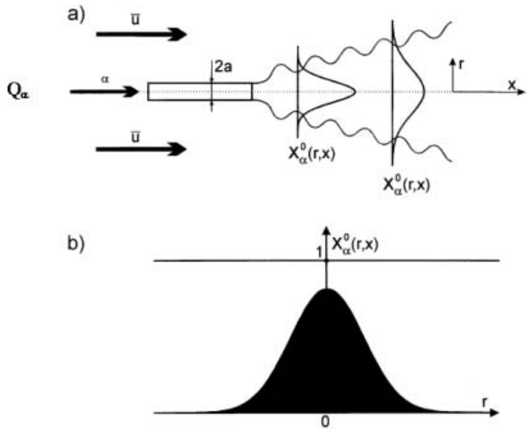

Figure 8. **Turbulent dispersion of feed giving Gaussian concentration distribution normal to flow direction.[1]**

4.7. Time Constant of Macromixing by Bulk Blending. Nonreactive material upon entering a stirred tank joins the circulating flow and during circulation is gradually dispersed by turbulence, so that it finally reaches all parts of the vessel. This bulk blending is followed experimentally by injecting a pulse of nonreactive tracer (e.g., electrolyte) at a particular position and measuring its concentration (e.g., by electrical conductivity) as a function of time at one or several positions. This signal oscillates, corresponding to circulation of the whole fluid, and is also damped by turbulent dispersion (the contribution of molecular diffusion is usually negligible). The oscillation's period is the mean circulation time (t_C). Tracer injection ultimately changes the concentration by Δc, and a possible definition of the macromixing (or bulk blending) time is the time following injection when the concentration change at the measuring point becomes equal to $0.95\Delta c$. This is the so-called "95% mixing time" (t_m). This definition is arbitrary, and methods used to measure it were not always consistent. Nevertheless, 95% mixing times have been reported for a range of mixers[43] and are often a small multiple of t_C (e.g., $t_m \approx 4t_c$).

When the liquid depth in a baffled stirred tank is approximately equal to the tank diameter (T), good estimates of t_m for a range of impeller types may be obtained from eq 4.12.[44]

$$t_m = 5.9(T^3/\epsilon_{av}d)^{1/3} \tag{4.12}$$

where d is the impeller diameter and ϵ_{av} is the *mean* rate of energy dissipation (W/kg)

$$\epsilon_{av} = P/\rho V = Po\, N^3 d^5/V \tag{4.13}$$

in which P is the power consumption of the stirrer, V the liquid volume, N the rotational stirrer speed, and Po the power number (dimensionless power consumption, depending on the stirrer type). In given equipment it follows from these equations that $t_m \approx N^{-1}$ as the stirrer speed is changed.

Consider, for example, a 1.36-L vessel, diameter 0.12 m, equipped with four wall baffles and a pitched-blade turbine, diameter 0.05 m, pumping downwards and rotating at 10 Hz (600 rpm) in an aqueous solution. Equation 4.13 gives $\epsilon_{av} = 0.30$ W/kg and eq 4.12 gives $t_m = 2.9$ s. Upon scaling up to 1.36 m^3 at constant power input per unit volume (i.e., ϵ_{av} constant) t_m would become 13.5 s. The influence of changing scale upon t_m and the other mixing time constants will subsequently be treated in detail (section 7).

4.8. Time Constant of the Process. The time constant for a continuously operated vessel is the mean residence time, which is equal to the volume in the vessel divided by the volumetric flow rate into and out of the vessel. For a batch operation the time constant is the duration of the batch. The time constant for semibatch operation is the reagent feed time (t_f).

4.9. Ranking of Time Constants. Considering in particular a semibatch reactor, the feed time (t_f) is usually much greater than all the other time constants to limit the rate of heat release and thus to match the reactor's cooling capacity. With fast reactions in a turbulent environment meso- and micromixing are often faster than bulk blending, so that the reaction zone is localised near the feed point and does not fill the whole vessel. Fast reactions are those whose half-lives are on the order of or smaller than the time constants for local meso- and micromixing. This mixing then plays a part in determining observed reaction rates and product distributions.

By ranking time constants the controlling step(s) can be clarified and those variables (feed location, viscosity, feed rate, stirring rate etc.) having most influence on the reactions can be identified. This will be shown in sections 6 and 7.

4.10. Conclusions. A mixing time constant indicates the rate of a particular mixing step, whereby the slowest one (largest time constant) is likely to determine the product distribution of multiple reactions. On the basis of the physical processes causing mixing at various scales, equations were presented for the time constants of micro-, meso-, and macromixing. When a stirred vessel is operated as a semibatch reactor, the relevant mixing step is likely to be micromixing at low reagent feed rates and small tank sizes with a transition to mesomixing as feed rates and vessel sizes increase. This generalisation can be checked by experiment or by ranking calculated time constants. Sections 6 and 7 contain many applications of these time constants.

5. Some Single-Phase Test Reactions

5.1. Introduction. Test reactions are employed in experiments to assess (1) the validity of models for the product distributions of fast, mixing-sensitive reactions and (2) the suitability of various reactors for carrying out such reactions. Test reactions must be fully chemically characterised (thermochemistry, equilibria including reagent's preequilibria, reaction kinetics, analytical methods, hazards, etc.), so that, for example, any measured change in product distribution can be unequivocally attributed to "mixing" and not to a chemical artefact. The required level of detail to validate a model completely usually exceeds the information available

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(43) Harnby, N.; Edwards, M. F.; Nienow, A. W. *Mixing in the Process Industries*; Butterworth-Heinemann: New York, 1992.

(44) Nienow, A. W. On Impeller Circulation and Mixing Effectiveness in the Turbulent Flow Regime. *Chem. Eng. Sci.* **1997**, *52*, 2557.

for many industrial reactions. Once a model has been validated, however, its time constants can be applied industrially to gain qualitative insight and possibly also to make semiquantitative predictions. Four sets of fast, single-phase test reactions are briefly described here, and further details, as well as some alternatives, are available.[1]

5.2. Parallel (or Competitive) Reactions. *5.2.1. General Characteristics.* The following scheme represents the competitive reactions of substances A and C for a common reagent B

$$A + B \xrightarrow{k_1} P \qquad (2.8)$$

$$C + B \xrightarrow{k_2} Q \qquad (2.9)$$

With second-order kinetics and B as the limiting reagent, asymptotic product distributions can be determined as follows

(a) Kinetically controlled regime (slow reactions: $t_r \gg t_{mix}$). Mixing on the molecular scale is assumed to be complete before any significant reaction has occurred so that mixing exerts no influence on the reactions.

Notation: the following notation will now be used for brevity. An upper case letter will not only denote a particular substance, as in the preceding text, but also the concentration of that substance.

Dividing the rate equation for A by that for C gives

$$dA/dC = (k_1A)/(k_2C) \qquad (5.1)$$

which, after integration with initial concentrations A_0 and C_0, can be written:

$$A/A_0 = (C/C_0)^{k1/k2} \qquad (5.2)$$

When reaction has stopped, the mass balance on the limiting reagent (B) is

$$B_0 = A_0 - A + C_0 - C = P + Q \qquad (5.3)$$

For example, using equimolar quantities of all reagents ($A_0 = B_0 = C_0$) and given $k_1 = 2k_2$, the final yields are $P/A_0 = 61.8\%$ and $Q/A_0 = 38.2\%$.

(b) Mixing controlled regime (instantaneous reactions: $t_R \ll t_{mix}$). Here the competition of A and C for B is not on the basis of reactivities (*k* values) but of statistics, that is, molar concentrations, so that reaction kinetics exert no influence on the reactions. The relative rate equation now becomes

$$dA/dC = A/C \qquad (5.4)$$

so that, after integration,

$$A/A_0 = C/C_0 \qquad (5.5)$$

The mass balance on B is unchanged, and eqs 5.3 and 5.5 define the final product distribution. When, as above in (a), $A_0 = B_0 = C_0$, the final yields are $P/A_0 = 50\%$ and $Q/A_0 = 50\%$.

(c) Intermediate regime (fast reactions: $t_R \approx t_{mix}$). Between the two asymptotic states lies a wide spectrum of less well defined states, whereby both reaction kinetics and mixing influence product distributions. These states require flexible models to describe them quantitatively as well as suitable test reactions for experimental investigations.[1] The following test reactions are suitable for use in the intermediate regime when employing stirred tank reactors.

5.2.2. Hydrolysis of Ethyl Monochloroethanoate and Neutralisation of HCl. The following reactions compete for NaOH (the limiting reagent) and have been widely used[1]

$$NaOH + HCl \xrightarrow{k_1} NaCl + H_2O \qquad (5.6)$$

$$NaOH + CH_2ClCOOC_2H_5 \xrightarrow{k_2} C_2H_5OH + CH_2ClCOONa \qquad (5.7)$$

In such experiments alkali is added to a stirred, acidic ester solution. Rate constants at 298 K are

$$k_1 = 1.3 \times 10^8\ m^3/mol{\cdot}s$$

$$k_2 = 0.030\ m^3/mol{\cdot}s$$

Denoting acid, ester and alcohol by A, C, and Q, respectively, the product distribution can be represented by the yield of alcohol relative to the limiting reagent (B) and denoted by X_Q.

$$X_Q = Q/B_0 \qquad (5.8)$$

and, as a check on experimental accuracy, the consumption of ester and the production of alcohol can be compared. Ester concentrations must be less than the ester's solubility and values up to 120 mol/m^3 at room temperature may be used. The ester's half-life is then approximately 0.3 s and, in turbulent water, X_Q varies with the mixing conditions when ϵ is on the order of 0.01−0.1 W/kg. Such values can occur in stirred tanks. The asymptotic values of X_Q are (a) 0 when kinetics control and (b) $C_0/(A_0 + C_0)$ when mixing controls.[1]

5.2.3. Hydrolysis of 2,2-Dimethoxypropane and Neutralisation of NaOH. The reactions are

$$NaOH + HCl \xrightarrow{k_1} NaCl + H_2O \qquad (5.9)$$

$$H_3CC(OCH_3)_2CH_3 + HCl + H_2O \xrightarrow{k_2} 2CH_3OH + (CH_3)_2\,CO + HCl \qquad (5.10)$$

Concentrated acid, which is added to an alkaline solution of the acetal, is neutralised in the first reaction and catalyses hydrolysis of the acetal in the second reaction. The limiting reagent is the acid. The rate constant k_1 was given in section 5.2.2. For hydrolysis at 298 K

$$k_2 = 0.60\ m^3/mol{\cdot}s$$

in a solvent containing 25 mass% ethanol (rest water) when employing initial HCl concentrations up to 1333 mol/m^3 (1.33*N*).[25] For example the acetal's half-life in 1 N HCl at 298 K is 1.2 ms, so that this reaction system can be significantly faster than that described in section 5.2.2 and its product distribution responds to correspondingly higher turbulence levels. This distribution is denoted by X_Q

$$X_Q = Q/B_0 \qquad (5.8)$$

where Q is the final propanone concentration and B_0 the initial acid concentration. Its asymptotic values are (a) 0 when kinetics control, since k_1 is orders of magnitude greater than k_2, and (b) 1.0 when mixing controls, since acid persists long enough to catalyse the hydrolysis.

5.3. Competitive−Consecutive Reactions. *5.3.1. General Characteristics.* In the following scheme two reagents (A and B) produce an intermediate R, which can react further with B giving a final product S.

$$A + B \xrightarrow{k_1} R \tag{2.1}$$

$$R + B \xrightarrow{k_2} S \tag{2.2}$$

With second-order kinetics and B as the limiting reagent, asymptotic product distributions can be found as follows:

(a) Kinetically controlled regime (slow reactions: $t_R \gg t_{mix}$). Mixing on the molecular scale is assumed to be complete. Dividing the rate equation for R by that for A gives

$$dR/dA = -1 + k_2R/k_1A \tag{5.11}$$

which, after integration with initial concentrations $R_0 = 0$ and A_0, can be written

$$R/A_0 = [k_1/(k_1 - k_2)]\,[(A/A_0)^{k2/k1} - (A/A_0)] \tag{5.12}$$

provided that k_1 is not equal to k_2.

Mass balances on A and B (the limiting reagent), when reaction has stopped, are

$$A_0 = A + R + S \tag{5.13}$$

$$B_0 = R + 2S \tag{5.14}$$

For example, using 10% excess of A ($A_0 = 1.1B_0$) and given that $k_1 = 20k_2$, the final product distribution is 85.7% conversion of A, 100% conversion of B, yield of R (R/A_0) = 80.5%, yield of S (S/A_0) = 5.2%. Defining as an index of product distribution, X_S as the fraction of the limiting reagent finally present in the secondary product (S)

$$X_S = 2S/(R + 2S) = 2S/B_0 \tag{5.15}$$

then, in this example, $X_S = 0.115$.

(b) Mixing controlled regime (instantaneous reaction: $t_R \ll t_{mix}$). Independently of the rate constants and their ratio, if mixing dominates then $R = 0$ and $S = B_0/2$, therefore, $X_S = 1.0$.

(c) Intermediate regime (fast reactions: $t_R \approx t_{mix}$). As explained in section 5.2.1c a mixing model for the product distribution is needed.

5.3.2. Azo-Couplings between 1-Naphthol and Diazotised Sulphanilic Acid (Benzenediazonium-4-sulphonic Acid). Denoting the naphthol and the diazo compound by A and B respectively, two primary products (o-R and p-R) are first formed and then couple further with B to form S. R and S are monoazo and bis-azo dyes, respectively. The reaction scheme is an expanded form of eqs 2.1 and 2.2 and may be written as follows

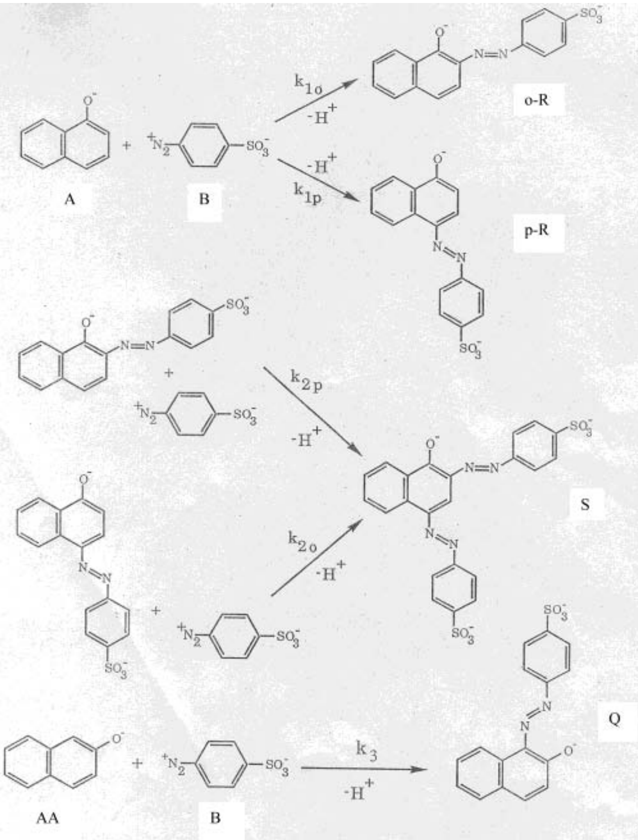

Figure 9. **Reaction scheme and rate constants for azo-coupling test reactions. The first four reactions are based on 1-naphthol (A) and the fifth reaction is based on 2-naphthol (AA).**

$$A + B \xrightarrow{k_{1,p}} p\text{-}R \tag{5.16}$$

$$A + B \xrightarrow{k_{1,o}} o\text{-}R \tag{5.17}$$

$$p\text{-}R + B \xrightarrow{k_{2,o}} S \tag{5.18}$$

$$o\text{-}R + B \xrightarrow{k_{2,p}} S \tag{5.19}$$

These compounds are shown in the upper part of Figure 9. The couplings take place when B, the limiting reagent, is added to A, which is buffered ($Na_2CO_3/NaHCO_3$) to pH = 9.9. Rate constants at 298 K, based on total reagent concentrations, are[1]

$$k_{1,p} = 12238\ m^3/mol{\cdot}s, \qquad k_{1,o} = 921\ m^3/mol{\cdot}s$$

$$k_{2,o} = 1.835\ m^3/mol{\cdot}s, \qquad k_{2,p} = 22.25\ m^3/mol{\cdot}s$$

The solubility of the diazo compound limits the B concentration to approximately 60 mol/m^3 in the concentrated B-rich feed solution.

Depending upon the ratio of the volumes of the A-rich and B-rich solutions, the B concentration after mixing, but before reaction, is often about 1 mol/m^3. Taking the same value for 1-naphthol (i.e. a stoichiometric ratio A/B of unity), the half-life of the limiting reagent (B) is around 0.1 ms in the primary couplings, which are dominated by mixing. The secondary couplings are much slower, an estimate of the half-life of B being 40 ms. These reactions are sufficiently fast that the product distribution responds to mixing in stirred tanks, but not in high intensity mixers (refer to section 5.3.3). Energy dissipation rates in stirred tanks vary locally, but often are in the range 0.01−10 W/kg. After reaction, unreacted 1-naphthol and the three dyes are present, and their concentrations can be measured spectrophotometrically. The yield of the bis-azo dye (S) is defined as (cf eq 5.15)

$$X_S = 2S/(\text{p-R} + \text{o-R} + 2S) = 2S/B_0 \qquad (5.20)$$

and its asymptotic values are the following:

(a) Kinetically controlled regime ($t_R \gg t_{mix}$). Because the primary couplings are much faster than the secondary ones (see *k* values above), $X_S \ll 0.01$. A suitable window for these reactions and their analytical method is $0.04 < X_S < 0.4$, so that X_S in the kinetically controlled regime is effectively zero.

(b) Mixing controlled regime ($t_R \ll t_{mix}$). The yields of the monoazo dyes are zero. Hence $X_S = 1.0$.

(c) Intermediate regime ($t_R \approx t_{mix}$). As with the previous reactions, a mixing model is needed (section 5.2.1c).

5.3.3. Azo-Couplings between 1- and 2-Naphthols and Diazotised Sulphanilic Acid. Denoting 2-naphthol by AA, the five couplings now taking place are eqs 5.16−5.19 plus eq 5.21

$$\text{AA} + \text{B} \xrightarrow{k_3} \text{Q} \qquad (5.21)$$

Figure 9 shows all five reactions in more detail. At 298 K and pH = 9.9

$$k_3 = 124.5\ \text{m}^3/\text{mol}\cdot\text{s}$$

By including 2-naphthol, this system is much faster than when only 1-naphthol is employed, so that high intensity mixers can also be studied. The distribution of dyes responds to mixing intensities up to approximately 10^5 W/kg, which is a higher dissipation rate than that achieved even locally in a stirred tank.[1]

The product distribution can be represented by the yields of S (X_S) and of Q (X_Q), which are defined as

$$X_S = 2S/(\text{p-R} + \text{o-R} + Q + 2S) \qquad (5.22)$$

$$X_Q = Q/(\text{p-R} + \text{o-R} + Q + 2S) \qquad (5.23)$$

Asymptotic values of these yields are

(a) Kinetically controlled regime ($t_R \gg t_{mix}$). $X_S \approx 0$ as in the coupling of 1-naphthol alone. The system of five reactions then reduces to eqs 5.16, 5.17, and 5.21, and adding the two primary couplings of 1-naphthol gives

$$\text{A} + \text{B} \xrightarrow{k_1} \text{R} \qquad (5.24)$$

where R = p-R + o-R and $k_1 = k_{1p} + k_{10}$. Effectively the two naphthols compete for the diazonium ion, and schematically, just two competitive reactions eqs 5.21 and 5.24, similar to eqs 2.8 and 2.9, remain.

Using the method given in section 5.2.1a with initially equimolar quantities of 1- and 2-naphthols and a 20% excess of 1-naphthol over diazotised sulphanilic acid, $X_Q = 0.019$ in this regime.[1]

(b) Mixing controlled regime ($t_R \ll t_{mix}$). Using again the method given in section 5.2.1, when B is again the limiting reagent, the limiting value of X_Q is given by

$$X_Q = \text{AA}_0/(\text{AA}_0 + 2\text{A}_0) \qquad (5.25)$$

for example, using equimolar quantities of 1- and 2-naphthols, $X_Q = {}^1/_3$ in this regime.

(c) Fast regime ($t_R \approx t_{mix}$). The interpretation of experimental results for this system (with up to five reactions and four products) in the intermediate regime requires a robust mixing model (section 5.2.1c).

5.4. Conclusions. Selectivity and yield are sensitive to mixing when the characteristic time scale of chemical reaction is approximately equal to that of the limiting mixing step. Mixing time constants depend on several factors, an important one being the turbulent energy dissipation rate in the zone where reagents mix and react. This quantity varies strongly with stirrer speed in an agitated tank and with flow rate in a continuously operated tubular reactor, as well as between various mixer types—refer to sections 6 and 7 for more details. When measuring the quality of mixing, as shown by a product distribution, test reactions are needed that have various rates (or time constants) which match approximately those of the various mixer types. Of the four sets of reactions presented here, the slowest is usually that in section 5.2.2, those in sections 5.2.3 and 5.3.2 have roughly comparable time constants, whereas the fastest set is described in section 5.3.3.

6. Interpretation of Experiments on Single-Phase Reactions

6.1. Introduction. An understanding of how mixing at various scales affects the product distributions of fast chemical reactions can be achieved at (a) qualitative, (b) semiquantitative, and (c) quantitative levels (section 1). Many variables—some chemical, such as rate constants, and some physical, such as stirrer speed—have to be considered, and it is necessary to clarify which and how many variables can influence product distributions. This will be illustrated for two competitive−consecutive reactions when the limiting reagent B is gradually added to A, which is in solution in a stirred tank. (This is semibatch operation).

$$\text{A} + \text{B} \xrightarrow{k_1} \text{R} \qquad (2.1)$$

$$\text{R} + \text{B} \xrightarrow{k_2} \text{S} \qquad (2.2)$$

The product distribution is denoted by X_S, which is the yield of S,

$$X_S = 2S/(R + 2S) \qquad (5.15)$$

The yield of *R* then follows from X_S and the mass balance on the limiting reagent, eq 5.14.

Application of the mechanisms and principles in section 4 shows that this yield is a function—denoted by *f*—of many physical and chemical quantities—denoted by the ratios in eq 6.1. The nine ratios are the independent variables (or degrees of freedom) which in principle can influence X_S.[1]

$$X_S = f(k_1/k_2,\ n_{B0}/n_{A0},\ V_A/V_B,\ t_{DS}/t_E,\ t_E/t_R,\ t_D/t_S,\ t_S/t_E,\ t_m/t_E,\ t_f/t_R) \tag{6.1}$$

Time does not appear here because X_S refers to the product distribution when all mixing and reaction have been completed. The dimensionless ratios in eq 6.1 have the following significances:

k_1/k_2 is the ratio of rate constants. A high value favours a high yield of R and a small X_S value.

n_{B0}/n_{A0} is the initial stoichiometric ratio of the reagents. A high value favours a high yield of S. If the ratio exceeds 2, $X_S = 1$ and the yield of R is zero, when reactions have stopped.

When both reactions are slow and unaffected by mixing, these two ratios are sufficient to define (and calculate) the final product distribution from a semibatch reactor, as shown in section 5.3.1a.

V_A/V_B is the ratio of the volumes of reagent solutions, which is only relevant when the regime is fast, i.e., when mixing affects the product distribution.

t_{DS}/t_E is the ratio of time constants for molecular diffusion and engulfment. It is frequently smaller than unity, so that t_{DS} and the diffusivity exert no influence on X_S.[1]

t_E/t_R is the ratio of time constants for micromixing by engulfment and the half-life of chemical reaction. It is customary to base this half-life on the second reaction, eq 2.2, noting that, when this is defined, the half-life of the first reaction is not a new and independent quantity because k_1/k_2 has already been specified. t_R is written for the limiting reagent (B) using its concentration after mixing, but before reaction (compare eq 4.1), which is defined by

$$(V_A + V_B)C_B = V_B C_{B0} \tag{6.2}$$

The ratio t_E/t_R is termed the Damkoehler number

$$k_2 C_B / E = Da \tag{6.3}$$

t_D/t_S is the ratio of time constants for turbulent dispersion of the feed stream and its disintegration to fine-scale eddies prior to engulfment. If, for example, this ratio is much smaller than unity, then disintegration is more relevant than dispersion.

t_S/t_E is the ratio of time constants for disintegration of the feed stream and engulfment i.e., of mesomixing to micromixing. Examples will subsequently be given where one of these mechanisms dominates as well as where a transition of the controlling mechanism occurs.

t_m/t_E is the ratio of time constants for bulk blending and engulfment. It is usually greater than unity and the zone within which mixing and reaction take place is localised within a stirred tank.

t_f/t_R is the ratio of the feed time to a semibatch reactor to the reaction's half-life. This is greatly in excess of unity indicating that the feed time can influence the product distribution as well as setting the time scale for the overall progress of reaction.

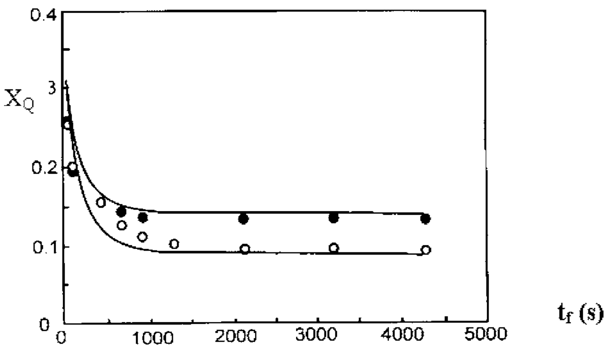

Figure 10. **Yield of dye from 2-naphthol at two viscosities as a function of feed time to jet-stirred vessel (jet velocity = 6 m/s).[1]**

6.2. Qualitative Interpretation of Experimental Results. *6.2.1. Reactivity.* Table 1 presented results for acylations of symmetrical diamines whose reactivities differed. In these competitive−consecutive reactions, eqs 2.1 and 2.2, higher reactivity (i.e., k value) promoted more S and hence less R. Faster reaction and shorter t_R {eq 4.1}caused larger deviations from complete mixing of the reagents and the kinetically controlled regime.

6.2.2. Concentration Level. With a given initial stoichiometric ratio the product distribution of slow competitive−consecutive reactions is independent of the concentrations of the reagents. The results in Table 1 show however lower yields of S at lower concentration levels, but constant stoichiometric ratio. Slower reaction and longer t_R {eq 4.1} caused yields to be closer to those expected in the kinetically controlled regime. The same applies to the results in Tables 2 and 6.

6.2.3. Stirring Speed and Agitation Intensity. In a well-baffled tank, so that the liquid surface remains flat during stirring, the agitation intensity represented by the power input per unit volume {P/V (kW/m^3)} and also the energy dissipation rate {ϵ (W/kg)} are related to the stirrer speed {N (Hz)} by the following proportionality (refer to eq 4.13)

$$\epsilon \approx P/V \approx N^3 \tag{6.4}$$

Table 3 for competitive−consecutive reactions and Tables 5 and 6 for competitive reactions show that with rising stirrer speed and agitation intensity the measured yields tend towards those expected from kinetically controlled reactions. All the time constants for mixing (t_{DS}, t_E, t_S, t_D, t_m) become shorter as ϵ increases, so that the results in these three tables do not discriminate between various mixing mechanisms.

6.2.4. Feed Rate and Viscosity. Figure 10 shows the yield of the dye formed from 2-naphthol, when using the reaction system described in section 5.3.3, at two viscosity levels and various feed times. The tank was stirred by a turbulent jet (Figure 20), and the agitation intensity was constant.[1] Two regions can be identified at high and low feed rates.

(a) Short feed times X_Q increases as t_f decreases (i.e., faster feeding) and becomes independent of viscosity.

(b) Long feed times X_Q is independent of t_f, but increases with rising viscosity.

Similar trends were seen at other agitation intensities, whereby with rising intensity X_Q decreased as expected.

Table 9. **Yield of bis-azo dye**

	B_0 (mol/m^3)				
	10	25	50	100	200
V_A/V_B	2	5	10	20	40
X_S	0.050	0.094	0.156	0.233	0.309

From eq 4.5 $t_E \approx \nu^{1/2}$, whereas from eqs 4.9 and 4.10 $t_S \approx Q_B^{1/3}$, where Q_B is the feed rate of diazotised sulphanilic acid, and from eq 4.11 $t_D \approx Q_B \approx t_f^{-1}$. Thus, with short feed times, mesomixing controls, whilst micromixing dominates at long feed times.

6.2.5. Feed Position. The turbulence in a stirred tank is inhomogeneous with ϵ varying from high values near the impeller to low values far removed from it. The time constants for mixing depend on ϵ, and since mixing and reaction can be strongly localised, the product distribution can depend on where the feed is added to the stirred contents of the vessel. Many experimental results have confirmed these statements.[1] The following example refers to adding 4.5 N NaOH to a solution containing 90 mol/m^3 each of the acid and ester referred to in section 5.2.2. The volume of concentrated alkali added was 2% that of the stirred solution (i.e., $V_A/V_B = 50$), whose volume was 0.019 m^3. The stirrer rotated at 75 rpm and was a Rushton turbine whose diameter was one-third that of the tank (0.29 m). Three alternative feed locations for the alkali were

S – just below the liquid surface $X_Q = 0.266$

D – in discharge stream of turbine $X_Q = 0.153$

I – in suction stream of turbine $X_Q = 0.138$

indicating that mixing was slowest near the surface and fastest for the suction side of the impeller in this particular example.[45]

6.2.6. Volume Ratio of Reagent Solutions. When the stoichiometric ratio of the reagents is fixed, varying the volumetric proportions of the two solutions has no effect on the product distribution of the reactions given in eqs 2.1, 2.2, 2.8, and 2.9 {refer also to section 6.1}, provided that they are kinetically controlled. When, however, mixing is relevant, selectivity can depend on the volume ratio of the reagent solutions.

Azo-coupling between 1-naphthol-6-sulphonic acid (A) and phenyldiazonium ion (B)—a system similar to that in section 5.3.2—using a constant stirrer speed and a constant stoichiometric ratio ($n_{B0}/n_{A0} = 0.5$) provides an example. Here V_A and A_0 were held constant and as B_0 was increased from 10 to 200 mol/m^3, V_B was decreased to maintain the given stoichiometric ratio. Measured values of the yield of S (X_S) are given in Table 9.

By adding a given quantity of B at progressively higher concentrations, but smaller volumes, larger gradients of the B-concentration are present during the brief mixing process and promote the secondary reaction (formation of S from R), which was sufficiently fast to occur during mixing. Further information is available.[1]

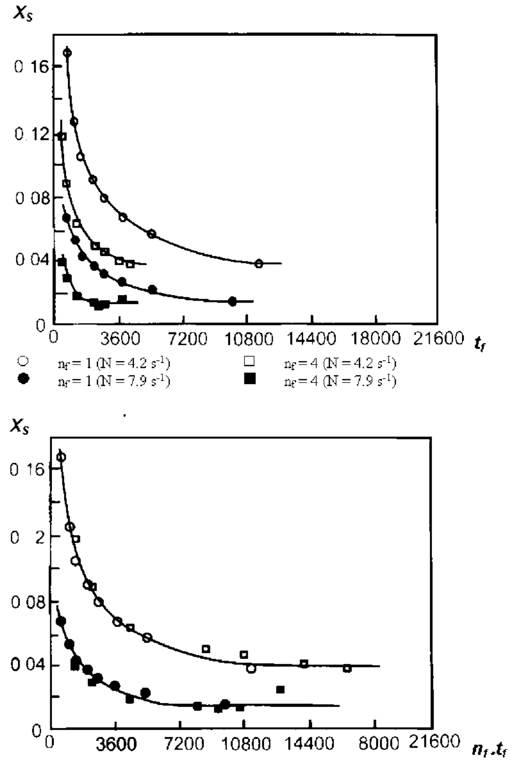

Figure 11. **Yield of bis-azo dye from 1-naphthol at two stirrer speeds as a function of (a) feed time t_f, (b) product of feed time and number of feed points $n_f t_f$.[1]**

6.2.7. Number of Feed Positions. Figure 11a, which is similar to Figure 10, refers to one and also four feed positions for entry of diazotised sulphanilic acid (B) solution during the semibatch azo-coupling with 1-naphthol (refer to section 5.3.2). With a given stirrer speed, B can be added faster to obtain a given product distribution (X_S) when employing more feed points in the mesomixing controlled regime. The flow rate (Q_B) in the time constant for mesomixing (refer to eqs 4.9 and 4.10) is related to the number of feed points (n_f) and the feed time (t_f) by

$$Q_B = V_B/(n_f \cdot t_f) \qquad (6.5)$$

When the number of feed points is changed, Q_B and hence t_S will be constant if $n_f{\cdot}t_f$ is constant, so that the product distribution (X_S) should then also be unchanged. This is confirmed in Figure 11b. A practical consequence is that when say, four equivalent feed points are employed, the feed time can be reduced by the factor 4 without changing either the agitation rate or the product composition, whilst productivity is 4 times higher.[1]

When micromixing controls (no effect of t_f on product distribution), the product distribution is unaffected by the number of feed points (Figure 11b).

6.3. Quantitative Interpretation of Experimental Results. Equation 6.1 expresses in general terms the dependence of the product distribution upon various chemical and mixing-characteristic factors, and qualitative examples of some of these were included in section 6.2. A fully

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(45) Bourne, J. R.; Yu, S. Investigation of Micromixing in Stirred Tank Reactors Using Parallel Reactions. *Ind. Eng. Chem. Res.* **1994**, *33*, 41.

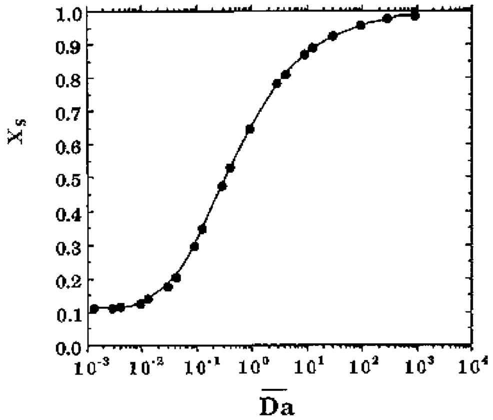

Figure 12. **Yield of secondary product S as a function of Damkoehler Number computed from E model of micromixing ($k_1/k_2 = 20$, $V_A/V_B = 20$, $n_{A0}/n_{B0} = 1.1$).**

quantitative treatment is possible given sufficient information about the reactions and the flow field in which they take place. The main features of such calculations will now be given when (a) micromixing and (b) both meso- and micromixing need to be considered. Further details are available elsewhere.[1]

6.3.1. Prediction of Product Distribution of Micromixing Controlled Azo-Couplings. When micromixing is the controlling mixing step, eqs 4.3, 4.4, and 4.8 represent the engulfment model and may be integrated to find the product distribution. Figure 12 shows results for competitive−consecutive reactions, eqs 2.1 and 2.2, when $k_1 = 20k_2$, $V_A = 20V_B$, $n_{A0}/n_{B0} = 1.1$ and semibatch operation is employed. The ordinate is the yield of S (X_S, refer to eq 5.15) and the abscissa is the Damkoehler number defined in eqs 6.2 and 6.3. The asymptotes are $X_S = 0.115$ if reactions are kinetically controlled and $X_S = 1.0$ if reactions are fully mixing controlled. Over the range $10^{-2} < Da < 10^{2}$ both micromixing and kinetics determine X_S. The S-shape is characteristic also of competitive (or parallel) reactions.[1,45]

Suppose that the product distribution is required for the azo-coupling of 1-naphthol and diazotised sulphanilic acid (refer to eqs 5.16−5.19) in a 0.019 m^3 stirred tank reactor with a sufficiently long feed time that micromixing is controlling. Equation 6.1 reduces to

$$X_S = f(k_1/k_2, n_{B0}/n_{A0}, V_A/V_B, Da) \qquad (6.1')$$

The quantity that still needs to be specified is Da, which by eq 6.3 needs E, which in turn by eq 4.4 needs ϵ in the reaction zone. It is relatively easy to calculate the mean rate of energy dissipation in the whole vessel from the stirrer's power consumption (refer to eq 4.13), but, because fast mixing-controlled reactions are localised and ϵ is spatially highly nonuniform in a stirred tank, its mean value is usually inadequate. Three methods to gain local ϵ values are:

(a) Computational fluid dynamics (CFD) in which, after the introduction of some empirical information and simplifications, the equations of motion are solved numerically. Even with substantial experience with this technique, local ϵ values in stirred tanks are often less accurate than is needed. Future developments are likely to improve accuracy.

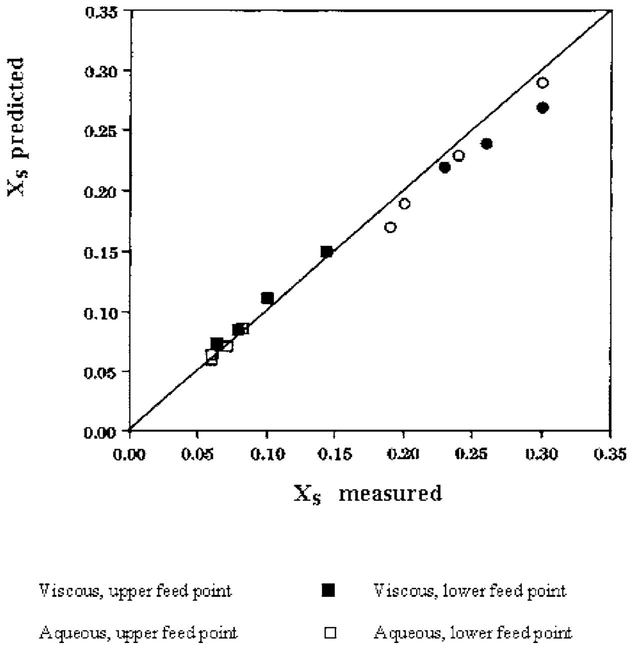

Figure 13. **Yield of bis-azo dye from 1-naphthol; predicted and measured employing various feed locations, solution viscosities and stirrer speeds.[1,46]**

(b) Noninvasive measurements of turbulence properties especially using laser Doppler velocimetry (LDV). Given adequate experience, good quality results are obtainable.

(c) Measurements using complex fast reactions and their evaluation with a mixing model. This will now be illustrated.

In a particular experimental study, two alternative feed points were available: one (termed upper) was submerged 0.03 m below the liquid surface, the other (termed lower) was just above the turbine impeller in its suction stream. The time constant for micromixing depends on viscosity (eq 4.5), so that reactions were carried out in solutions whose viscosities were 0.9 and 6.2 mPa·s. To find local ϵ values, the test reactions described in section 5.2.2 were run at various stirrer speeds, using each of the two viscosities and feed points in turn. The product distribution (X_Q, eq 5.8) was measured and the Damkoehler number appropriate to eq 5.7 was found from the engulfment model of micromixing (refer to section 4.4), so that finally ϵ in the reaction zone was evaluated. Values of ϵ and E, which depend on stirrer speed and feed location, not on the reaction, could then be substituted in eq 6.3 and X_S for azo-coupling could be predicted from the engulfment model. Figure 13 compares the predicted and measured values of X_S, the agreement being generally satisfactory.[46]

6.3.2. Prediction of Product Distribution of Meso- and Micromixing Controlled Azo-Couplings. The five reactions, represented by eqs 5.16−5.19 and 5.21, were carried out in a tubular reactor, which contained turbulence-generating elements, so that the flow was more turbulent than that in an empty tube. The energy dissipation rate (ϵ), which is needed to predict mixing-time constants, is significantly more

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(46) Bourne, J. R.; Gholap, R. V. An Approximate Method for Predicting the Product Distribution of Fast Reactions in Stirred Tank Reactors. *Chem. Eng. J.* **1995**, *59*, 293.

Table 10. **Time constants for static mixer**[1]

		t_E (ms)		t_D (ms)	t_S (ms)
Q (dm^3/s)	ϵ (W/kg)	0.9 mPa•s	3.6 mPa•s		
0.25	0.177	39	78	0.4	41
2.5	177	1.2	2.5	0.04	4.1

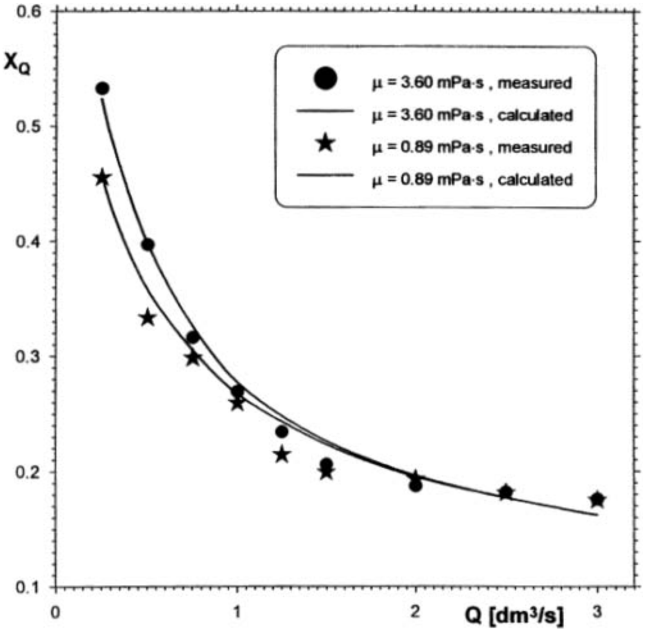

Figure 14. **Yield of dye from 2-naphthol at two viscosities as a function of flow rate in a tubular reactor containing static mixer elements.**[1]

uniform in this reactor than in a stirred tank and can be well estimated from pressure drop-flow rate information.[1,47]

In this example the tube diameter was 0.04 m, and the flow rate (Q) of the alkaline buffered solution of 1- and 2-naphthols was in the range 0.25−3.0 dm^3/s. Two feed points were used for the solution of diazotised sulphanilic acid, the flow rate through each being Q/6000 and its half-life (t_R) being 3.7 ms.

Mixing time constants were calculated from the equations in section 4, and the results are shown in Table 10.

Turbulent dispersion (t_D) was fast in this particular mixer and negligible. At low flow rates micro- and mesomixing were much slower than reaction, particularly in the more viscous case. At high flow rates mixing was more controlled by eddy disintegration (t_S) i.e., by mesomixing. It was required to predict the yield of the monoazo dye formed from 2-naphthol (X_Q defined in eq 5.23). Its asymptotic values were (i) kinetically controlled $X_Q = 0.067$ and (ii) fully mixing controlled $X_Q = 0.667$.

The quantitative modelling of micro- and mesomixing is described in detail elsewhere.[1] The results are given in Figure 14 and compare well with measurements. The effects of flow rate (Q) and viscosity (ν) on product distribution, seen in this figure, can be interpreted through their effects on meso (t_S)- and micro (t_E)-mixing time constants, noting also that $\epsilon \approx Q^3$. Therefore, in this problem

$$t_S \approx Q^{-1} \qquad \text{and} \qquad t_E \approx \nu^{1/2}\cdot Q^{-3/2}$$

the differing exponents on the flow rate Q show that with rising flow rate t_E decreases faster than t_S. It is also shown that only t_E depends on viscosity. The mixing mechanism, which controls the yield of dye Q, changes from micro- and mesomixing at low flow rates to mesomixing at high flow rates.

When calculating X_Q, equations for the various concentrations are integrated with respect to time, so that, for example, the actual half-life of the limiting reagent (B) can also be determined. When the flow rate (Q) was 1 dm^3/s, this half-life was 78 ms, which may be compared to 3.7 ms (t_R) when only kinetics control showing how much reaction was retarded by insufficient mixing. X_Q was then 0.269 compared to 0.067 under kinetic control.

6.4. Conclusions. Measured product distributions were found in section 6.2 to respond consistently to a range of variables according to the principles of competition between reaction and micro- or mesomixing or both, given in section 4. More rigorous, quantitative validations were shown in section 6.3 for cases where full reaction schemes and kinetics as well as turbulence information were available. In an industrial setting this level of detail is seldom available: the approach in section 6.2 is then more suitable, offering qualitative understanding of how mixing can affect product distributions.

7. Scale-Up of Mixing-Sensitive Single-Phase Reactions

7.1. Introduction. When scaling up, the practical requirement is likely to be maintaining a constant product composition whilst the chemical conditions are unchanged (i.e. same temperature, solvent, initial concentrations, and stoichiometric ratios etc.). It follows from eq 6.1—an analogous expression is valid for competitive reactions—that, with t_R constant, X_S or X_Q should be unchanged provided that the various mixing time constants are held constant. As already shown, not all of these are relevant in a particular reaction scenario, so it is the relevant ones which should be the same. A possible difficulty can arise in the application of this principle, namely that the relevant or controlling mixing mechanism (with its associated time constant) can change with the changing scale.

Many of the experimental results in sections 2 and 6 refer to vessels fitted with mechanical agitators, although in sections 6.2.4 and 6.3.2 mixing was caused by a liquid jet and static mixer elements in a tube, respectively. These results were all well interpreted by the time constants explained in section 4, so it may be concluded that this approach applies irrespective of the particular mixer type.

Commercially available mixers are very diverse and their flow fields, including turbulence characteristics, are usually not fully known, although current applications of computational fluid dynamics (CFD), laser Doppler velocimetry (LDV) (section 6.3.1), etc. are beginning to fill some gaps. Further applications of the principles of reactive mixing

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(47) Hearn, S. J. Turbulent Mixing Mechanisms in Motionless Mixers. Ph.D. Thesis, University of Birmingham, U.K. 1995.

(section 4) and test reactions (section 5) are needed to guide the selection of suitable devices to control the product distributions of fast reactions.

Although alternatives to stirred tank reactors are now being seriously considered[48] (section 7.5), stirred vessels are widely employed in the Fine Chemicals area[49] and therefore must be considered here. Experimental results in this section as well as in section 6 were usually obtained in stirred tank reactors of standardised design (including wall baffles and a turbine impeller), whose flow field has been thoroughly studied. This allowed validation of the time constants and mixing models outlined in section 4. Other designs (e.g., retreat blade impeller, beaver-tail baffles) used in Fine Chemicals manufacture have as yet been less well characterised. The current Chemical Engineering literature should be followed for recent determinations of flow fields, turbulence and reactive mixing.

7.2. Micromixing Control. *7.2.1. Introduction.* When micromixing, whose rate-limiting step is engulfment, is the controlling mixing mechanism, eq 6.1 reduces to eq 6.1′. To maintain constant product distribution, $t_E/t_R = Da$ {eq 6.3} must be constant, which then reduces to

$$\epsilon = \text{const} \tag{7.1}$$

Here ϵ is the energy dissipation rate in the reaction zone. It was relatively easy to specify this quantity for the flow in a tubular static mixer (section 6.3.2), but the spatial gradients of ϵ in a stirred tank can seriously complicate its specification in such reactors (section 6.3.1). The magnitude of these gradients in stirred tanks depends on the type of impeller and also on its size: impellers which are large relative to the tank size generally produce smaller gradients. Direct scale-up when using stirred tanks is usually impossible, unless geometrical similarity is maintained, e.g. a particular violation is (i) at small scale: feed onto surface and (ii) at large scale: feed near impeller. Given, however, homologous feed locations at the two scales (i.e. same angular coordinate and same radial and axial coordinates relative to tank diameter), the local value will be the same if the power input per unit of reactor volume (kW/m^3) is unchanged upon scale-up. Examples now follow where gradients are initially small. Subsequently, large gradients will be treated.

7.2.2. Small ϵ-Gradients. The azo-coupling of 1-naphthol with diazotised sulphanilic acid (B) (section 5.3.2) was run under micromixing control (long feed times) in geometrically similar stirred tank reactors of 2.5 and 65 dm^3 capacities. A feed position, designated K and shown in Figure 15, and a feed concentration of 25.5 mol B/m^3 were employed, and X_S was measured at various stirrer speeds (N), which were chosen so that the power input per unit volume (P/V) was the same for both tanks. Results are given in Table 11.[50]

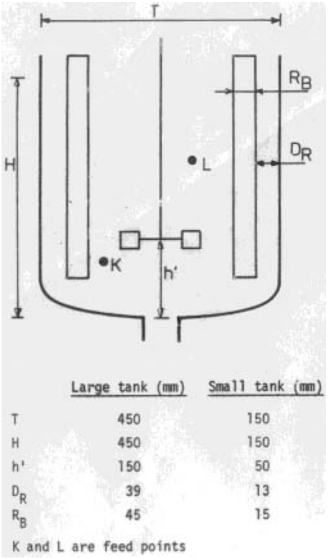

Figure 15. **Geometrically similar baffled stirred tank reactors with feed points K and L.[50]**

Table 11. **Scale-up results for feed point K**

	N (s^{-1}) small tank				N (s^{-1}) large tank			
	3.05	4.28	5.60	8.90	1.45	2.05	2.68	4.25
X_S	0.182	0.148	0.119	0.079	0.183	0.149	0.122	0.092

Comparing the product distributions in the four columns, it may be concluded that the constant power input per unit volume criterion was acceptable—the standard error in measuring X_S was 0.004.

Similar confirmation of this simple P/V = const. criterion was obtained running the competitive reactions eqs 5.6 and 5.7 in 2.3, 19, and 71 dm^3 tanks for a feed point in the radial discharge stream of a Rushton turbine,[45] although it was less satisfactory for other feed locations.

The feed point K used for Table 11 is near the eye of the circulation flow produced by a Rushton turbine (Figure 15), signifying that the flow in the reaction zone near K is turbulent, but not rapidly moving. The mixing and reacting fluids were not transported far from K and so ϵ did not vary significantly during mixing. This matter is discussed again in section 7.2.3.

7.2.3. Large ϵ-Gradients. Large signifies here that over the path taken by the mixing and reacting fluids as they flow in a tank, the local ϵ value varies by a factor of at least two in either direction. This is the more common situation than that of small gradients (section 7.2.2) and the P/V = const. criterion for scale-up is no longer so accurate. Some examples and their interpretation will illustrate this.

Using the same tank, chemicals etc. as for the experiments referred to in Table 11, the feed point was changed from K to L,[50] where the position of L is shown in Figure 15. The flow at L is directed towards the turbine with a speed of approximately 15% of the tangential speed at the tip of the turbine blades. Results are given in Table 12.

Comparing the results in Tables 11 and 12 it is seen that (a) the stirrer speed needed to achieve a particular product distribution is higher for feed point L and therefore, by eqs 4.13 and 6.4, the power consumption is substantially higher. L is further than K from the impeller and turbulence is

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(48) Special feature section: Process Intensification/Continuous Processing in the Fine Chemicals Arena. *Org. Process Res. Dev.* **2001**, *5*, 612−664.

(49) Carpenter, K. J. Chemical Reaction Engineering Aspects of Fine Chemicals Manufacture. *Chem. Eng. Sci.* **2001**, *56*, 305.

(50) Bourne, J. R.; Dell'Ava, P. Micro- and Macro-Mixing in Stirred Tank Reactors of Different Sizes. *Chem. Eng. Res. Des.* **1987**, *65*, 180.

Table 12. **Scale-up results for feed point L**

N (s^{-1})		X_S
	2.5 dm^3	
6.63		0.140
12.23		0.094
	65 dm^3	
3.17		0.196
5.85		0.112

Table 13. **Scale-up results at three vessel sizes**

reactor volume (dm^3)	2.3	19	71
X_Q [eq 5.8]	0.103	0.107	0.114

weaker at L (see also section 6.2.5) and (b) employing constant power per unit volume at the two scales, X_S is higher for the larger tank. This effect is discussed below.

Reference was briefly made in section 7.2.2 to carrying out ester hydrolysis competing with neutralisation in tanks of three sizes.[45] Table 13 reports some product distributions for a different feed point to that in section 7.2.2, namely feeding into the suction stream of the turbine. Table 13 reports X_Q when $P/V = 0.014$ W/dm^3 at the three scales.

Again micromixing, as registered by the product distribution, is somewhat slower at larger scale. What the experiments in Tables 12 and 13 have in common is that, after leaving the feed pipe, mixing and reacting fluid moved towards the impeller along a trajectory where ϵ gradually rises.

Three methods, outlined below, have shown that the larger the vessel, the more localised mixing and reaction become, i.e., relative to the vessel diameter (T) the reaction zone shrinks when scaling up with $P/V =$ const. This will have no effect on product distribution when there is zero gradient of energy-dissipation rate. When, as in the two examples above, ϵ increases in the direction of flow, shrinkage means that the local values of ϵ decrease with increasing vessel size, causing X_S and X_Q to increase. Evidence for this interpretation is:

(a) Photographic. Figure 16 is a sketch based on photographs of the extent of neutralisation using feed point L at 2.5 and 65 dm^3 scales. Two trends are evident:[50] (1) with a given vessel size, increasing the stirrer speed promotes shrinkage of the reaction zone, and (2) with a given power input per unit volume, increasing the vessel size also promotes shrinkage.

(b) Through approximate proportionalities. Assuming that over a small range of changes in ϵ, $t_{MR} \approx E^{-1}$, where t_{MR} is the time needed for micromixing and reaction, it follows from eqs 4.5 and 4.13 that $t_{MR} \approx N^{-3/2}$. During this time reacting fluids move a distance L_R, given by $v_{MR}t_{MR}$, where v_{MR} is the local fluid velocity, which is proportional to Nd (d is the impeller diameter). In a given size of tank ($d =$ const.), it follows that $L_R \approx N^{-1/2}$, indicating that the reaction zone shrinks with increasing stirrer speed, as shown in Figure 16. When scaling up at constant power per unit volume t_{MR} should not change, but from eq 4.13 $v_{MR} \approx Nd \approx d^{1/3}$ and $L_R \approx d^{1/3}$. This indicates a longer reaction zone in the larger vessel. However, relative to the vessel diameter, $L_R/T \approx d^{-2/3} \approx T^{-2/3}$; hence, the reaction zone shrinks, as shown in Figure 16.

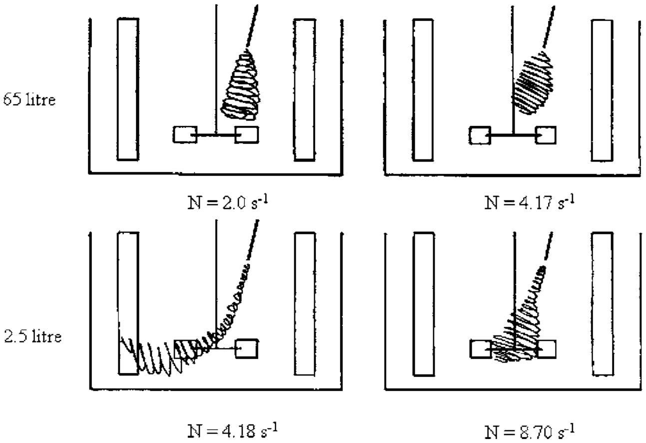

Figure 16. **Sketches of spreading neutralisation zones at two scales and two turbine speeds at each scale. The power per unit volume is constant in the left-hand pair of sketches. It is also constant, although higher, in the right-hand pair.[50]**

(c) Through full modelling. Given the complete velocity distribution in the tank, the trajectory of the mixing and reacting fluids is known. The position of the reaction zone can then be calculated from this flow pattern as a function of the time since leaving the end of the feed pipe. Given also the spatial distribution of ϵ, the local engulfment rate at this time follows from eq 4.4 and the concentrations of the various substances also at this time can be determined by numerically integrating eqs 4.3 and 4.8. This quantitative method is of course only applicable when the flow field and the reactions (kinetics, etc.) can be fully described. Successful applications are available:[1] for example, calculated and measured X_S values at feed point L (Table 12) agreed well showing more S formation in the 65 dm^3 vessel, whereas at feed point K (Table 11) almost the same X_S values were calculated independent of vessel size.[51] Figure 17 refers to feed point L (Figure 15) and shows the reaction zones in the 2.5 and 65 dm^3 tanks at the beginning (B) and end (E) of the azo-coupling when the stirrer speeds (N) are the same. The computed extents of the reaction zone agree quite well with the photographs sketched in Figure 16, including shrinkage of the reaction zone in the larger vessel.

A further scale-up example when micromixing controls is given at the end of section 7.3.3.

7.3. Mesomixing Control. *7.3.1. Introduction.* The time constant for eddy disintegration in turbulent flow is given by eq 4.9. When the conditions described in section 4.5 (a) are satisfied, the following proportionality for the mesomixing time constant (t_S) may be derived.

$$t_S \approx (Q_B/\epsilon\bar{u})^{1/3} \tag{7.2}$$

Provided that mesomixing is the controlling mixing mechanism, t_S must be the same to secure constant product composition at both scales. A change of mechanism with

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(51) Baldyga, J.; Bourne, J. R. Calculation of Micromixing in Inhomogeneous Stirred Tank Reactors. *Chem. Eng. Res. Des.* **1988**, *66*, 33.

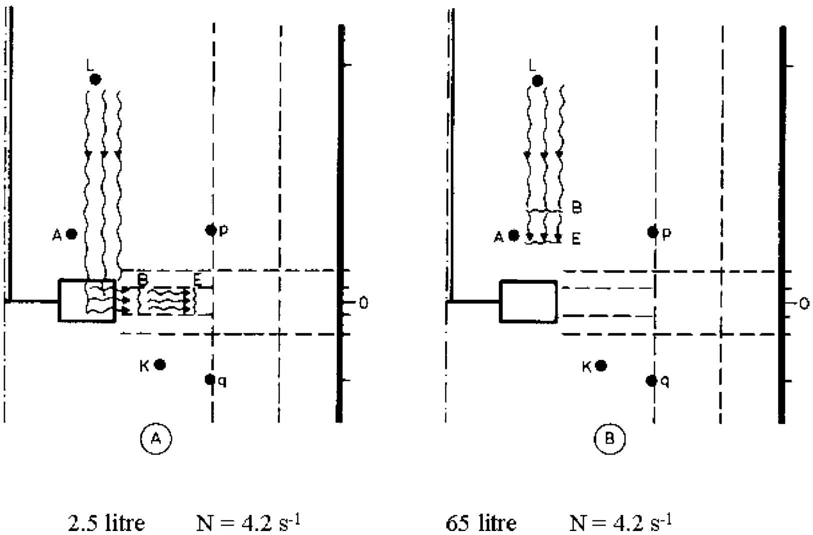

Figure 17. **Computed reaction zones for azo-coupling of 1-naphthol using feed point L at two scales. B and E show extents of these zones at beginning (B) and end (E) of semibatch operations.[51]**

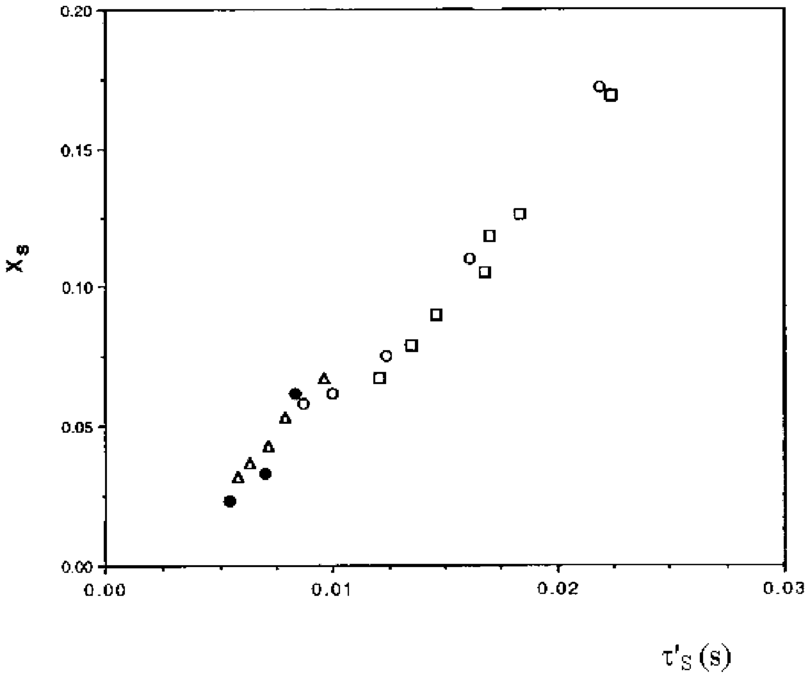

Figure 18. **Yield of bis-azo dye from 1-naphthol using 2.5 dm^3 (○, ●) and 20 dm^3 (□, △) tanks, operated at constant power per unit volume, as a function of mesomixing time constant.[52]**

scale (analogous to the change with flow rate described in section 6.3.2) would invalidate application of either eq 7.1 or eq 7.2. In this equation Q_B is the volumetric feed rate to a semibatch reactor of B-rich solution, ϵ is the energy dissipation rate in the zone where mixing and reaction take place, and $\bar{u}$ is the velocity of the bulk flow and also of the fresh feed liquid in the mixing and reaction zone.

7.3.2. Mechanically Stirred Vessel. Application of eq 7.2 is aided by relating $\bar{u}$ and ϵ to the stirrer speed (N) and its diameter (d), which for geometrically similar vessels is proportional to the tank diameter ($d \approx T$). The local ϵ value is proportional to the mean value and so, from eq 4.13, $\epsilon \approx N^3d^2$ for homologous feed points in geometrically similar vessels ($V \approx T^3 \approx d^3$). Similarly $\bar{u} \approx Nd$. Equation 7.2 for stirred vessels employing a single feed point then becomes

$$t_S' = (Q_B/N^4d^3)^{1/3} \tag{7.2′}$$

Figure 18 refers to the azo-coupling of 1-naphthol with diazotised sulphanilic acid (B) in 2.5 and 20 dm^3 tanks.[52] Comparisons of measured product distributions (X_S, refer to eq 5.15) are shown at two levels of agitation intensity. Equation 7.2′ was employed to calculate t_S' from the known values of Q_B, N, and d. It is clear from Figure 18 that X_S is dependent upon t_S'.

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(52) Baldyga, J.; Bourne, J. R.; Dubuis, B.; Etchells, A. W.; Gholap, R. V.; Zimmermann, B. Jet Reactor Scale-Up for Mixing-Controlled Reactions. *Chem. Eng. Res. Des.* **1995**, *73*, 497.

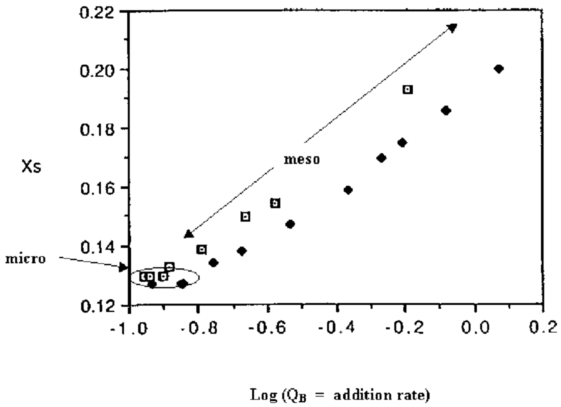

Figure 19. **Yield of bis-azo dye from 1-naphthol using 19 dm^3 (⊡) and 65 dm^3 (◆) stirred-tanks operated at constant power per unit volume as a function of reagent feed rate.[1]**

When scaling up with constant chemical conditions, the feed rate must be related to the stirrer speed and scale by

$$Q_B \approx N^4 d^3 \tag{7.3}$$

Two specific cases have been validated.

(i) Constant productivity. When the feed time (t_f) is constant, the flow rate of reagent (Q_B) is proportional to the reactor volume ($Q_B = V_B/t_f$), which in turn is proportional to d^3. To hold t_S' constant, the stirrer speed (N) must therefore be the same at both scales, giving a constant product distribution. Using the reactions described in section 5.2.2, this was verified at 2.2, 20, 178 and 600 dm^3 scales.[53] There are, however, two disadvantages with this procedure (N = const and t_f = const.), namely the power consumption per unit volume increases rapidly with rising vessel size ($P/V \approx d^2 \approx V^{2/3}$) and the dissipation of this power causes heating, e.g., 1 W/dm^3 in a laboratory scale (2 dm^3) tank causes the temperature of an aqueous solution to rise by approximately 0.9 K/h; this is seldom serious, but scaling to a production scale of 2 m^3 would cause an unacceptably high temperature increase of 90 K/h. Cooling could be provided, but this solution is complex and costly.

(ii) Constant power per unit volume. In this case N^3d^2 = const. and from eq 7.3 $Q_B \approx d^{1/3} \approx T^{1/3} \approx V^{1/9}$. Figure 19 shows how X_S varied with the feed rate Q_B in experiments using 19 dm^3 and 65 dm^3 stirred tanks when P/V = const. The proportionality $Q_B \approx d^{1/3}$ was confirmed.[54] The productivity (Q_B/V) $\approx d^{-8/9}$, indicating a substantial decrease with rising scale.[1] This procedure is therefore also unattractive when mesomixing controls.

Considerably improved productivities can be achieved when multiple feed points (section 6.2.7) are employed at large scale instead of a single-feed point as in the small scale. Using n_f feed points creates n_f reaction zones, provided that these do not overlap. The reagent flow rate in eq 7.2′ is now the flow rate through each feed pipe into each reaction zone, giving

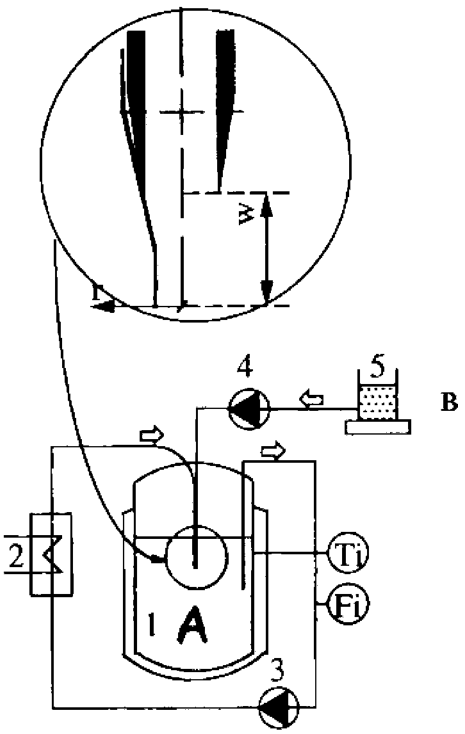

Figure 20. **Jet-stirred vessel.[52]**

$$Q_B = V_B/n_f t_f \tag{7.4}$$

When P/V = const and $V_B \approx V$, eq 7.2′ becomes

$$t_S' \approx (V^{8/9}/n_f t_f)^{1/3} \tag{7.5}$$

and so if t_S' must be constant to give constant product distribution, it follows that $n_f t_f \approx V^{8/9}$. The productivity is V_B/Vt_f (mol/m^3·s) and this will remain constant when t_f is held constant. Constant yield and productivity therefore require

$$n_f \approx V^{8/9} \tag{7.5′}$$

for example, using one feed point at small scale and scaling up the volume by a factor of 10 would call for $n_f = 8$ in the larger vessel. Practical difficulties (construction and equally feeding too many feed pipes) can limit application of eq. 7.5′, requiring a compromise between yield and productivity, e.g. doubling the feed time would halve the number of feed points necessary to keep the product distribution constant.

Finally it should be noted that the procedure described here keeps t_S and t_E constant and is also appropriate when meso- and micromixing simultaneously influence the product distribution at the two scales.

7.3.3. Jet-Stirred Vessel. Many widely different devices which can act as mixers are available. Here the mechanically driven impeller is replaced by a jet, submerged in a tank, which provides turbulence and bulk circulation of its contents.

Figure 20 shows how a pump (3) sends liquid from the tank through a heat exchange (2) and then through a nozzle

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(53) Tipnis, S. K.; Penney, W. R.; Fasano, J. B. An Experimental Investigation To Determine a Scale-Up Method for Fast Competitive Reactions in Agitated Vessels. *AIChE Symp. Ser. No. 299* **1994**, *90*, 78.

(54) Bourne, J. R.; Thoma, S. A. Some Factors Determining the Critical Feed Time of a Semibatch Reactor. *Chem. Eng. Res. Des.* **1991**, *69*, 321.

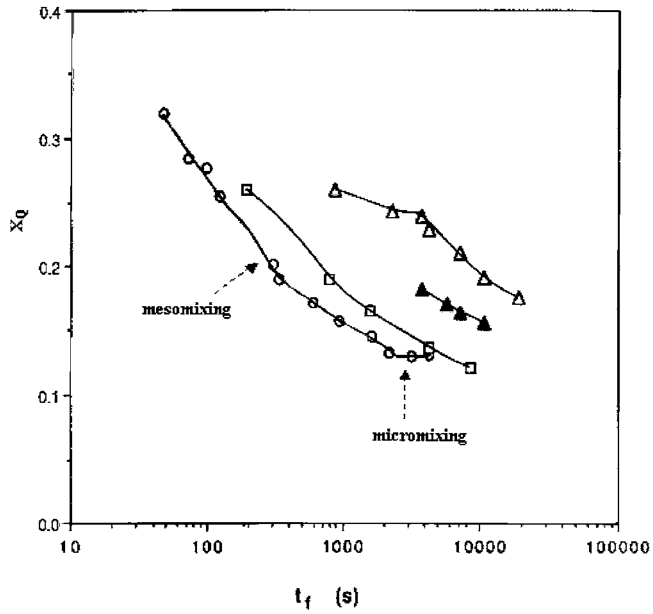

Figure 21. **Yield of dye from 2-naphthol from three sizes of jet-stirred vessels as a function of feed time.[52] (○) Small (0.037 m^3) $d = 8$ mm, $U_o = 4$ m/s. (□) Medium (0.10 m^3) $d = 12$ mm, $U_o = 4.6$ m/s. (△, ▲) Large (0.25 m^3) $d = 31$ mm, $U_o = 4.85$ and 7.28 m/s.**

to form a jet in the tank (1) where reagent A is dissolved. The solution of reagent B is stored on a balance (5) and pumped (4) down a single small diameter feed tube into the jet at a distance w from the exit of the nozzle. The flow field in the jet is complex, but at geometrically similar locations the local value of ϵ is proportional to U_o^3/d, where U_o is the velocity in the nozzle whose diameter is d.

Figure 21 shows experimental results for three tank sizes and three nozzle diameters. X_Q (defined in eq 5.23) varied with the feed time (t_f), indicating control of product distribution by mesomixing. The only exception to this statement refers to two points for the longest feed times in the smallest tank where X_Q did not depend on t_f signaling control by micromixing. The results refer to four values of U_o in the range 4−7.3 m/s.[52]

Applying eq 7.2 to these jet-stirred vessels gives

$$t_S \approx Q_B^{1/3} d^{1/3} / U_o^{4/3} \qquad (7.2'')$$

All three variables were changed in these experiments. Figure 22 shows how X_Q could be satisfactorily correlated by the mesomixing time constant t_S.

Suppose, for example, that the measured value of X_Q for the smallest tank (0.037 m^3, nozzle diameter $d = 8$ mm, nozzle velocity $U_o = 4$ m/s) is 0.24 in a solution of viscosity 6.2 mPa·s when using a feed time $t_f = 2.8$ min. It is required to find the feed time for the largest tank (0.25 m^3) whose nozzle diameter is 31 mm, keeping X_Q unchanged, when the viscosity of the reagent solutions is 0.9 mPa s. From Figure 10, which refers to the smallest tank and $U_o = 6$ m/s, there is negligible effect of viscosity when $t_f = 2.8$ min and so mesomixing is the controlling mechanism. Knowing that $\epsilon \approx U_o^3/d$, the nozzle velocity for the largest tank is 4 $(31/8)^{1/3} = 4.85$ m/s. Equation 7.2″ is rearranged to include the feed time ($t_f = V_B/Q_B \approx V/Q_B$) giving

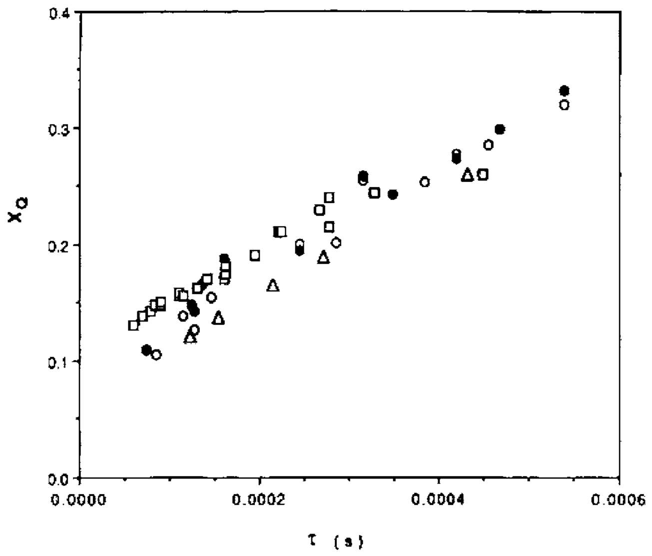

Figure 22. **Yield of dye from 2-naphthol from three sizes of jet-stirred vessel as a function of mesomixing time constant.[52]**

Table 14. **Scale-up of jet-stirred tanks controlled by micromixing**

smallest tank (0.037 m^3)			medium sized tank (0.10 m^3)		
U_o (m/s)	t_f (min)	X_Q	U_o (m/s)	t_f (min)	X_Q
4	54	0.120	4.6	143	0.121
6	54	0.091	6.9	143	0.091

$$t_f \approx Vd/U_o^4 \; t_f = 2.8[(0.25 \times 31)/(0.037 \times 8)](4/4.85)^4 = 34 \text{ min}$$

When the largest tank was operated with $U_o = 4.85$ m/s and $t_f = 34$ min, the measured X_Q was 0.24, confirming the above calculations for scale-up when mesomixing controls.

This paragraph will now illustrate the scale-up of jet-stirred vessels when *micromixing controls*. The smallest tank (0.037 m^3) is operated with long feed times, so that X_Q is independent of t_f, but dependent upon viscosity, showing that micromixing controlled the product distribution. Given a feed time of 54 min to this tank, it is required to find the feed time for the medium-sized tank (0.10 m^3) when the product distribution is to be kept constant. Denoting the small and medium tanks by S and M respectively, constant ϵ requires $U_o(M) = U_o(S)\,[d(M)/d(S)]^{1/3}$. The nozzle sizes are $d(M) = 12$ mm and $d(S) = 8$ mm, giving $U_o(M) = 1.15\,U_o(S)$. From eq 7.5 $t_f \approx V^{8/9}$ (given ϵ = const.) in order to remain under micromixing control, giving $t_f(M) = 54\,(0.1/0.037)^{8/9} = 131$ min. Table 14 reports measured X_Q values using a slightly longer feed time and the required 15% higher nozzle velocities when scaling up.

As this table shows, the product distribution was the same at both scales.

The information given here about jet-stirred vessels shows that the methods applied to mechanically stirred tanks can easily be adapted to more general use. The analysis of how

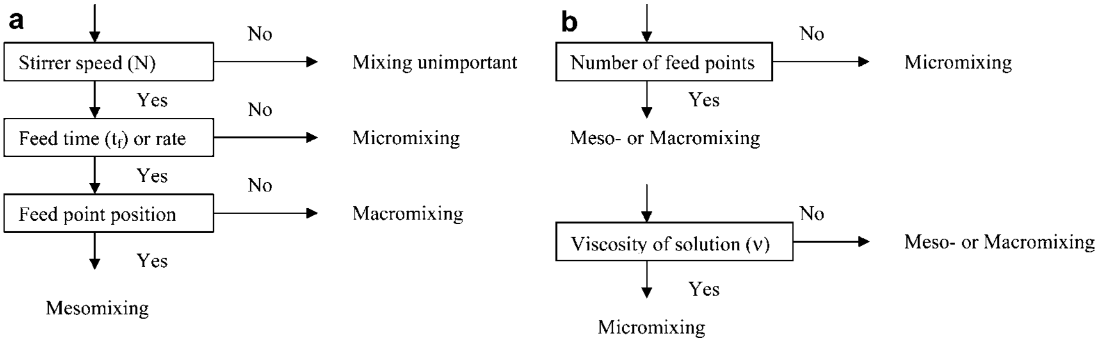

Figure 23. **Screening experiments. (a) Sequence showing the minimum experiments which must be carried out. (b) Sequence showing additional experiments which can confirm some conclusions in sequence a.**

micro- and mesomixing can influence product distribution is widely applicable and further examples of its use for these and other types of mixer/reactor are available.[1]

7.4. Protocol for Laboratory-Scale Experiments. *7.4.1. Introduction.* A simple, laboratory-scale procedure is needed to identify those reactions which are or will become mixing-sensitive when scaled up. Often agitation intensities (measured for example in kW/m^3) in large vessels are lower than in small-scale reactors and reproduction of the large-scale conditions in the laboratory (scale down) can also be needed.

One basic requirement to attaining comparable results is that the laboratory-scale reactor should be geometrically similar to the large-scale one. It is not realistic to employ a round-bottomed flask, a magnetic stirrer, and surface addition of reagent in the laboratory, when the full-scale vessel has a different shape, a mechanically driven impeller, and a dip pipe for subsurface feed addition. When the operating pressure is not too high, a 100−150-mm diameter ($1-3$ dm^3) dished-bottom glass vessel (thus allowing direct observation of the reaction), fitted with four vertical baffles and the same type of impeller as the large vessel, operating in the range 100−1000 rpm, is desirable in the laboratory.

Another basic requirement for ease of interpretation of small-scale results is that also at this scale the flow is fully turbulent. This is because the equations given in section 4 onwards are inapplicable when the flow is not turbulent. The Reynolds number ($Re = Nd^2/\nu$), based on the impeller speed (N, Hz), the impeller diameter (d, m) and the kinematic viscosity of the fluid (ν, m^2/s), is dimensionless and should exceed a critical value which is often in the range 1000−5000. The Reynolds number almost always increases with vessel size (e.g. scale-up with $P/V =$ const. implies $Re \approx d^{4/3} \approx V^{4/9}$), so that a check should be made that Re exceeds the critical value for the laboratory-scale reactor.

Although the influence of mixing on selectivity is the main topic here, heat transfer rates and thermal hazards should not be overlooked and can sometimes become controlling in large-scale reactors.

7.4.2. Laboratory Protocol. It is suggested that the following screening experiments will often yield information about the mixing mechanism which controls the product distribution and therefore which must be considered in scale-up. Each variable in the following Sequence a) should be changed individually, keeping all other variables constant, to decide whether (Yes) or not (No) it influences product distribution.

The experiments in Figure 23a are the minimum which should be carried out. Additional experiments, which can confirm some conclusions in the sequence in Figure 23a, but for practical reasons are not always feasible, are given in Figure 23b. The question is again "Does the product distribution depend on...?"

The feed time for a semibatch reactor is usually so long that macromixing is not controlling.

When application of the laboratory protocol has shown the controlling mixing mechanism, the information given in sections 7.2 (Micromixing) and 7.3 (Mesomixing) can be directly applied to reactor scale-up. Information is given in section 7.3.2 for the case when micro- and mesomixing simultaneously control the product distribution.

7.5. Selection of a Large-Scale Reactor. In section 7.4.1 the choice of a laboratory-scale reactor, to explore a possible influence of mixing on yield and product distribution, was described. Given such an influence, some factors governing the specification of a suitable large-scale reactor are included here.

In low-viscosity solvents such as water, lower alcohols, ketones, and so forth, flows are turbulent, and eqs 4.5 and 4.9 show that the time constants for micromixing by engulfment and feed-stream disintegration, respectively, depend on the energy dissipation rate (ϵ). This quantity varies strongly with the location and with the operating conditions in a given piece of equipment, as well as between different types of equipment. The following values are very approximate, but nevertheless show how widely dissipation rates vary. (Experimental results in section 6 were obtained in reactors exhibiting this range of values.)

stirred tanks	0.01−10 W/kg
rotor-stator mixers	500−2000 W/kg
centrifugal pumps	0.5−5 W/kg
empty tube	0.1−1 W/kg
tube with static mixing elements	100−1000 W/kg
turbulent jet	100−50000 W/kg

Time constants for micromixing are likely to fall in the range (0.1−100) ms, and given sufficiently intensive turbulence, mixing down to molecular scale can often be achieved in 0.1−1 s. The rational specification of a reactor for mixing-sensitive reactions is therefore (a) high-energy dissipation rate in the region where reagents come together, mix, and react, and (b) a residence time of a few seconds in this region. A suitable configuration is a static mixer in a tube, through which reagents flow (as in section 6.3.2) and which might also form part of a recycle loop. Stirred tanks would seldom meet the specification: reaction is highly localised, whilst most of the volume consists of circulating unreactive fluid.

Tanks, however, often carry out more than one operation simultaneously and this flexibility is valued. Their scale-up was therefore included in this section. The scale-up of static mixers, with or without a recycle loop, is discussed elsewhere.[1]

7.6. Conclusions. The mixing conditions needed to ensure the same product distribution and yield when scaling-up have been derived and validated. They presuppose that the laboratory and full-scale vessels are geometrically similar (section 7.4.1) and that the chemical conditions (e.g., all initial concentrations) remain the same.

If micromixing is the controlling mixing step, its time constant (t_E) is unchanged when the energy dissipation rate in the region where mixing and reaction occur is held constant. Ways of doing this with stirred-tank reactors were shown (section 7.2).

If mesomixing controls, requiring its time constant (t_S) to be held constant, a difficulty can arise. This was shown theoretically and experimentally with respect to stirred-tank reactors for two specific situations (section 7.3)

When operating a semibatch reactor with a constant feed (or cycle) time, the productivity (mol product per unit time) increases in direct proportion to the vessel volume. The mesomixing time constant and hence also the product distribution will be the same when the rotational speed of the stirrer is held constant. This incurs the penalty that the power consumption increases much faster than the vessel volume, which can become uneconomic and impracticable.

When operating with a power consumption which is directly proportional to the vessel volume (constant power per unit volume), t_S and the product distribution can only be held constant if the feed time is significantly extended with increasing vessel size. The penalty is now a substantial fall in productivity upon scale-up. It was shown that the best way out is to increase the number of feed points in the large vessel.

Frequently a full reaction scheme, including kinetics, is unavailable, and mixing and reaction time constants cannot be calculated. A laboratory protocol (section 7.4) was then recommended to target those key variables which should be changed to determine whether they influence the product distribution.

8. Mass Transfer and Time Constants in Two-Phase Reactions. Part 1: Single Reactions

8.1. Introduction. Mass transfer, which was introduced in section 3.1, refers here to the transfer of a substance B from one phase (phase 1) (gaseous, liquid, or solid) into a liquid phase (phase 2) containing a substance A with which B reacts.

Reaction can occur at the interface between the two phases, in the liquid film of phase 2 or in the bulk of phase 2: its location has an important influence on the rates and selectivities of two-phase reactions and some examples were given in section 3. It will now be shown that the location depends strongly on the ratio of the time constants for molecular diffusion through the film and for chemical reaction. Fundamental concepts and rate equations are developed first for a single chemical reaction having second-order kinetics

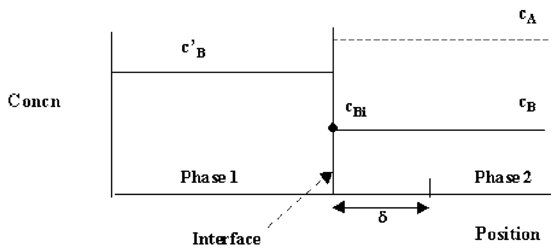

Figure 24. **Concentration profiles in very slow reaction regime.**

$$A + B \rightarrow P \tag{8.1}$$

which occurs in phase 2 between the A dissolved there and the B which has been transferred from phase 1 and dissolved in phase 2 (P is product). Concentrations in phase 2 are denoted by

c_A	bulk concentration of A
c_B	bulk concentration of B
c_{Bi}	concentration of B at the interface between phases 1 and 2

whilst concentrations of B in phase 1 are

c_B'	bulk concentration of B
c_{Bi}'	concentration of B at the interface

Substance A is not present in phase 1. Phase equilibrium at the interface will always be assumed and will usually be represented by a constant distribution coefficient ϕ defined by

$$c_{Bi}' = \phi c_{Bi} \tag{8.2}$$

The distribution coefficient is not, however, always constant (at constant temperature), e.g. when the solute associates or dissociates.[55]

The volume fraction of the phase within which A and B react (i.e., phase 2) is denoted by $/$ and δ denotes the thickness of the diffusion film within this phase (section 3.1).

Depending upon the location of the reaction, different regimes and rate equations arise. They are presented in the following sections.

8.2. Regime 1: Very Slow Reaction. Reaction is so slow that B saturates the A-rich phase and $c_B = c_{Bi}$, so that there is no concentration gradient of B in phase 2 (Figure 24). Basing the reaction rate on the whole volume (phases 1 and 2), the rate of formation of product (mol/s·m^3 of dispersion) is given by

$$r = k/c_A c_{Bi} \tag{8.3}$$

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(55) Prausnitz, J. M.; Lichtenthaler, R. N.; de Azevado, E. G. *Molecular Thermodynamics of Fluid-Phase Equilibria*; Prentice Hall: New York, 1986.

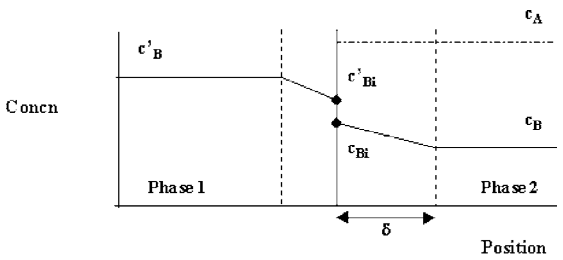

Figure 25. **Concentration profiles in slow reaction regime.**

Clearly the variables characterising mass transfer rates (k_L, a, H, etc., refer to section 3.1) are not needed when the reaction is very slow. A criterion for the occurrence of this regime follows in the next section.

8.3. Regime 2: Slow Reaction. Here reaction is sufficiently slow not to take place in the liquid film (thickness δ), but B diffuses across the film and reacts with A in the bulk of the liquid in phase 2. The concentration difference driving this diffusion is ($c_{Bi} - c_B$) (Figure 25). The interfacial area per unit volume of the whole dispersion (phases 1 and 2) is represented by the symbol a (section 3.1). The rates of diffusion and reaction of B in phase 2 as well as diffusion of B out of phase 1 are all equal.

$$k_L' a(c_B' - c_{Bi}') = k_L a(c_{Bi} - c_B) = k c_A c_B = r \qquad (8.4)$$

Provided that the distribution coefficient in eq 8.2 is constant, eq 8.4 can be written

$$r = c_B'/[(1/k_L' a) + (\phi/k_L a) + (\phi/k c_A)] \qquad (8.5)$$

which contains the bulk concentrations of A in phase 2 and B in phase 1. Equation 8.5 recalls Ohm's law (r = current, c_B' = potential, reciprocal terms = three resistances in series). Several special cases of eq 8.5 arise.

(a) Phase 1 is pure, so $c_B' = c_{Bi}'$ and the term $(1/k_L' a)$ vanishes.

(b) Reaction is very slow (k is very small), so both mass transfer terms in the denominator vanish and eq 8.3 is recovered.

(c) The distribution coefficient ϕ is very high (B is much more soluble in phase 1 than in phase 2, where reaction occurs) and the term $(1/k_L' a)$ vanishes.

For cases (a) and (c), eq 8.5 simplifies giving

$$r = c_{Bi}/[(1/k_L a) + (1/k c_A)] \qquad (8.5')$$

(d) Reaction is sufficiently fast that $c_B \approx 0$, but not so fast that B reacts in the film region of phase 2, then eq 8.5 simplifies further to give

$$r = k_L a c_{Bi} \qquad (8.5'')$$

and the reaction rate depends entirely on the rate of mass transfer across the film of phase 2.

An essential characteristic of regimes 1 and 2 is that there is no reaction in the film, and the necessary criterion for this condition will now be derived.

When the concentration of A is much higher than the solubility of B in phase 2 ($c_A \gg c_{Bi}$), the reaction rate will be pseudofirst order in B, the rate constant being kc_A. A time constant for consumption of B in the film is then $(kc_A)^{-1}$ (eq 4.1). Transport of B through the film is by molecular diffusion, for which Fick's second law gives a time constant of (δ^2/D_B). When diffusion is fast relative to reaction, hardly any B can react in the film: this occurs when

$$\delta^2/D_B << (kc_A)^{-1} \quad \text{or} \quad kc_A\delta^2/D_B << 1 \qquad (8.6)$$

Employing the definition of k_L given in eq 3.1, it has become conventional to write the dimensionless group in eq 8.6 as

$$Ha = \delta(kc_A/D_B)^{1/2} = (kc_A D_B)^{1/2}/k_L = [\text{diffusion time/reaction time}]^{1/2} \qquad (8.7)$$

Ha is the dimensionless Hatta number, and when $Ha \ll 1$, there is no reaction in the film, whereas when $Ha \gg 1$ the regime cannot be 1 or 2. The following conventions are widely used: $Ha < 0.3$ signifies no reaction in film and $Ha > 3$ signifies complete reaction in film.

8.4. Worked Examples: Regimes 1 and 2. *8.4.1. Introduction.* Both examples in this section refer to the two-phase nitration of aromatic compounds. Although such reactions can be single-phase (e.g. nitronium salt in nitromethane), industrially two-phase nitration usually employs an acid mixture consisting of, for example, 15 mol % (19.4 mass %) HNO_3, 30 mol % (60.3 mass %) H_2SO_4, and 55 mol % (20.3 mass %) H_2O. The rate-determining chemical step in this case is frequently the reaction between the nitronium ion (NO_2^+) and the aromatic compound.[56] Because the concentration of this ion is small and outside the range of most analytical methods, the rate equation is usually written as

$$r = kc_{Ar}c_{HNO3}$$

where HNO_3 replaces NO_2^+, c_{Ar} is the concentration of the aromatic in the mixed acid (not in the organic phase) and nitration occurs in the acid phase (phase 2). Because sulphuric acid is involved in the preequilibria forming NO_2^+, the second-order rate constant (k) is a strong function of the sulphuric acid concentration.[56]

8.4.2. Nitration of Chlorobenzene. At 298 K and using 70.2 mass % H_2SO_4 single-phase kinetic measurements gave $k = 1.75 \times 10^{-5}$ m^3/mol·s.[57] Equal volumes of chlorobenzene (B) and mixed acid containing 32 mol/m^3 HNO_3 (A) were dispersed in a weakly stirred vessel. The regime is to be determined.

(a) First, the Hatta number is evaluated to decide where reaction takes place. D_B in eq 8.7 is estimated using the Wilke–Chang method as applied in ref 58.

$$D_B\ (\text{cm}^2/\text{s}) = 7.4 \times 10^{-8}\ (\beta M)^{1/2}\, T/\mu V_B^{0.6} \qquad (8.8)$$

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(56) Schofield, K. *Aromatic Nitration*; Cambridge University Press: Cambridge, UK, 1980.

(57) Cox, P. R.; Strachan, A. N. Two-Phase Nitration of Chlorobenzene. *Chem. Eng. Sci.* **1971**, *26*, 1013.

(58) Cox, P. R.; Strachan, A. N. Two-Phase Nitration of Toluene: Part 2. *Chem. Eng. J.* **1972**, *4*, 253.

where V_B is the molar volume of chlorobenzene at its normal boiling point, T is the absolute temperature, μ is the viscosity of phase 2, β is a parameter for molecular association in phase 2, and M is a molecular mass. Here $V_B = 117$ cm^3/mol,[59] $T = 298$ K, $\mu = 9.4$ cP,[58] $\beta M = 91.6$.[58]

Substitution in eq 8.8 gives $D_B = 1.3 \times 10^{-6}$ cm^2/s or 1.3×10^{-10} m^2/s. With a low agitation intensity in a stirred tank, k_L is approximately 10^{-5} m/s.[60] Hence

$$Ha = (kc_A D_B)^{1/2}/k_L = 0.027$$

{Alternatively characteristic times for diffusion and reaction are $\delta^2/D_B = D_B/k_L{}^2 = 1.3$ s and $(kc_A)^{-1} = 1790$ s}. Clearly no reaction in the diffusion film is indicated, and the regime is 1 or 2.

(b) Second, to distinguish between regimes 1 and 2 the relative magnitudes of the resistances in eq 8.5′ must be estimated. The kinetic resistance is $(k\ell c_A)^{-1}$, where $\ell = 0.5$, giving 3580 s. The mass transfer resistance is $(k_L a)^{-1}$ and with weak agitation a is approximately 2000 m^2/m^3, giving 50 s. The nitration rate is dominated by the reaction kinetics, not the mass transfer of the aromatic into the acid phase.

Despite the need to estimate certain quantities, the conclusion is that in this case[57] chlorobenzene (B) was nitrated in regime 1: very slow reaction. Phase 2—the acid phase—is saturated with chlorobenzene ($c_B = c_{Bi} = 2.1$ mol/m^3) and eq 8.3 gives the reaction rate ($r = 5.9 \times 10^{-4}$ mol/s·m^3)

8.4.2.1. Comments. (i) From the measured two-phase reaction rate, the chlorobenzene solubility, the known nitric acid concentration and the volume fraction of the acid phase, k was calculated from eq 8.3 to give $k = 1.57 \times 10^{-5}$ m^3/mol·s.[57]

This is 10% lower than the value from single-phase measurements quoted above (1.75×10^{-5} m^3/mol·s). It must be recognized, however, that in the two-phase experiments a small quantity of nitric acid was added to 70.2 mass% H_2SO_4 to form mixed acid, thereby slightly reducing the H_2SO_4 concentration. Because k is a strong function of the sulphuric acid concentration, a lower rate constant must be expected when using mixed acid.

(ii) It is incorrect to conclude from this example that nitration of chlorobenzene is always in regime 1. Ha depends on k, c_A, D_B, and k_L, and only when $Ha \ll 1$ can nitration not occur in the diffusion film, e.g., $Ha \approx (kc_A)^{1/2}$ so that at higher H_2SO_4 and HNO_3 concentrations, Ha can exceed 1. With an acid-phase composition typical of industrial use (section 8.4.1) measured temperature coefficients of k (over 10 K) were 2.6 for single-phase and 1.24 for two-phase nitrations.[61] The two-phase value, which includes the effects of temperature on at least k and solubility, is much smaller and implies an effect of mass transfer on this nitration.

8.4.3. Nitration of Toluene (Part 1). The rate constant (k) for the nitration of toluene in 70 mass % H_2SO_4 at 298 K is some 250 times that for chlorobenzene (section 8.4.2); thus, it seems likely that mass transfer will be more relevant in the case of toluene.

A mixed acid containing 69.6 mass % H_2SO_4 and an initial concentration of 560 mol HNO_3/m^3 was contacted in a stirred tank with toluene which formed the dispersed phase having a volume fraction of 0.052. The reaction regime is to be determined.

The Hatta number, eq 8.7, must first be estimated, given the following information: $D_B = 1.6 \times 10^{-10}$ m^2/s,[62] $k = 2.8 \times 10^{-3}$ m^3/mol s,[56] $c_{Bi} = 2.3$ mol/m^3,[63] $k_L = 5 \times 10^{-5}$ m/s,[60] $a = 5000$ m^2/m^3,[60] and $\ell = 0.948$ (given). Thus,

$$Ha = (kc_A D_B)^{1/2}/k_L = 0.32$$

{The time constants for diffusion and reaction are 0.064 and 0.64 s, respectively.} The values indicate only weak nitration of toluene as it diffuses through the film, so that most nitration occurs in the bulk of the acid phase (phase 2).The regime is either 1 or 2.

Resistance in the organic phase (phase 1) is zero for pure toluene, and eq 8.5′ applies.

The mass transfer and kinetic resistances are $(k_L a)^{-1} = 4$ s and $(k\ell c_A)^{-1} = 0.67$ s, respectively, indicating regime 2. By increasing the agitation intensity—essentially the power input per unit volume—a would be increased and the reaction, which is mainly controlled by mass transfer, would proceed faster and could perhaps attain regime 1.

Under the given conditions ($a = 5000$ m^2/m^3), $r = 0.49$ mol/m^3·s, whereas if the mass-transfer resistance could be eliminated (to give regime 1) r would be 3.4 mol/m^3·s. A highly similar conclusion about the influence of mass transfer on rate can be obtained from eq 8.4, solved for c_B—the concentration of toluene in the bulk acid phase. Under the given conditions $c_B = 0.33$ mol/m^3, compared to 2.3 mol/m^3 when in regime 1, where there is no mass transfer resistance and the acid phase is saturated by toluene.

8.4.3.1. Comments. Experimental results on the two-phase nitration of toluene are available.[58] In one experiment using 66.6 mass% H_2SO_4 containing $c_A = 560$ mol HNO_3/m^3, the measured nitration rate (r) was 0.107 mol/m^{3}s. Single-phase kinetic measurements at this H_2SO_4 concentration gave $k = 2.63 \times 10^{-4}$ m^3/mol·s, and the toluene solubility (c_{Bi}) was 2.08 mol/m^3. The dispersed phase volume fraction was 0.052 (pure toluene). From eq 8.5′ it follows that $k_L a = 0.081$ s^{-1}, where a is expressed in m^2/m^3 of dispersion. [In ref 58 the unit of a was m^2/m^3 of acid phase]. Similar values of $k_L a$ were found at other H_2SO_4 concentrations when nitration was in regime 2. There is no independent information to judge the correctness of these $k_L a$ values. They are, however, of the correct order of magnitude for a round-bottomed flask with a paddle as stirrer,[57] corresponding to relatively weak agitation.

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(59) Sherwood, T. K.; Pigford, R. L.; Wilke, C. R. *Mass Transfer*; McGraw-Hill: New York, 1975.

(60) Doraiswamy, L. K.; Sharma, M. M. *Heterogeneous Reactions*; Wiley: New York, 1984; Vol. 2.

(61) Hanson, C.; Marsland, J. G.; Naz, M. A. Macrokinetics of Chlorobenzene Nitration. *Chem. Eng. Sci.* **1974**, *29*, 297.

(62) Hanson, C.; Ismail, H. A. M. Diffusion of Benzene and Toluene into Aqueous Nitric Acid-Sulphuric Acid Mixtures. *J. Appl. Chem.* **1976**, *26*, 111.

(63) Hanson, C.; Ismail, H. A. M. Solubility and Distribution Data for Benzene and Toluene between Aqueous and Organic Phases. *J. Appl. Chem.* **1975**, *25*, 319.

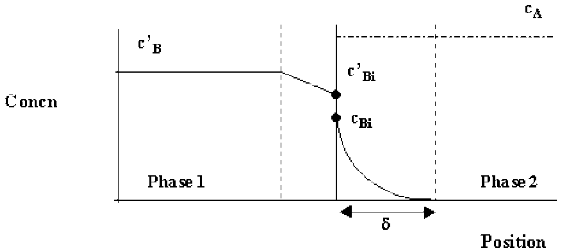

Figure 26. **Concentration profiles in fast reaction regime.**

8.5. Regime 3: Fast Reaction. Here reaction is sufficiently fast so that all the dissolving and diffusing substance B reacts completely within the diffusion film. (It is also possible for only part of B to react in the film, whilst the rest reacts in the bulk of phase 2, giving a condition intermediate between regimes 2 and 3—this will subsequently be treated.) A detailed analysis of the reaction−diffusion equations shows that, when the diffusion time is more than an order of magnitude longer than the reaction time (therefore $Ha > 3$), B reacts almost entirely in the film (c_B is effectively zero).

When the concentration of A in phase 2 greatly exceeds the solubility of B in this phase (i.e. when $c_A \gg c_{Bi}$), the concentration of A is almost constant in the film despite its consumption there by reaction. In this situation the reaction becomes pseudo-first-order in c_B throughout the film. The reaction rate is found from a rather lengthy derivation[2−4] to be

$$r = a(kD_Bc_A)^{1/2}c_{Bi} \qquad (8.9)$$

provided that $c_A/c_{Bi} \gg Ha$. If this inequality is not satisfied, but $Ha > 3$, reaction in the film has second-order kinetics (i.e. c_A is not uniform), and a numerical solution for the reaction rate is often needed to replace eq 8.9.[2,3]

The inequality to be satisfied before eq 8.9 may be used will now be derived. In the film c_A will be essentially constant if the maximum rate of transfer of A into the film (k_Lac_A) is much greater than its maximum rate of consumption there ($a(kc_AD_B)^{1/2}c_{Bi}$). Rearranging these terms, pseudo-first-order kinetics prevail if $c_A/c_{Bi} \gg Ha$.

Equation 8.9 can also be written

$$r = k_Lac_{Bi}Ha \qquad (8.10)$$

The term k_Lac_{Bi} is the maximum rate of diffusion of B across the film in phase 2 in the absence of reaction, which is the case when $c_B = 0$. Equation 8.10 shows enhancement of this rate by the factor Ha when reaction in the film is complete and c_A is uniform there.

The concentration profiles corresponding to eqs 8.9 and 8.10 are shown in Figure 26, where the concentration of A is uniform, but that of B falls to zero within the film.

When any mass-transfer resistance within phase 1 also needs to be considered, eq 8.10 becomes

$$r = ac_B'/[(\phi/k_LHa) + (1/k_L')] \qquad (8.11)$$

When, however, the second term in the denominator, representing the resistance in phase 1, is negligible relative to the first, eq 8.11 reduces to eq 8.10. This frequently happens when the distribution coefficient (ϕ, refer to eq 8.2) is much larger than unity, i.e., when the solute B favours phase 1.

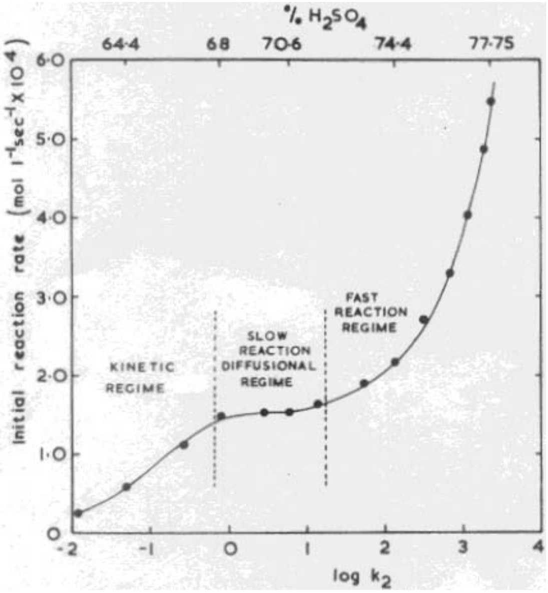

Figure 27. **Measured rate of nitration of toluene versus rate constant and H_2SO_4 concentration. Reprinted from Cox, P. R.; Strachan, A. N. Two-phase nitration of toluene: Part 2. *Chem. Eng. J.* 1972, *4*, 257−258, copyright 1972, with permission from Elsevier.**

Using, as a rough estimate, $Ha \gg 1$ for the occurrence of significant reaction in the film, it follows from eq 8.6 that this happens if $(kc_A)^{-1} \ll \delta^2/D_B$ (this latter term can also be written D_B/k_L^2). The first term is the half-life of the diffusing species B. Hence if the half-life is much less than D_B/k_L^2, substantial reaction of B will occur in the film, e.g., if $D_B = 10^{-9}$ m^2/s and $k_L = 1.5 \times 10^{-5}$ m/s, reactions having half-lives shorter than 5 s take place in the film of phase 2 and may therefore be called fast.

For reactions in the transition region between regimes 2 and 3, a simple interpolation formula, valid when the resistance in phase 1 may be neglected, is as follows

$$r = k_Lac_{Bi}(1 + Ha^2)^{1/2} \qquad (8.12)$$

This reduces to eq 8.5″ when $Ha \ll 1$ and to eq 8.10 when $Ha \gg 1$.

8.6. Worked Examples: Regime 3. *8.6.1. Nitration of Toluene (Part 2).* The reaction's half-life $(kc_A)^{-1}$, where A = HNO_3, was progressively decreased by increasing the concentration of sulphuric acid in a mixed acid whose nitric acid concentration was constant ($c_A = 560$ mol/m^3). The organic phase was pure toluene.[58] By increasing from 62.4 to 77.8 mass % H_2SO_4, the rate constant (measured in a single phase) rose by the factor 2×10^5 (refer to section 8.4.1).

The measured nitration rate rose by the factor 22, showing a strong mass-transfer resistance. Figure 27, taken from ref 58, plots the reaction rate (r) against the rate constant (logarithmic scale), illustrating changes in reaction regime.

(i) $H_2SO_4 < 68$ mass%. The increase in rate as k rises is less than the direct proportionality expected in regime 1. As

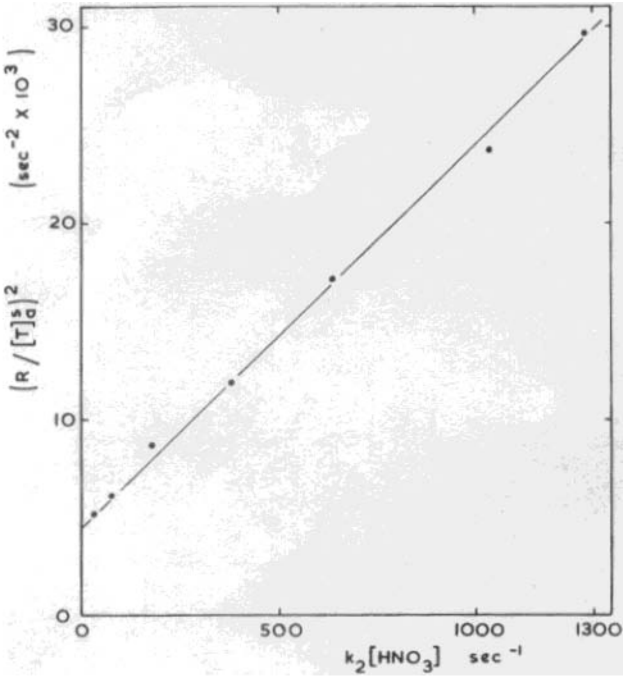

Figure 28. **Rate of toluene nitration in fast regime: Danckwerts plot. Reprinted from Cox, P. R.; Strachan, A. N. Two-phase nitration of toluene: Part 2. *Chem. Eng. J.* 1972, *4*, 257−258, copyright 1972, with permission from Elsevier.**

k rises by a factor 74, *r* increases by a factor 6, indicating regime 2, eq 8.5′.

(ii) 68 mass% < H_2SO_4 < 71 mass%. Over this range *r* is almost constant and independent of *k*. This is consistent with the transition region between regimes 2 and 3 and eq 8.5″.

(iii) H_2SO_4 > 71 mass%. Again *r* increases with *k*. The proposal that this is regime 3 cannot be properly checked by calculating *Ha* because k_L for the stirred vessel is not accurately known. By rewriting eq 8.12 as

$$r = ac_{Bi}(k_L^{\,2} + kc_AD_B)^{1/2} \qquad (8.12')$$

a plot of $(r/c_{Bi})^2$ against (kc_A) should be linear. Figure 28 confirms this for the seven measurements on the right-hand side of Figure 27 {eq (8.12′) was derived by Danckwerts[64]}. There was evidence, subsequently supplemented,[65] that the rate-determining step in the reaction mechanism changed, as the H_2SO_4 concentration rose, from the reaction between toluene and the nitronium ion to the latter's formation. Further experiments used highly dilute toluene to reduce the nitration rate and return to the earlier rate-determining step.[65]

8.6.2. Nitration of Toluene (Part 3). In a series of rate measurements at 298 K the HNO_3 concentration was varied from $c_A = 1.57$ to 62.6 mol/m^3 in 76.45 mass % H_2SO_4.[65] The diffusivity of toluene in this mixed acid was $D_B = 9.2 \times 10^{-11}$ m^2/s {estimated from eq 8.8 and ref 62}. The organic phase consisted of 1% toluene in 2,2,4-trimethylpentane, its volume fraction being 0.14. Single-phase kinetic measurements gave $k = 0.74$ m^3/mol·s.[56] The organic phase was nonideal and solubility measurements gave $c_{Bi} = 7.16 \times 10^{-2}$ mol/m^3.

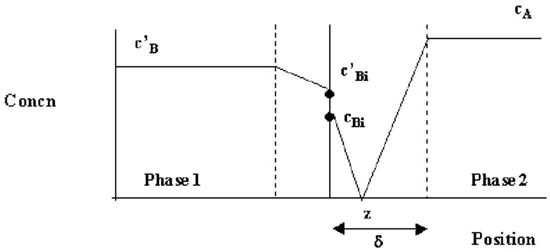

Figure 29. **Concentration profiles in instantaneous reaction regime.**

In a stirred tank, having a constant stirrer speed, the rate of nitration was measured at seven HNO_3 concentrations, thereby varying the half-life of toluene in the range 0.022—0.86 s. Using eq 8.12′ the results were plotted as explained in section 8.6.1, giving a straight line of slope a^2D_B and intercept $(k_La)^2$. Hence $k_L = 1.0 \times 10^{-5}$ m/s and $a = 3830$ m^2/m^3 of dispersion. From eq 3.2 the average size of the hydrocarbon drops was 0.22 mm.

Now that k_L is known, the minimum and maximum values of the Hatta number, corresponding to $c_A = 1.57$ and 62.6 mol/m^3, respectively, can be found. These were 1.0, corresponding to the transition from regime 2 to 3 and 6.5, corresponding to regime 3.

Knowing k_L and *a*, eq 8.12 can be used to compare calculated and measured reaction rates, e.g., when $c_A = 31.3$ mol HNO_3/m^3, then $Ha = 4.62$; thus, from eq 8.12 $r = 1.29 \times 10^{-2}$ mol toluene/s·m^3 of dispersion, which compares well with the measured value 1.27×10^{-2} mol/s·m^3.[65]

8.7. Regime 4: Instantaneous Reaction. Instantaneous signifies that the time scale of the chemical reaction (as given by its kinetics) is extremely short relative to that of the diffusion through the liquid film. The reagents A and B do not coexist anywhere but react as soon as they encounter each other at the position *z* in the diffusion film (Figure 29).

For the simple reaction A + B → P the diffusive fluxes of A and B to the reaction plane at *z* must be equal: in phase 2 these are $D_Ac_A/(\delta - z)$ and D_Bc_{Bi}/z and are equal to the flux of B in Phase 1, namely $k_L'(c_B' - c_{Bi}')$. Eliminating the interfacial concentrations and using a constant distribution coefficient (eq 8.2) gives

$$r = a[(c_B'/\phi + D_Ac_A/D_B)/(1/\phi k_L' + 1/k_L)] \qquad (8.13)$$

When the resistance in Phase 1 is negligible ($\phi \cdot k_L' \gg k_L$), then $c_B' = c_{Bi}'$ and eq 8.13 simplifies to

$$r = k_Lac_{Bi}\,[1 + (D_Ac_A/D_Bc_{Bi})] \qquad (8.13')$$

In the absence of chemical reaction and of resistance to mass transfer in Phase 1, the rate of transfer of B into Phase 2 is $k_La(c_{Bi} - c_B)$ [mol/s·m^3]. This is highest when $c_B = 0$ and equal to k_Lac_{Bi}. Referring to eqs 8.5″, 8.10, and 8.13′, it is seen that a reaction in the film enhances (or accelerates) the maximum physical mass-transfer rate by the factors *Ha* in regime 3 and $\{1 + (D_Ac_A/D_Bc_{Bi})\}$ in Regime 4.

When c_A is substantially larger than c_{Bi}, eq 8.13′ simplifies to $r = k_Lac_A(D_A/D_B)$, which shows that the reaction rate can

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(64) Danckwerts, P. V. *Gas−Liquid Reactions*; McGraw-Hill: New York, 1970.

(65) Chapman, J. W.; Cox, P. R.; Strachan, A. N. Two-pchase Nitration of Toluene: Part 3. *Chem. Eng. Sci.* **1974**, *29*, 1247.

sometimes become independent of the solubility of B. If, however, $c_A \gg c_{Bi}$ the reaction can move to the interface—see below.

The criteria for the validity of the profiles sketched in Figure 29 and eq 8.13 are (i) reaction in film: $Ha \gg 1$ and (ii) insufficient supply of A to keep its concentration constant, i.e., maximum rate of supply $k_L c_A \ll$ potential reaction rate $(kc_A D_B)^{1/2} c_{Bi}$, which simplifies to $c_A/c_{Bi} \ll Ha$. (This is the opposite of the criterion for eq 8.9 in regime 3).

As stated in section 8.5 a numerical solution to find the reaction rate is available[2,3] when $Ha \gg 1$ and $c_A/c_{Bi} \approx Ha$, which is the transition zone between regimes 3 and 4.

From the equality of the diffusional fluxes of A and B given above, the location of the reaction plane within the film can be found giving

$$z = [D_B c_{Bi}/(D_B c_{Bi} + D_A c_A)]\,\delta \qquad (8.14)$$

When a large excess of A is employed relative to the solubility of B ($c_A \gg c_{Bi}$), $z = 0$, the rate of mass transfer in phase 1 controls and the reaction moves to the interface. In this case eq 8.13 gives

$$r = k_L{}' a c_B{}' \qquad (8.13'')$$

In regime 4 and sometimes also in regime 3, a mass-transfer resistance in phase 1 can be significant.

8.8. Worked Example: Regime 4. Solid and liquid esters can readily be hydrolyzed, for example by sodium hydroxide solutions, the reaction taking place in the aqueous phase. Methyl dichloroethanoate (liquid) is hydrolyzed at 303 K by 0.1 N NaOH in a stirred cell having a diameter of 67 mm (section 3.1). The reaction regime is to be determined.

The solubility in water (c_w) is 74 mol /m³.[66] Its value in 0.1 N NaOH, namely (c_{Bi}), will be estimated with the Setchenow equation.[64,66]

$$\log(c_w/c_{Bi}) = K_s I$$

where I is the ionic strength (0.1 g·ion/L) and K_s is a sum of the contributions of the ions and the other solute (ester) giving $K_s = 0.091 + 0.066 + 0.020 = 0.177$ (L/g·ion). Hence, $c_{Bi} = 70.5$ mol/m³.

The diffusivity of NaOH is $D_A = 1.85 \times 10^{-9}$ m²/s.[59] That of the ester (D_B) will be estimated by the Wilke–Chang method.[59] From the ester's formula the molar volume at the boiling point is 124.9 cm³/mol,[59] and in a predominantly aqueous solution $D_B = 1.06 \times 10^{-9}$ m²/s.

The aqueous film mass-transfer coefficient (k_L) when the average stirrer speed in the cell was 22 rpm, was approximately 1.6×10^{-5} m/s.[66] The hydroxyl ion concentration (c_A) was 100 g·ion/m³. The hydrolysis rate constant at 298 K and the activation energy are 1.5 m³/mol·s and 6.75 kcal/mol, respectively,[67] giving $k = 1.81$ m³/mol·s at 303 K.

Table 15. **Exponents on variables affecting *r***

regime	equation	c_a	c_{bi}	ℓ	k	k_L	a
1 very slow	8.3	1	1	1	1	0	0
2 slow	8.5′	0−1	1	0−1	0−1	0−1	0−1
2 slow	8.5″	0	1	0	0	1	1
3 fast	8.9	0.5	1	0	0.5	0	1
4 instantaneous	8.13′	0−1	0−1	0	0	1	1

From eq 8.7 $Ha = 27$, whilst diffusion and reaction times are 4.1 s and 5.5 ms, respectively. Clearly, hydrolysis takes place only in the film. To decide between regimes 3 and 4, $c_A/c_{Bi} = 1.4 \ll Ha$ and so the regime is 4 (instantaneous reaction).

From the molecular mass (143) and the density (1370 kg/m³) of the ester, $c_B{}' \approx 9600$ mol/m³ and $\phi \approx 9600/70.5 \approx 136$ (eq 8.2). From eq 8.14 $z/\delta = 0.29$. The reaction is not interfacial, and resistance to mass transfer in the organic phase is negligible. The enhancement (or acceleration) factor, given by the term in square brackets in eq 8.13′, is 3.5. Rate measurements gave enhancement factors in the range 3.2–3.3[66] in reasonable agreement with the calculations above. {Insufficient experimental information was published to allow measured and calculated reaction rates to be compared.}

If hydrolysis had taken place in the fast regime (regime 3), the enhancement factor would have been $Ha = 27$. Because, however, the bulk hydroxyl ion concentration (c_A = 100 g·ion/m³) was not sufficiently high, the resistance to transfer of A in the film reduced its film concentrations below the bulk value. The actual enhancement factor (3.5) in regime 4 was therefore lower than 27,which would have been expected in regime 3.

8.9. Single Reaction: Synopsis and Laboratory Protocol. Thus far a single reaction $A + B \rightarrow P$, whose kinetics is first-order in each of the reagents A and B and where irreversible reaction takes place in the A-rich phase, has been considered. The A-rich phase (phase 2) was liquid, whereas the B-rich phase (phase 1) could be solid, gas, or liquid. Extension of the general principles to other reaction orders, reversibility, etc. is available.[60,64]

The four most important regimes, each characterised by a Hatta number—this is the square root of the ratio of diffusion and reaction times—amongst other quantities, were treated. Reference was also made to the overlap or transition zones between the regimes. The regime can change as reaction progresses, for example A is gradually consumed in phase 2, causing c_A to decrease; the solubility of B in phase 2 can change as reaction products accumulate in phase 2; in a semibatch, liquid–liquid reaction, phase inversion might occur. The general principles given above are still valid, but their application becomes more complex and calls for much physicochemical information.

Table 15 summarises the exponents on variables affecting the reaction rate (r) in the various regimes. For simplicity a mass-transfer resistance in the B-rich phase (phase 1) is neglected.

Table 15 also clarifies diagnosing (using reaction rate measurements) which regime applies, for example if r is

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(66) Sharma, M. M.; Nanda, A. K. Extraction with Second-Order Reaction. *Trans. Inst. Chem. Eng.* **1968**, *46*, 44.

(67) Bamford, C. H.; Tipper, C. F. H. *Comprehensive Chemical Kinetics*; Elsevier: Amsterdam, 1972; Vol. 10.

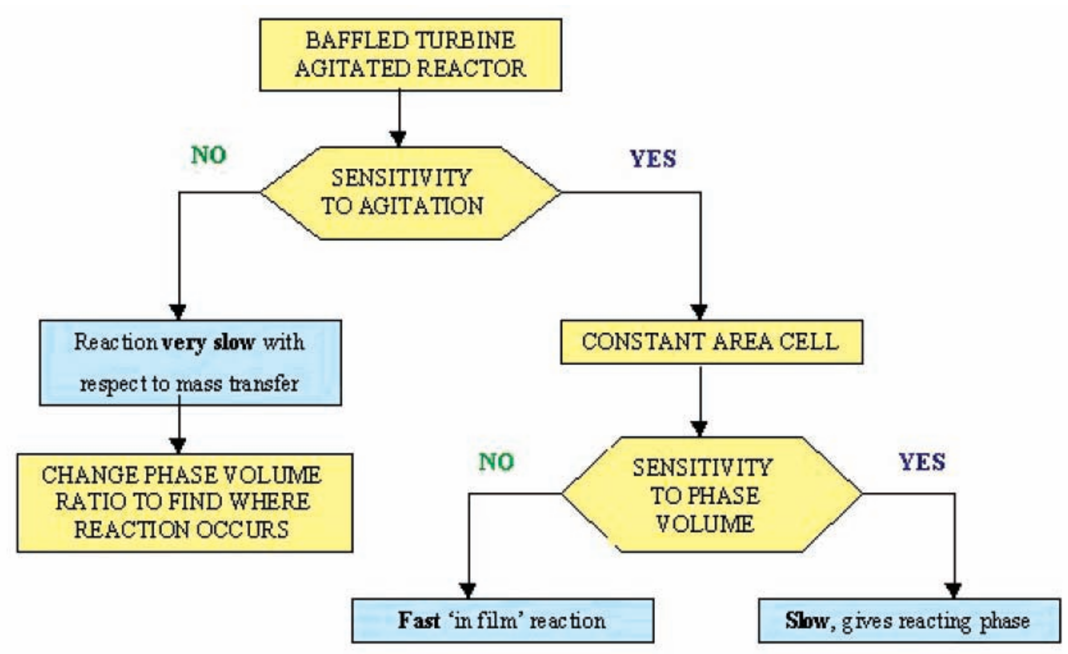

Figure 30. **Identification of reaction regime in a liquid−liquid system.**[68]

observed to be directly proportional to c_{Bi}, k_L, and a, but unaffected by c_A, ⁄, and k, then regime 2 and eq 8.5″ apply.

Often insufficient basic information is available for direct application of the equations given above. A laboratory protocol is needed to determine the regime from relatively few, well-planned rate measurements. Figure 30, which refers specifically to a liquid system, is a good example.[68] In Figure 30 and Table 15 the following responses of the reaction rate can be identified.

(i) By using baffles in a laboratory-scale tank (e.g., glass vessel with diameter approximately 0.1 m[69] or Mettler RC1 heat flow calorimeter) the flow pattern is well-defined and suitable for creating and maintaining any kind of dilute dispersion.

(ii) Over small ranges of stirrer speed (N), the proportionality $a \approx N$ holds (section 3.1). If the reaction rate is then unchanged, the regime is 1 (Table 15).

(iii) The phase volume ratio influences ⁄: if this affects r in a constant area cell (Figure 3), the regime is 2 (Table 15).

(iv) Fast "in film" reaction in Figure 30 covers regimes 3 and 4. To distinguish between them (a) in regime 4, $r \approx k_L$ and changing stirrer speed in a Lewis cell (Figure 3) changes k_L, and (b) in regime 3, $r \approx c_A^{1/2}$ (Figure 28 illustrates this response).

When reaction takes place in the fast regime (regime 3), its rate is independent of the film mass-transfer coefficient (k_L): refer to Table 15. Many factors—some of them difficult to know and control—determine k_L (e.g., turbulence level, flow pattern, reactor type, viscosity). If r/a has been measured in a stirred cell, which has a known interfacial area, it follows from eq 8.9 that $c_{Bi}(kD_Bc_A)^{1/2}$ is also known and can be applied to any type of contacting device, even though its value of k_L differs from that of the stirred cell. This result has been used many times for reactions in regime 3, since it avoids individual determinations of solubility (c_{Bi}), reaction rate constant (k), and solute diffusivity (D_B).[60,64,66]

Many two-phase reactions have been sufficiently well characterised that they can serve as test reactions, for example when the interfacial area in a novel contactor needs to be measured as a function of liquid flow rate.

Some examples of test reactions include

(a) gas−liquid systems: absorption of CO_2 or H_2S into an alkaline solution[64]

(b) solid−liquid systems: alkaline hydrolysis of a solid ester, dissolution of an organic acid in an alkaline solution[60]

(c) liquid−liquid systems: transfer of 2,4,4-trimethyl-2-pentene from a toluene solution into sulphuric acid,[60,70,71] alkaline hydrolysis of a liquid ester.[60,72]

Detailed information about the characteristics of various reactor types and of dispersions of solids, gases, and liquids in liquids is available.[60,73,74]

This section offers an introduction to the coupling between mass transfer/diffusion and chemical reaction. The concepts and methods given here form the basis for considering the influence of mass transfer on more complex reactions,[60]

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(68) Atherton, J. H. Methods for Study of Reaction Mechanisms in Liquid−Liquid and Liquid−Solid Reaction Systems and Their Relevance to the Development of Fine Chemical Processes. *Trans. Inst. Chem. Eng. A* **1993**, *71*, 111.

(69) Atherton, J. H.; Carpenter, K. J. *Process Development: Physicochemical Concepts*; Oxford University Press: New York, 1999.

(70) Sankholkar, D. S.; Sharma, M. M. A New System for the Measurement of Effective Interfacial Area in Agitated Liquid−Liquid Contactors by the Chemical Method. *Chem. Eng. Sci.* **1973**, *28*, 2089.

(71) Zaldivar, J. M.; Molga, E.; Alos, M. A.; Hernandez, H.; Westerterp, K. R. Aromatic Nitrations by Mixed Acid: Fast Liquid−Liquid Reaction Regime. *Chem. Eng. Prog.* **1996**, *35*, 91.

(72) Woezik, B. A. A.; Westerterp, K. R. Measurement of Interfacial Area with the Chemical Method for a System with Alternating Dispersed Phases. *Chem. Eng. Prog.* **2000**, *39*, 299.

(73) Harnby, N., Edwards, M. F., Nienow, A. W., Eds. *Mixing in the Process Industries*; Butterworth-Heinemann: Woburn, MA, 1997.

(74) Sharratt, P. N., Ed. *Handbook of Batch Process Design*; Blackie: London, 1997.

including phase-transfer catalysis,[75,76] as well as on the selectivity of multiple reactions (section 9).

9. Mass Transfer and Time Constants in Two-Phase Reactions. Part 2: Multiple Reactions

9.1. Introduction. When several reactions occur, involving reagents initially present in different phases, interphase mass transfer can influence their rates and product distributions. Some examples were given in section 3. Discussion of such reactions now moves from the qualitative level employed there to the semiquantitative level by use of the time constants given in section 8. Details of quantitative modelling are available in the literature,[60] although the full treatment of multiple reactions becomes quite involved and much can be learned from the simpler semiquantitative approach developed in Chap. 8 and further used here.

9.2. Competitive−Consecutive Reactions. *9.2.1. Introduction.* Employing the notation and conventions from sections 2, 3, and 8, the following scheme will be the principal object of study in this section.

$$\mathrm{A} + \mathrm{B} \xrightarrow{k_1} \mathrm{R} \qquad (2.1)$$

$$\mathrm{R} + \mathrm{B} \xrightarrow{k_2} \mathrm{S} \qquad (2.2)$$

The reactions occur in phase 2, where A is present and into which B is transferred from phase 1. In many practical cases the intermediate R is the required product and $k_1 > k_2$, so that when the reaction conditions are properly chosen a high selectivity for R can be expected. Different definitions of selectivity are in use. Here selectivity is the ratio of the reaction rates of B with A and R (forming R and S respectively).

9.2.2 General Principles. Differing scenarios and consequently different selectivities arise depending upon where each reaction takes place: this depends in turn on the ratio of the time constants for diffusion and reaction, expressed by Hatta numbers (refer to section 8.3). Some examples follow.

(a) First reaction fast, second reaction slow or very slow.

Here the words fast, slow etc. are used in the sense defined in section 8. Therefore Ha_1, referring to eq 2.1 and employing its rate constant k_1, should exceed approximately 3. Similarly Ha_2, referring to eq 2.2 and employing its rate constant k_2, should be less than approximately 0.3. The concentrations appearing in Ha_1 and Ha_2 are c_A and c_R respectively (refer to eq 8.7). When the following conditions are satisfied

$$Ha_1 > 3,\ Ha_2 < 0.3,\ c_A/c_{Bi} \gg Ha_1 \qquad (9.1)$$

reagent B will react completely in the diffusion film of phase 2 and most of the B will react with A, not R. In this scenario a high selectivity for R will result.

As reactions proceed the concentrations change, which can of course allow the regime to change (e.g., from fast to slow). For the reaction 2.2 Ha_2 is usually initially zero, because R has not yet been formed: subsequently Ha_2 and Ha_1 can increase and decrease respectively with a fall in selectivity. In the limit where all A has reacted, the yield of R is zero, so that the conversion of A needs to be less than 100%,when R is the desired product. For example, the influence of the conversion of 4-hydroxytoluene on the yield of its monochloro-derivative has been published.[33,34] (Formally a distinction is made between the differential (or instantaneous) yield, corresponding to the formation and consumption of very small quantities of product and reagent respectively, and the integral (or overall) yield, corresponding to finite changes in product and reagent quantities. Selectivity can also be understood in these two ways, although here the selectivity refers to the instantaneous state (refer to definition in 9.2.1). This matter of definitions will not be discussed further here).

(b) Both reactions slow or very slow when the following conditions are fulfilled.

$$Ha_1 < 0.3,\ Ha_2 < 0.3 \qquad (9.2)$$

B does not react in the film, but in the bulk of phase 2, where reagent A and intermediate R are present. Both R and S will be formed in the bulk and the selectivity for R will be lower than in scenario a).

Ha is inversely proportional to k_L (eq 8.7), which varies by roughly a factor 10 between various conventional contactors.[60] In addition to a change in *Ha* due to changing concentrations (discussed above), the reaction regime can also be different in different contactors. If, for example, $Ha_1 = 3$ when k_L is low and the contactor is changed to one whose k_L value is 10 times larger, then $Ha_1 = 0.3$: in this case the regime for the first reaction would change from fast to slow with a decrease in the R-selectivity.

If, however, both reactions remain in the slow regime when changing the contactor, the selectivity will be unaffected, although the observed reaction rates can change.

(c) Both reactions fast and pseudofirst order in B.

The following conditions need to be satisfied

$$Ha_1 > 3,\ Ha_2 > 3,\ c_A/c_{Bi} > Ha_1,\ c_R/c_{Bi} > Ha_2 \qquad (9.3)$$

The last of these four conditions is unlikely to be met early in the reaction. R must initially be formed by the first reaction, leading only gradually to a high R-concentration in the film and the bulk and so satisfying the last condition.

When all the conditions in eq 9.3 are met, there are negligible gradients in the concentrations of A and R in the film and the kinetics of the consumption of B is pseudofirst order in B. The selectivity is then independent of k_L. If, however, k_L can be sufficiently increased that $Ha_2 < 0.3$ whilst $Ha_1 > 3$, scenario (a) will be attained and the R-selectivity will increase.

(d) Both reactions fast and second order.

When the following conditions are satisfied

$$Ha_1 > 3,\ Ha_2 > 3,\ c_A/c_{Bi} < Ha_1,\ c_R/c_{Bi} < Ha_2 \qquad (9.4)$$

the concentrations of A and R in the film differ from their values in the bulk and the kinetics becomes second order.

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(75) Asai, S.; Nakamura, H.; Furuichi, Y. Alkaline Hydrolysis of *n*-Butyl Acetate with Phase Transfer Catalyst Aliquat 336. *AIChE J.* **1992**, *38*, 397.

(76) Asai, S.; Nakamura, H.; Sumita, T. Oxidation of Benzyl Alcohol Using Hypochlorite Ion via Phase Transfer Catalysis. *AIChE J.* **1994**, *40*, 2028.

The local rate of formation of R is $k_1 c_A c_B$ and the local concentration of A in the film must be lower than in scenario (c), where c_A equals the bulk value. Depletion of A in the film, expressed by the third inequality in eq 9.4, means that the selectivity for R is lower in scenario (d) than (c).

If $Ha_1 \gg c_A/c_{Bi}$ the first reaction occurs in the instantaneous regime and then reactions take place between the interface and z (refer to Figure 29).

The influence of mass transfer on the selectivity for R in the reactions 2.1 and 2.2 is clearly complex. The selectivity will be highest if the conditions given in scenario (a) and summarised in eq 9.1 can be realised.

9.2.3. An Alternative Reaction. In contrast to eqs 2.1 and 2.2, an alternative competitive−consecutive reaction scheme is

$$A + B \xrightarrow{k_1'} R \qquad (9.5)$$

$$A + R \xrightarrow{k_2'} S \qquad (9.6)$$

It will again be supposed that (i) $k_1' > k_2'$, (ii) the selectivity for the intermediate R should be high, (iii) reactions take place in phase 2 which is A-rich and (iv) B is initially present in phase 1 and has a low solubility in phase 2 ($c_{Bi}/c_A \ll 1$). Condition (i) favours high selectivity, but conditions (iii) and (iv) are very unfavourable, causing over-reaction as R reacts with excess A to form S.

An example of such reactions has been published,[77] where A is OH^-, B is a very slightly water-soluble carboxylic acid ester (X−R−COOMe) containing another reactive group (X), R is the first hydrolysis product ($X-R-COO^-$), and S is the final hydrolysis product ($HO-R-COO^-$). The reactivity of the X-group was considerably smaller than that of the methyl ester. When one equivalent of concentrated aqueous NaOH was added to the ester and the agitation intensity was low, the yield of S was 50% and the conversion of A was 50%. The intermediate R was not present, although $k_1' \gg k_2'$. The low solubility of the ester (B) in the aqueous phase with its associated low dissolution rate caused B and its intermediate R to be transitorily in solution with a large excess of alkali (A), allowing R to react fully to S. The time constant for the dissolution of the ester was much greater than that for the second hydrolysis. It was further reported[77] that, when concentrated alkali was slowly added to a solution of the ester dissolved in a lower alcohol, taking care to maintain a single phase, the product distribution was that corresponding to the reaction kinetics and the stoichiometric ratio (A/B = 1). This example well illustrates the need to identify the reactions and where they occur as well as to pay attention to the conditions (i−iv) given above.

Detailed modelling of reactions 9.5 and 9.6 has been published[60] with particular reference to the rate of dissolution and reaction of the reagent B. When both reactions are in the slow regime, the R-yield decreases as B increasingly favours phase 1 (increasing distribution coefficient) and as the interfacial area per unit volume (a) decreases.[69]

9.2.4. Chlorination of 4-Hydroxytoluene (p-Cresol). The purpose of this section is to illustrate applications of the general principles in 9.2.2 to experimental results for well-characterised competitive−consecutive reactions following eqs 2.1 and 2.2. Several experimental studies have been published[60] (section 3.2), including the chlorination of *p*-cresol[35,60] for which A is 4-hydroxytoluene, B is Cl_2, R is 3-chloro-4-hydroxytoluene, and S is 3,5-dichloro-4-hydroxytoluene. The HCl simultaneously formed during these two substitutions need not be further mentioned.

In the present case[35] the solvent was 1,2,4-trichlorobenzene, the reaction temperature was 373 K, and the second-order rate constants were $k_1 = 0.19$ m^3/mol·s and $k_2 = 0.015$ m^3/mol·s. The diffusivity of Cl_2 varied with the viscosity and composition of the reaction mixture: here an average value $D_B = 3 \times 10^{-9}$ m^2/s may be employed. Henry's law related the partial pressure of Cl_2 to its solubility in the reaction mixture, the proportionality constant being 270 mol/m^3·bar. Liquid film mass-transfer coefficients (k_L) were available for a bubble column (diameter 23 mm) and, as a function of stirrer speed, for a stirred cell (diameter 55 mm), which served as alternative reactors.[35,60]

(i) bubble column: the following conditions applied

first reaction $c_A = 4450$ mol/m^3, $Ha_1 = 4.0$,
$k_L = 4 \times 10^{-4}$ m/s
second reaction $c_R = 1340$ mol/m^3, $Ha_2 = 0.61$,
$c_A/c_{Bi} = 4450/220 = 20 \gg Ha_1$

Comparing these three values with eqs 9.1−9.4, it is seen that the first chlorination took place in the film ($Ha_1 > 3$) under pseudo-first-order conditions (c_A = const. through the film). The condition for the second chlorination not to occur in the film ($Ha_2 < 0.3$) was not fully satisfied ($Ha_2 = 0.61$), although no S could form in the bulk because Cl_2 was consumed forming R in the film. Therefore, a high selectivity for R would be expected: the measured value was 12.4, which as will subsequently be seen was the highest value in this investigation.[35]

If by increasing the turbulence in the bubble column, k_L had been increased, the first reaction could also have taken place in the bulk, thereby decreasing the selectivity (refer to section 9.2.2. (b)).

(ii) stirred cell: the following conditions applied

$c_A = 4000$ mol/m^3, $c_R = 1700$ mol/m^3, $c_{Bi} = 132$ mol/m^3, $c_A/c_{Bi} = 30$, $c_R/c_{Bi} = 13$

$k_L = (2.8- 5.1) \times 10^{-5}$ m/s for stirrer speeds in the range 40−100 rpm

maximum Ha values: $Ha_1 = 54$, $Ha_2 = 10$ (smallest k_L)
minimum Ha values: $Ha_1 = 30$, $Ha_2 = 5.4$ (largest k_L)

Comparing these quantities with the criteria in eqs 9.1−9.4, it can first be seen that both reactions occurred in the film. From eqs 9.3 and 9.4 a depletion (i.e., concentration gradient) of *p*-cresol in the film must be expected with the first chlorination being either fast, second-order with the largest k_L value, or instantaneous with the smallest k_L value. The second chlorination would have been second-order with the smallest k_L value and probably pseudo-first-order with the largest value of k_L. From section 9.2.2 (c) and (d) lower

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(77) Atherton, J. H. Chemical Aspects of Scale-Up. In *Pilot Plants and Scale-up of Chemical Processes*, 2nd ed.; Hoyle, W., Ed.; Royal Society of Chemistry: Cambridge, UK, 1999.

selectivities than in the bubble column (12.4) must be expected in the stirred cell. This was confirmed experimentally, measured values being 6.4 (highest k_L value and stirrer speed) and 3.1 (lowest k_L value and stirrer speed).

(iii) stirred cell: the following conditions applied

stirrer speed 40 rpm − $k_L = 2.8 \times 10^{-5}$ m/s variable ratio c_A/c_{Bi}

With $c_A = 4000$ mol/m^3, $c_{Bi} = 255$ mol/m^3 and $c_R = 1400$ mol/m^3, $Ha_1 = 54$ and $c_A/c_{Bi} = 15.7$, indicating depletion of A and instantaneous first reaction in the film—scenario (d). $Ha_2 = 8.9$ and $c_R/c_{Bi} = 5.5$. The measured selectivity was 2.3.

When the ratio c_A/c_{Bi} was reduced to 7.8, indicating more depletion of A and less competition from the first, R-forming reaction in the film, the measured selectivity fell to 1.6.

Detailed modelling of these chlorinations was also carried out, and good agreement with the experiments was found.[35,60] At the semiquantitative level shown here, the experimental results are well interpreted by the general principles given in section 9.2.2. The variation in the selectivity from 1.6 to 12.4 illustrates the substantial influence of mass transfer on the chlorination of 4-hydroxytoluene.

9.2.5. Alkylation of Phenols with 2-Methylpropene (Isobutene). Although less detailed information (e.g., diffusivities and mass-transfer coefficients) is available for the alkylation of 4-hydroxytoluene (*p*-cresol) with isobutene[60,78] than for its chlorination (section 9.2.4), these alkylations exhibited some different characteristics, principally because they did not usually take place in the diffusion film.

Absorption of gaseous isobutene (B) into molten *p*-cresol (mp 308 K) (A) at temperatures in the range 333−343 K using 500 mol H_2SO_4/m^3 as catalyst was shown to follow eqs 2.1 and 2.2. The intermediate R was 2-*tert*-butyl-*p*-cresol, and S was 2,6-di-*tert*-butyl-*p*-cresol. The solubility of isobutene in molten *p*-cresol was 450 mol/m^3 at a partial pressure of 1 bar. The concentration ratio c_A/c_{Bi} was then 25.5.

Using a stirred cell the first reaction took place in the fast pseudo-first-order regime ($Ha_1 \approx 3.5$, $c_A/c_{Bi} \gg Ha_1$), giving $k_1 \approx 6.2 \times 10^{-4}$ m^3/mol·s (±30%).[78] In a small stirred tank reactor with a high stirrer speed the second reaction occurred in the very slow regime ($Ha_2 < 0.3$) with no mass transfer limitation, giving $k_2 = 4.0 \times 10^{-5}$ m^3/mol·s (±20%). Therefore, $k_1/k_2 = 15.5$, and selective reaction to produce R should be attainable.

By varying the flow rate of isobutene in a bubble column to give superficial gas velocities between 0.053 and 0.22 m/s, the gas hold-up, the interfacial area (a) and to some extent also the mass transfer coefficient (k_L) were changed. It was estimated that k_La increased by a factor of 2.7 as the gas rate was increased.[60] Because of higher k_L values in the bubble column relative to those in the stirred cell, there should have been no reaction in the film and eq 9.2 for scenario (b) should have been satisfied. This also means that the gas velocity should have had no effect on the product distribution, but would have influenced measured reaction rates.

The variations in the concentrations of A, R, and S with time were measured at three gas velocities, showing that:[78]

(i) The product distribution did not change significantly despite changes in k_La. The R yield first increased and later decreased with increasing A conversion and time, its maximum value being approximately 70%, almost irrespective of gas velocity.

(ii) Reaction proceeded some 2.7 times faster at the highest gas velocity relative to the lowest. This change is consistent with eq 8.5″ for the slow regime, where both reactions are in the bulk and have rates proportional to k_La. Note that the ratio of rates and hence also the selectivity should then be independent of gas velocity: see (i).

9.2.6. Sulphonation of Benzene with Sulphur Trioxide. A detailed study[42] of benzene sulphonation, which included quantitative modelling and substantial experimentation, showed that less by-product formation took place in reactors having high k_L values and that the first reaction, forming benzenesulphonic acid (R), was in the instantaneous regime and took place in the film. In turbulent liquids having physical properties similar to those of water, *very* approximate values of k_L are: stirred cell 5×10^{-5} m/s, bubble column and stirred tank 10^{-4} m/s, concurrent gas−liquid flow in a pipe 5×10^{-4} m/s, and cyclone 10^{-3} m/s. Increasing and decreasing yields of R and S, respectively, were calculated and also measured when changing from stirred cell to tube and finally to cyclone for this particular sulphonation.[42]

9.3. Competitive Reactions. *9.3.1. Introduction.* The second-order reaction scheme in eqs 2.8 and 2.9 will be considered here.

$$A + B \xrightarrow{k_1} P \qquad (2.8)$$

$$C + B \xrightarrow{k_2} Q \qquad (2.9)$$

For two-phase reactions there are two important possibilities.

(i) B is present in phase 2 where the reactions take place. A and C, initially present in phase 1, are both transferred into phase 2.

(ii) A and C are present in phase 2—the reactive phase—and B, initially present only in phase1, is transferred into phase 2.

Examples of these two possibilities include:

(i) simultaneous competitive nitrations of benzene and methylbenzene

$B = NO_2^+$, $C = C_6H_6$, $A = C_6H_5CH_3$, phase 1 = organic, phase 2 = aqueous

(ii) absorption of an acid gas into a solution of two amines

A = amine 1, C = amine 2, B = H_2S (or CO_2), phase 1 = gas, phase 2 = liquid

Thus, two substances change phase in case (i), whereas in case (ii) only one substance is transferred between phases.

9.3.2. General Principles. The principles applying to cases (i) and (ii) are no different from those already explained in section 9.2.2. Further details for both cases may be found in the literature.[60] Each reaction can take place in the film or the bulk—in principle reaction at the interface is a further

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(78) Gehlawat, J. K.; Sharma, M. M. Alkylation of Phenols with Isobutylene. *J. Appl. Chem.* **1970**, *20*, 93.

possibility, although an infrequent one—depending on the value of its Hatta number. In case (i) for example Ha_1 (refer to eq 8.7) for the P-forming reaction (eq 2.8) includes k_1, D_A and c_B, whereas Ha_2 for the Q-forming reaction (eq 2.9) includes k_2, D_C and c_B. The differential selectivity can be defined as the ratio of the instantaneous rates of formation of P and Q. The following examples apply the general principles to interpreting experiments on pairs of competitive reactions and include cases (i) and (ii).

9.3.3. Competitive Nitrations of Methylbenzene (A) and Benzene (C). Reference to results on competitive nitrations ($B = NO_2^+$) was made in section 3.3.1. The organic phase was an equimolar mixture of toluene and benzene. The aqueous phase contained 15, 30, and 55 mol % of HNO_3, H_2SO_4, and H_2O, respectively, and with this high nitric acid concentration both nitrations would be expected to take place in the fast regime.[37,39,71] When two-phase competitive nitrations were carried out in a stirred tank reactor and the rate constant ratio k_1/k_2 was calculated from the measured product distribution (P/Q) on the assumption of fully kinetically controlled reactions in the very slow regime, the result was k_1/k_2 in the range 1.3−1.8.[37] It is, however, well-established that methylbenzene (A) nitrates some 20−27 times faster than benzene (C) so that k_1/k_2 should be about 23. The actual regime is likely to have been fast and pseudo-first-order (c_{Ai} and $c_{Ci} \ll c_B$) for both nitrations. Equation 8.9 applied to each reaction gives

$$r_P/r_Q = (k_1 D_A/k_2 D_C)^{1/2} \cdot c_{Ai}/c_{Ci} \tag{9.7}$$

The ratios of the solubilities and diffusivities of toluene and benzene in the acid phase are approximately 0.28[63] and 0.9,[62] respectively. Substituting in eq 9.7 gives

$$r_P/r_Q = [(23 \times 0.9)^{1/2}]0.28 = 1.3$$

The low selectivities given above (1.3−1.8) are consistent with nitrations in the fast regime for which the calculated selectivity is approximately 1.3.

In homogeneous, single-phase competitive nitration of an equimolar mixture of benzene and toluene using small degrees of conversion, the selectivity is equal to k_1/k_2, which is approximately 23.

In two-phase nitration in the very slow regime it follows from eq 8.3 that the selectivity is ($k_1 c_{Ci}/k_2 c_{Ai}$), which is approximately (23 × 0.28) = 6.5.

This simple example illustrates some influences of solubility and diffusion—in addition to the more obvious difference in the values of the rate constants—on the selectivity of two-phase reactions.

9.3.4. Reactions between Cyanuric Chloride and an Aqueous Amine Solution. Cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, $C_3N_3Cl_3$) (mp 427 K) hydrolyses slowly in aqueous solution according to

$$C_3N_3Cl_3 + H_2O \xrightarrow{k_2} C_3N_3Cl_2(OH) + H^+ + Cl^-$$

with $k_2 \approx 0.0036\ s^{-1}$ at 298 K. It also couples with the amine DMPA (*N*,*N*-dimethyl-*p*-phenylenediamine) in aqueous solution, the reactive species being the once protonated amine ($DMPAH^+$, pK = 6.4) in the pH range from approximately 5.5 to 7.0. The second-order rate constant is $k_1 = 0.77\ m^3/mol \cdot s$.[79]

In terms of eqs 2.8 and 2.9 B is cyanuric chloride, A is $DMPAH^+$, and C is water. The solubility of B is approximately 2.6 mol/m^3 at 298 K.[80] Diffusivities are $D_A \approx 6.6 \times 10^{-10}\ m^2/s$ and $D_B \approx 3.3 \times 10^{-10}\ m^2/s$.[79] The amine concentration is $c_A = 200\ mol/m^3$. In a stirred tank reactor $k_L = 5 \times 10^{-5}$ m/s.

It is required to know whether cyanuric chloride is used selectively in the coupling reaction or wasted by hydrolysis.

$$Ha_1 = (0.77 \times 200 \times 3.3 \times 10^{-10})^{1/2}/5 \times 10^{-5} = 4.5$$

$$Ha_2 = (0.0036 \times 3.3 \times 10^{-10})^{1/2}/5 \times 10^{-5} = 0.02$$

$$c_A/c_{Bi} = 200/2.6 = 77$$

The coupling is fast ($Ha_1 > 3$) and pseudo-first-order ($c_A/c_{Bi} \gg Ha_1$) in the film. Cyanuric chloride (B) should be fully consumed there. Its hydrolysis does not take place in the film ($Ha_2 < 0.3$) and also not in the bulk, because it is consumed by the coupling in the film. Highly selective use of cyanuric chloride is therefore made in this example.

9.3.5. A Schotten−Baumann Acylation with Benzoyl Chloride. The desired reaction is between benzoyl chloride (C_6H_5COCl) (B) and benzylamine ($C_6H_5CH_2NH_2$) (A) to form *N*-benzylbenzamide (P) and takes place in the alkaline aqueous phase. The reactive species of the amine is the unprotonated form (A), which is in equilibrium with the protonated form (A^+) depending upon the pH of the solution[81]

$$A^+ \leftrightarrow A + H^+ \qquad pK_a = 9.34$$

Benzoyl chloride hydrolyses in neutral and alkaline solutions with pseudofirst order and second order rate constants of $k_w = 1.4\ s^{-1}$ and $k_{0H} = 0.4\ m^3/mol \cdot s$ respectively according to the equations

$$\left.\begin{aligned} B + H_2O &\rightarrow \text{waste} \qquad k_w \\ B + OH^- &\rightarrow \text{waste} \qquad k_{OH} \end{aligned}\right\} \tag{2.9′}$$

The product forming reaction at 298 K is

$$A + B \xrightarrow{k_N} P + HCl \tag{2.8′}$$

where $k_N = 16\ m^3/mol \cdot s$ and the concentrations of A and B increase and decrease respectively with rising pH. When the concentration of the nucleophile (A) is much greater than that of the electrophile (B), so that the product-forming reaction becomes pseudofirst order in B, the optimal pH

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(79) Compton, R. G.; Harding, M. S.; Atherton, J. H.; Brennan, C. M. Mechanism of a Solid/Liquid Interfacial Reaction: The Reaction of an Aqueous Solution of an Aromatic Amine with Cyanuric Chloride. *J. Phys. Chem.* **1993**, *97*, 4677.

(80) Horrobin, S. The Hydrolysis of some Chloro-1,3,5-triazines: Mechanism, Structure and Reactivity. *J. Chem. Soc.* **1963**, 4130.

(81) King, J. F.; Rathore, R.; Lam, J. Y. L.; Guo, Z. R.; Klassen, D. F. pH Optimization of Nucleophilic Reactions in Water. *J. Am. Chem. Soc.* **1992**, *114*, 3028.

maximizing the rate of eq 2.8′ relative to eq 2.9′ may be calculated from[81]

$$\mathrm{pH}_{\max} = 0.5[\log (k_w/k_{OH}) + \mathrm{p}K_w + \mathrm{p}K_a]$$

where $\mathrm{p}K_w$ refers to the dissociation of water ($H_2O \leftrightarrow H^+ + OH^-$). Therefore $\mathrm{pH}_{\max} = 10.44$ in this example.

When the total concentration of the amine (free A and protonated A^+) in the aqueous phase is 10 mol/m^3, that of the free amine at pH = 10.44 can be found since $\mathrm{p}K_a$ is known (9.34). Therefore $c_A = 9.26$ mol/m^3.

The diffusivity of dissolved benzoyl chloride can be estimated by the Wilke−Chang method[59] (refer to section 8.4.2) giving $D_B \approx 8 \times 10^{-10}$ m^2/s at 298 K. Two possible liquid film mass-transfer coefficients will be considered corresponding to

(i) weak agitation: $k_L = 10^{-5}$ m/s and to (ii) strong agitation: $k_L = 2 \times 10^{-4}$ m/s.

For the product-forming reaction with weak agitation (refer to eq 8.7)

$$\text{(i) } Ha_1 = (16 \times 9.26 \times 8 \times 10^{-10})^{1/2}/10^{-5} = 34$$

whereas, with strong agitation

$$\text{(ii) } Ha_1 = (16 \times 9.26 \times 8 \times 10^{-10})^{1/2}/(2 \times 10^{-4}) = 1.7$$

This reaction takes place mainly in the film.

For the wasteful hydrolyses, ($k_w + k_{OH}\, c_{OH}$) is the total pseudo-first-order rate constant where $c_{OH} = 10^3 \times (10^{-14}/10^{-10.44})$ mol/m^3. Hence

$$k_{\text{total}} = (1.4 + 0.40)0.27 = 1.5 \text{ s}^{-1}$$

The Hatta number for hydrolysis is therefore

$$\text{(i) } Ha_2 = (1.5 \times 8 \times 10^{-10})^{1/2}/10^{-5} = 3.5 \text{ (weak agitation)}$$

$$\text{(ii) } Ha_2 = (1.5 \times 8 \times 10^{-10})/(2 \times 10^{-4}) = 0.17 \text{ (strong agitation)}$$

It may be concluded that the product-forming reaction is fast, taking place almost entirely in the film. With weak agitation the wasteful hydrolysis also occurs in the film, but shifts to the bulk of the aqueous phase when agitation is vigorous. This latter condition should ensure selective use of benzoyl chloride. Experimental evidence for this prediction is available.[81] Using vigorous agitation and adding pure B over 30 min, the product yield was in the range 97−99% when the pH was 10.4−10.45.

9.3.6. Selective Absorption of H_2S in the Presence of CO_2. Hydrogen sulphide can be removed from a gas stream for example by absorption into an amine solution, where usually instantaneous reaction occurs.

Depending upon the nature of the reagent (e.g., amine) in solution, carbon dioxide, also present in the gas stream, can react too. A selective absorbent is one reacting instantaneously with H_2S, but not with CO_2. The extensive literature on this reactive separation may be consulted for further detail.[60,64]

9.4. Conclusions. It was shown in section 8 that reactions in two-phase systems can occur in the bulk of a liquid phase, in the liquid film adjacent to the interface or possibly at the interface. This location depends strongly on the ratio of the time constants for diffusion of reagents through the film and chemical reaction in the film. The square root of this ratio is termed the Hatta number. With multiple reactions a key selectivity-determining factor is the locations of product-forming as well as undesired reactions, summarised in the question “Where does each reaction occur?”. Many scenarios arise. High selectivity is favoured when the dissolved and dissolving reagents form product in the film, whilst by-products form in the bulk. Various scenarios, having widely different selectivities, were illustrated for competitive as well as competitive−consecutive reactions.

Closing Remarks

This review offers an introduction to the principles determining the influence of mixing and mass transfer on chemical reactions, especially on the selectivity of single- and two-phase reactions. It aims to provide Chemists working on such reactions with a suitable starting point for their study, whereby some words of Winston Churchill (10 November 1942) seem appropriate: “This is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.”

Acknowledgment

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LIST OF SYMBOLS

A, B, C	reagents A, B, and C
a	interfacial area per unit volume of dispersion
b	molar reagent ratio
c_B'	concentration of B in nonreactive phase
c_{Bi}	concentration of B at interface in reactive phase
c_i	concentration of substance i
d	diameter of stirrer or nozzle
D_i	diffusivity of i
D_T	turbulent diffusivity
E	engulfment rate coefficient
H	hold-up (volume fraction) of dispersed phase
I	ionic strength
i	any substance, interface
k	rate constant
K_S	Setchenow constant
k_L	liquid-film mass transfer coefficient
L_R	length of reaction zone
L_c, Λ_c	scale of unmixed region
ℓ	volume fraction of reactive phase

M	molecular mass
N	rotational speed of stirrer
n_f	number of feed points
n_i	number of moles of i
P	power consumption
P, Q	products of competitive reactions
Q_B	flow rate of stream containing B
r_i	reaction rate of i
R, S	products of competitive−consecutive reactions
T	temperature, tank diameter
t	time
t_{-}	characteristic times with suffix C circulation, D turbulent dispersion, DS molecular diffusion and shrinkage, E engulfment, Mix mixing, m bulk blending, MR micromixing and reaction, R reaction, S eddy breakup
t_{crit}	critical feed time
t_f	feed time
t_{95}	time to attain 95% macroscopic homogeneity
u	velocity
u_f	feed velocity
U_o	velocity through nozzle
V	volume
V_B	molar volume
V_E	engulfed volume
V_i	volume of i-rich solution
v_{MR}	local fluid velocity
X_A	volume fraction of A-rich liquid
X_Q, X_S	yields of Q and S
z	position of instantaneous reaction

β	Wilke−Chang parameter
δ	thickness of diffusion layer
ϵ	dissipation rate of turbulent kinetic energy per unit mass
ϵ_{av}	volume-averaged value of dissipation rate
Λ_c	see L_c
λ_K	Kolmogorov scale
μ	dynamic viscosity
ν	kinematic viscosity
ρ	density
ϕ	distribution coefficient

Da	Damkoehler number − eq 6.3
Ha	Hatta number − eq 8.7
Po	Power number − eq 4.13
Re	Reynolds number − section 7.4.1. (a)

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