Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.62; N, 10.77. Found: C, 60.20; H, 4.45; N, 10.55.

Methyl Pyrrolo[2,3-*f*]quinoxaline-6-carboxylate (7). Reaction conditions: 25 °C, 1.5 h, mp 186–187 °C dec (EtOAc–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.40 (br s, 1 H, NH), 8.88 and 8.79 (two d, 1 H, $J = 1.8$ Hz, C2-H and C3-H), 7.99 (d, 1 H, $J = 8.9$ Hz, C9-H), 7.76 (d, 1 H, $J = 8.9$ Hz, C8-H), 7.39 (d, 1 H, $J = 2.1$ Hz, C7-H), 4.00 (s, 3 H, CO_2CH_3); IR (KBr) ν_{max} 3307, 2952, 1713, 1514, 1440, 1372, 1334, 1272, 1250, 1202, 1108, 1058, 998, 862, 830, 758, 700 cm^{-1}; EIMS, *m/e* (relative intensity) 227 (M^+, base), 195 (94), 167 (46), 141 (25), 114 (17), 87 (16), 76 (8), 62 (14), 52 (10); CIMS (2-methylpropane), *m/e* 228 ($M^+ + H$, base); HRMS, *m/e* 227.0690 ($C_{12}H_9N_3O_2$ requires 227.0695).

In addition, methyl pyrrolo[2,3-*e*]benzoxazole-5-carboxylate (**6g**, 12%) was isolated from the reaction mixture.

Acknowledgment. This work was assisted by the financial support of the National Institutes of Health (CA 41986) and the Alfred P. Sloan Foundation.

Registry No. **5** ($R = CH_2Ph$), 103781-89-1; **5** (R = H), 116350-38-0; **6a**, 116350-39-1; **6b**, 116350-40-4; **6c**, 116350-41-5; **6d**, 116350-42-6; **6e**, 116350-43-7; **6f**, 116350-44-8; **6g** (R = H), 116350-45-9; **6g** ($R = CH_2OH$), 116350-46-0; **6h**, 116350-47-1; **7**, 116350-48-2; $H_2N(CH_2)_3CH_3$, 109-73-9; $H_2NCH_2CH{=}CH_2$, 107-11-9; $H_2N(CH_2)_3SMe$, 4104-45-4; $H_2NCH_2CO_2Me$, 616-34-2; n-$C_7H_{15}CH_2NH_2$, 111-86-4; $H_2N(CH_2)_2OH$, 141-43-5; $H_2N(CH_2)_3OH$, 156-87-6; $H_2N(CH_2)_2NH_2$, 107-15-3; 4-(benzyloxy)benzaldehyde, 4397-53-9; methyl α-azidoacetate, 1816-92-8; methyl α-azide-4-(benzyloxy)cinnamate, 115663-17-7; benzylamine, 100-46-9; 7- or 8-(*n*-octylamino)-2-*n*-heptylpyrrolo[2,3-*e*]benzoxazole-5-carboxylate, 116350-49-3.

Control of Product Distribution in Mixing-Controlled Reactions

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Received January 20, 1988

Introduction

The product distribution from fast reactions is often influenced by the way in which reagents are mixed. The concentration gradients present during the mixing of miscible reagent solutions determine the local absolute and relative rates of individual reactions. Qualitative understanding of this situation has been available since 1926,[1] when the relative rates of bromination of some organic substrates were found to differ less than the differences in reactivity. Similar results have been obtained in the competitive single-phase nitration of benzene and toluene.[2] The competitive method of determining relative reactivities will fail when the rate of reaction is similar to, or greater than, the rate of mixing, although it is not widely known that the mixing rate can now be predicted.

Fast competitive–consecutive reactions, typified by

$$A + B \xrightarrow{k_1} R \tag{1}$$

$$R + B \xrightarrow{k_2} S \tag{2}$$

exhibit lower yields of R and higher yields of S when mixing is insuffiently rapid to homogenize the reagents. Reactions falling in this category include diamines with isocyanates,[3] nitration of durene,[4] iodination of *l*-tyrosine,[5] coupling of 1-naphthol with diazotized sulfanilic acid,[6,7] and acylation of diamines.[8] Mixing effects in nitration have been extensively described.[9] More complex reactions are known to be mixing-sensitive.[10,11] In some cases hydrogen ions, which are products of rapid reactions, influence the ionic preequilibria of the reagents and the product distribution, e.g., bromination of resorcinol,[12] coupling of 1-hydroxynaphthalene-6-sulfonic acid with benzenediazonium ion,[13] and coupling of 6-amino-4-hydroxy-2-naphthalenesulfonic acid with 3-(trifluoromethyl)benzenediazonium ion.[14]

Measures to improve yields in mixing-controlled reactions comprise changing factors that determine the reaction kinetics and the mixing rate. Kinetic factors considered in the literature already cited are concentration (increasing the dilution often improves the yield) and stoichiometric ratio (e.g., a large excess of A relative to B raises the yield of R in eq 1 and 2). Mixing-rate factors are stirrer speed and type of mixer. It is intended here to show that these results are fully consistent with the theory of mixing. This theory also identifies other options available to the synthetic chemist for increasing yield.

Principles of Mixing

Mixing in a reaction vessel occurs on different scales. Macromixing refers to mixing on a scale much coarser than the molecular. It brings about homogeneity in the vessel by bulk transport of materials. Micromixing refers to mixing on the molecular scale. Molecular diffusion, which brings about encounters between the different species, is an important micromixing mechanism. Detailed consideration of macromixing will be avoided here by concentrating on the slow addition of one reagent (B) solution to the other (A). The rate at which A is transported by the general circulation in the vessel to the point of addition of B will greatly exceed the rate of feeding in fresh B. The concentration of A (and of any other substances present in the vessel) entering the mixing zone will then be the average value for the vessel. Micromixing will be the controlling step in the whole mixing process and has a half-life t_{D}[15] given by

$$t_{\mathrm{D}} \simeq 2(\nu/\epsilon)^{1/2}\ \mathrm{arc\ sinh}\ (0.05\nu/D) \tag{3}$$

where ν is the kinematic viscosity of the solution, D is the diffusivity of the solute, and ϵ is the rate of energy dissipation per unit mass of solution. Parameter ϵ, whose units are watts per kilogram, is a measure of the rate of stirring, and t_{D} is the time at which the molecular mixing process, which occurs by diffusion and fine-scale fluid deformation, is 50% complete. Comparing t_{D} with t_{R}, the half-life of the chemical reaction, three possibilities arise.

(i) $t_{\mathrm{D}} \ll t_{\mathrm{R}}$. Reaction is so slow that mixing on a mo-

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Table I. Results

pH	speed, rpm	t_D, s	t_R, s	τ_D/τ_R	yield, %	regime
10	75	0.28	0.0008	350	84.0	$t_D > t_R$
10	300	0.035	0.0008	44	98.1	$t_D > t_R$
7	75	0.28	0.14	2	99.4	$t_D \simeq t_R$
7	300	0.035	0.14	0.25	99.9	$t_D < t_R$
2–10	75	$\simeq 0$			99.9	$t_D < t_R$
2–10	300	$\simeq 0$			99.9	$t_D < t_R$

lecular scale occurs before any significant chemical conversion. The time evolution of the reaction and the product distribution are fully described by the reaction kinetics.

(ii) $t_D \gg t_R$. Reaction is so fast that reagents do not coexist, but react in the zone of contact between the two solutions. The time evolution is controlled by mixing and is independent of reaction kinetics; for example, a stopped-flow instrument ($t_D = 10^{-3}$ s) cannot measure the neutralization kinetics of HCl with NaOH ($t_R < 10^{-6}$ s).

(iii) $t_D \simeq t_R$. Reaction is localized in the region near the zone of contact, and the time evolution depends upon both kinetics and mixing.

Assuming second-order kinetics for the reactions of eq 1 and 2 and considering the practically relevant case where $k_1 \gg k_2$, t_R may be estimated as follows:

$$t_R \simeq (k_1 c_0)^{-1} \qquad (4)$$

where c_0 is the concentration of the reagents A and B after mixing for a stoichiometric ratio of 1. The yields of R in the three regimes are then (i) maximum, (ii) 0, and (iii) intermediate between i and ii. The factors influencing t_R are kinetic (concentrations of reactive species, temperature, homogeneous catalysis, solvent, etc.), while t_D reflects physical mixing variables (viscosity, diffusion coefficients, volumes of solutions, and power consumption, which in turn depend upon the size, speed, and shape of the stirrer).

Results

Couplings of 1-naphthol (A) with diazotized sulfanilic acid (B) were conducted to confirm the theory. The yield obtained in the slow reaction regime ($t_D \ll t_R$) should depend only upon the stoichiometric ratio and the ratio of rate constants (k_1/k_2) and should slightly exceed 99.9%.

The first reaction attains its maximum rate at pH 10. (This can be calculated from the ionic preequilibria and the pK values of the reagents.[6]) As shown in the Experimental Section, mixing and reaction conditions correspond to $t_D > t_R$: these results are summarized in Table I.

By decreasing the pH to 7, but with all other conditions the same, we changed the preequilibrium concentrations of the reactive species, producing a drastic retardation of the reaction rate. Thus $t_D < t_R$ (Table I).

Addition of acidic diazonium ion solution to unbuffered 1-naphthol solution results in a pH value so low that coupling hardly occurs. Upon slow addition and mixing of buffer, the pH rises to a level where reaction occurs. However, since A and B had been premixed, t_D was effectively 0 during buffer addition ($t_D < t_R$), and coupling was controlled only by reaction kinetics. Therefore yields were high (Table I).

Table I shows that as the ratio t_D/t_R increases, the yield decreases from its value in the kinetically controlled regime (>99.9%).

Discussion

Table I shows that the yields measured at pH 7 and 10 and at two stirrer speeds agree well with the classification of the reaction regime according to t_D/t_R. The value of t_R, which depends upon the concentration(s) of the reactive species, was varied by changing the ionic preequilibria of A and B. High yields of R were achieved either by coupling at pH 7, thereby slowing reaction and reducing concentration gradients, or by adding alkaline buffer to an acidic premixed solution. This result indicates that the *sequence* used to mix reagents, buffer, soluble catalysts, etc., can influence yield. A similar idea has recently been used in improving yields in esterification.[16]

A further application of eq 3 is to determine the influence of fluid viscosity on the yield of R. In addition to coupling in aqueous solution at 298 K, where $\nu = 0.89 \times 10^{-6}$ m^2 s^{-1}, a 0.3 wt % aqueous solution of (carboxymethyl)cellulose (CMC) (Hercules 7 MFD) was also used as solvent.[17] At this concentration of CMC, the reaction kinetics and extinction coefficients are the same as in the aqueous solution. The viscosity increased to 3.5×10^{-6} m^2 s^{-1}; otherwise, nothing was changed; t_R was 0.0004 s in both solvents. Stirring was adjusted to give $\epsilon = 0.039$ W kg^{-1}, so that t_D was 0.047 s in water ($\tau_D/\tau_r = 118$), but 0.11 s in the CMC solution ($\tau_D/\tau_R = 275$). The yields of R were 91.9% (aqueous) and 86.1% (aqueous CMC), as expected from the τ_D/τ_R ratio.

Equation 3 indicates that the half-life for diffusion t_D is independent of concentration, while eq 4 indicates an inverse proportionality between t_R and reagent concentration. This difference arises because diffusion and azo coupling are first- and second-order, respectively, in concentration. Couplings were also conducted at different concentration levels and constant stirring conditions.[18] With $\epsilon = 0.068$ W kg^{-1}, $t_D = 0.036$ s. With $c_A = 0.21$ mol m^{-3}, $t_R = 0.0004$ s and $\tau_D/\tau_R = 90$, while when $c_A = 0.525$ mol m^{-3}, $t_R = 0.000\,15$ s and $\tau_D/\tau_R = 240$. The yields of R were 89.4% at the lower and 80.4% at the higher concentration, again as expected from the τ_D/τ_R ratios.

Four factors (stirrer speed, addition sequence, viscosity, and concentration) influencing chemical yield are included here. These as well as others have been modelled quantitatively.[15]

Experimental Section

Couplings of 1-naphthol (A) with diazotized sulfanilic acid (B) were conducted. The values of k_1 and k_2 in eq 1 and 2 and extinction coefficients for the spectrophotometric measurement of the product concentrations c_r and c_S are available.[7] The standard error of the yield of R was 0.35%.

Experimental conditions were as follows: 1-L laboratory beaker stirred by a 5 cm diameter turbine; initial 1-naphthol concentration 0.1071 mol m^{-3}; 20 °C, $\nu = 10^{-6}$ m^2 s^{-1}, $D = 8.5 \times 10^{-10}$ m^2 s^{-1}; stoichiometric ratio 1.05 mol of A per mol of B; volumetric ratio 1 volume of B added to 25 volumes of A in beaker; diazonium ion concentration 2.754 mol m^{-3} before mixing. Three sets of conditions were studied:

(a) pH 10. The 1-naphthol solution (500 mL) was buffered (Na_2CO_3 and $NaHCO_3$) to pH 10, and 20 mL of diazotized sulfanilic acid solution (pH $\simeq$ 2) was slowly added with stirring. Application of eq 4 gave $t_R \simeq 8 \times 10^{-4}$ s. At a stirrer speed of 75 rpm, the specific power input in the zone where reaction occurred was 1.1×10^{-3} W kg^{-1}. At the higher speed of 300 rpm,

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ϵ rose to 7.2×10^{-2} W kg^{-1}. Application of eq 3 gave $t_D = 0.28$ s (75 rpm) and 0.035 s (300 rpm). Measured yields of R were 84% (75 rpm) and 98.1% (300 rpm).

(b) pH 7. The 1-naphthol solution (500 mL) was buffered (KH_2PO_4 and Na_2HPO_4) to pH 7.0, and 20 mL of B was added as before. The value of t_R rose to 0.14 s, whereas t_D was unchanged. Measured yields were 99.4% (75 rpm) and ≃99.9% (300 rpm).

(c) pH 2–10. Acidic B (20 mL, pH 2) was first added rapidly to 500 mL of unbuffered A solution. Then 20 mL of Na_2CO_3/$NaHCO_3$ buffer solution, pH 10, was added over 4 min so that coupling could proceed. (In the context of homogeneous catalysis, this is equivalent to initiating reaction by addition of catalyst.) At 75 and 300 rpm, yields of R were ≃99.9%.

In all experiments, the total B content of R and S, namely, $c_R + 2c_S$, was within ±1% of the quantity of diazonium ion added. These good mass balances indicate satisfactory experiments and conformance with eq 1 and 2.

Registry No. A, 90-15-3; B, 305-80-6.

Synthesis of Hexacyclo[6.5.1.0^{2,7}.0^{3,11}.0^{4,9}.0^{10,14}]tetradeca-5,12-diene[1]

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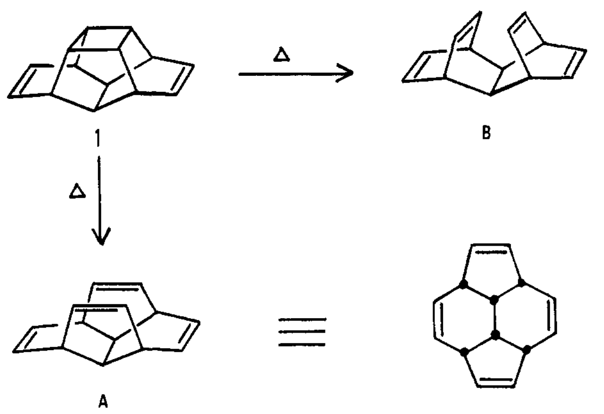
Received May 4, 1988

Polycyclic cage compounds that possess novel molecular frameworks have attracted considerable interest among organic chemists for many decades.[2] Recent attention to 1,3-bishomopentaprismane systems[3,4] and their applications to the construction of tetraquinane derivatives via thermal cleavage of the inherent cyclobutane ring[4] prompts us to report a new route to the title compound (1).[4d] Compound 1 is a C_{2v}-symmetric $(CH)_{14}$-diene, bearing structural resemblance to 1,3-bishomopentaprismane.[5] As shown in Scheme I, this diene holds promise as a potential precursor to hitherto unknown 1,8:4,5-dietheno-naphthalene A and/or 1,4:5,8-diethenonaphthalene B, since its strained cyclobutane ring may likewise be thermally induced to cleave.[4d]

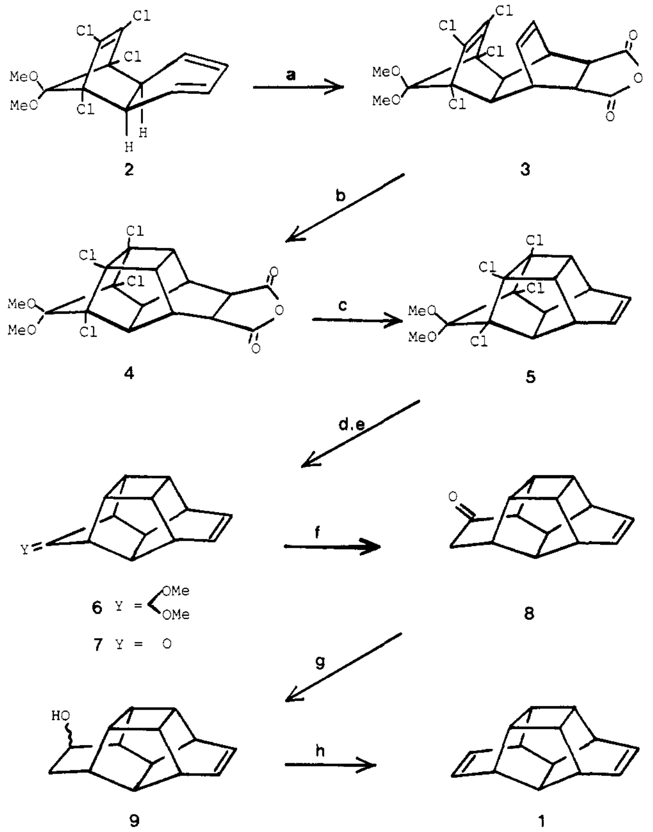
Our synthetic approach to diene 1 is outlined in Scheme II. The required *endo*-1,8,9,10-tetrachloro-11,11-dimethoxytricyclo[6.2.1.0^{2,7}]undeca-3,5,9-triene (2) is readily accessible from the Diels–Alder cycloadduct of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and *p*-benzoquinone in three steps.[6] Basically, the elaboration of tricyclic 2 into the framework of hexacyclic diene 1 consists of three key operations: (1) the addition of an acetylene equivalent to the diene unit of 2 by a Diels–Alder reaction; (2) photocycloaddition of two suitably oriented C=C double bonds to form the hexacyclic cage skeleton; and (3) the transformation of the bicyclo[2.2.1]heptane moiety to the bicyclo[2.2.2]octane substructure by ring expansion.

Although triene 2 is more stable than the unsubstituted parent hydrocarbon[7] toward retro-Diels–Alder reaction to yield benzene and the respective cyclopentadiene, it does show such a tendency in solution at temperatures above 100 °C.[6] The decision was therefore made to employ

Scheme I



Scheme II^a



^{a} (a) Maleic anhydride, benzene, 80 °C, 4 h (3, 98%); (b) acetone, light, 30 h (4, 98%); (c) electrolysis, Et_3N, Py, H_2O, CH_3CN (5, 60%); (d) Na, *t*-BuOH, THF, reflux, 36 h (6, 74%); (e) H_2O-THF, TsOH (catalytic amount), reflux, overnight (7, 92%); (f) CH_2N_2, Et_2O, 0–4 °C, 2 days (8, 96%); (g) $NaBH_4$, MeOH, room temperature, 10 min (9, 97%); (h) benzene, TsOH (catalytic amount), azeotropic reflux, 3 days (1, 80%).

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