ORGANIC
LETTERS

2004
Vol. 6, No. 6
1021−1024

Extractive Phase Vanishing Reactions with Dichloromethane, Perfluorohexanes, and Dibromoethane: Slow Addition in a Test Tube

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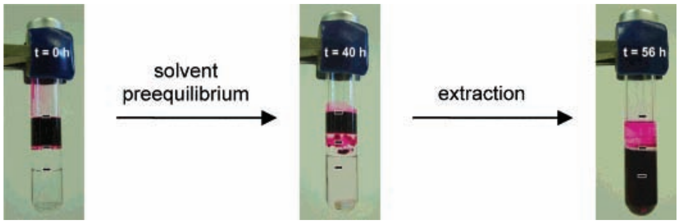
Received January 13, 2004

ABSTRACT



Partition coefficient measurements and experiments with a dye show that a new fluorous "phase vanishing reaction" described by Jana and Verkade occurs by an extractive mechanism. This mechanism is contrasted with the original diffusive phase-vanishing reactions introduced by Ryu and co-workers.

"Phase vanishing reactions" are a variant of fluorous triphasic reactions[1] recently introduced by Ryu and co-workers.[2] In these reactions, an organic or inorganic reagent in a first phase diffuses through a second fluorous phase to meet a reactant in a third organic phase. During the course of the reaction, the reagent phase disappears, hence the name. Very recently, Jana and Verkade[3] described new phase vanishing reactions that, on the surface, appear to be similar to earlier work. We show herein that these new reactions occur by a fundamentally different mechanism involving extraction rather than diffusion. Extractive phase vanishing reactions are of potential interest because they allow slow addition of one phase to another without the need for any apparatus such as an addition funnel or a syringe pump.

The bromination of cyclohexene is a typical example of a diffusive phase vanishing reaction,[2a] and is summarized in the upper part of Figure 1. Liquid bromine ($d = 3.12$ g/mL) is overlaid by FC-72 (perfluorohexanes, $d = 1.67$ g/mL), which is in turn overlaid by hexane ($d = 0.66$ g/mL) containing cyclohexene. A three-phase reaction mixture results. Though not miscible in FC-72, bromine is somewhat soluble and it diffuses up through the FC-72 phase to react with the cyclohexene. Toward the end of the reaction, the bromine phase vanishes leaving an organic phase with the product overlaying an FC-72 phase. The net result is a slow addition of bromine that is effected chemically by diffusion through FC-72 rather than mechanically. This type of reaction is not limited to reagents more dense than FC-72, and various halogenated reagents including BBr_3, $SnCl_4$, $POCl_3$, and $SOCl_2$ have been used.[2] However, it does appear to be limited to reagents with some solubility in FC-72 since insoluble reagents would not diffuse through the fluorous phase.

Recently, Jana and Verkade[3] describe phase vanishing reactions such as the oxidation of alkyl phenyl sulfides **1** shown in the lower part of Figure 1. A bottom phase of dibromoethane ($d = 2.18$ g/mL) containing *m*-chloroper-

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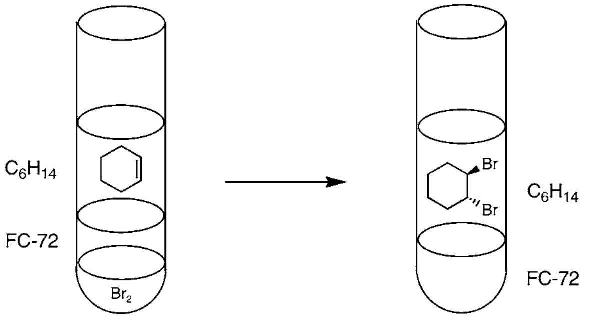
[1] (a) Nakamura, H.; Linclau, B.; Curran, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 10119−10120. (b) Luo, Z. Y.; Swaleh, S. M.; Theil, F.; Curran, D. P. *Org. Lett.* **2002**, *4*, 2585−2587.

[2] (a) Ryu, I.; Matsubara, H.; Yasuda, S.; Nakamura, H.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 12946−12947. (b) Matsubara, H.; Yasuda, S.; Ryu, I. *Synlett* **2003**, 247−249. (c) Nakamura, H.; Usui, T.; Kuroda, H.; Ryu, I.; Matsubara, H.; Yasuda, S.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1167−1169. (d) Iskra, J.; Stavber, S.; Zupan, M. *Chem. Commun.* **2003**, 2496−2497.

[3] Jana, N. K.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 3787−3790.

10.1021/ol0499248 CCC: $27.50

Bromination according to Ryu and coworkers:
Bromine diffuses up through the fluorous phase.



Oxidation according to Jana and Verkade:
How do two phases become one?
When/where does the reaction occur?

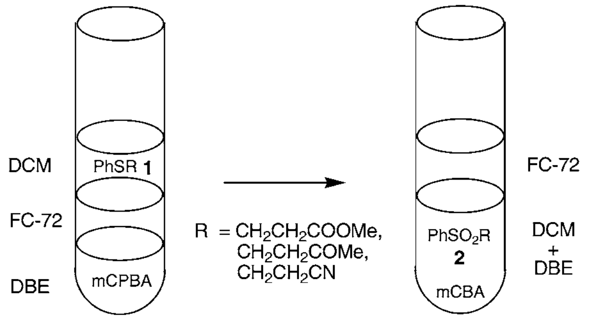


Figure 1. Top: Original diffusive phase vanishing reaction of Ryu and co-workers. Bottom: New phase vanishing reaction of Jana and Verkade.

benzoic acid (mCPBA) was overlaid with FC-72 ($d = 1.67$ g/mL), which in turn was overlaid with dichloromethane ($d = 1.33$ g/mL) containing the alkyl phenyl sulfide **1**. Over 2 days, the upper organic phase vanished resulting in an FC-72 phase overlaying an organic phase containing the alkyl phenyl sulfone **2** and *m*-chlorobenzoic acid (mCBA). This reaction is superficially similar to the bromination in Figure 1 because three phases reduce to two. But unlike bromine, neither alkyl phenyl sulfide **1** nor mCPBA is expected to have much solubility in FC-72. How does the alkyl phenyl sulfide get from the top to the bottom? And why does the top phase disappear? We addressed these questions by measuring partition coefficients and by observing the behavior of an organic dye in this triphasic system.

We determined the mole fraction of dichloromethane (DCM), dibromoethane (DBE), and FC-72 in biphasic systems of DCM/FC-72, DBE/FC-72, and FC-72/DCM+DBE (Table 1). GC-analysis showed that the FC-72 phase in a DCM/FC-72 biphasic system contains 13.60 mol % of DCM, but in a DBE/FC-72 biphasic system it contains only 1.64 mol % of DBE. FC-72 has a low solubility in both DCM and DBE (<1 mol %). When the nonfluorous phase is a 1:1 mixture of DCM and DBE, the FC-72 phase contains only 7.21 mol % of DCM and 1.15 mol % of DBE. Accordingly, DBE expels some DCM out of the FC-72 phase. Because of its higher solubility, DCM must diffuse down through the FC-72 phase in a triphasic system faster than DBE diffuses up.

Table 1. Molfraction of DCM, DBE, and FC-72 in Biphasic Systems of the Same Solvents at Room Temperature[a]

biphasic system	solvent	mole fraction [%]
DCM/FC-72	DCM in FC-72 phase	13.60 ± 0.06
	FC-72 in DCM phase	0.29 ± 0.03
FC-72/DBE	FC-72 in DBE phase	0.0034 ± 0.0002
	DBE in FC-72 phase	1.64 ± 0.07
FC-72/DCM+DBE	FC-72 in DCM/DBE phase	0.056 ± 0.020
	DCM in FC-72 phase	7.21 ± 0.22
	DBE in FC-72 phase	1.15 ± 0.11

[a] Determined by GC analysis with biphenyl as internal standard; standard deviations are based on three independent experiments.

To visualize the process of phase vanishing, we conducted a pair of experiments with a red dye (Sudan Red 7B) in triphasic systems containing 1.5 mL of DCM, 1.5 mL of FC-72, and 2.0 mL of DBE. In one experiment, the dye was added to the bottom DBE phase, while in the other, it was added to the top DCM phase. Only the bottom phase was stirred. Sudan Red 7B does not colorize FC-72, and we conclude that it is substantially insoluble and therefore cannot diffuse through the FC-72 phase during the time course of these experiments. When the dye was added to the bottom DBE phase, no color transport was observed. The top DCM phase remained colorless until it disappeared about 2.5 days later.

The experiment with the dye added to the top DCM phase was much more informative, and a photographic time course of this experiment over 56 h is shown in Figure 2. Three black and white bars mark the original phase boundaries for reference. The transformation of the three-phase system to a two-phase system occurred in two distinct stages. In a first slow stage (about 1.5 days), the volume of the top DCM phase decreased while the volume of the bottom DBE phase increased. During this phase, the dye remained fixed in the top DCM phase and there was no color in the bottom phase (a small amount of dye adheres to the wall of the tube, giving a pink tinge to the upper part of the FC-72 phase as it moves up to occupy the space vacated by the vanishing DCM phase).

After about 1.5 days, a second stage started and we began to observe small colored droplets break off from the top phase and creep down the wall of the test tube through the FC-72 to meet the lower phase. The photograph at 40 h shows the droplets creeping down, but the bottom phase is only very lightly tinged with color. By 42 h, there is now significant color in the bottom phase. At 54 h, both top and bottom phases were richly colored but roughly 40% of the volume of the top phase still remained. The second stage then accelerated and after 56 h, the top phase had vanished leaving a bottom colored phase containing most of the DCE and DBE and the top FC-72 phase that is colorless (although

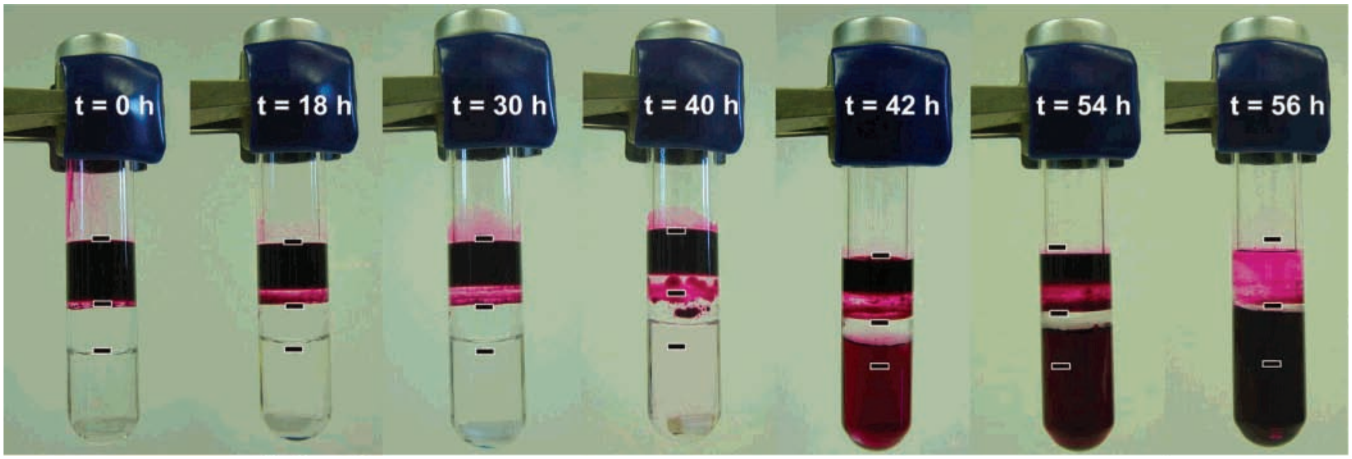


Figure 2. Photographic time course of a phase vanishing reaction over a period of 56 h (1.5 mL of DCM, 1.5 mL of FC-72, 2 mL of DBE, concentration of dye is 0.01 M, inner diameter of tube is 12 mm); original phase levels are marked. Sudan Red 7B was added to the top phase.

the residual dye on the walls of the tube gives it a pink cast in the photo).

These results provide significant insights into how Jana and Verkade's phase vanishing reactions are occurring. The initial three-phase system strives to reach equilibrium by diffusion of DCM and DBE through FC-72. Because DCM and DBE are miscible and because a 3/4 mixture is more dense ($d = 1.80$ g/mL[4]) than FC-72, a single final organic phase must result and this phase must be on the bottom. During the initial slower stage of the phase vanishing process (0 to about 36 h), the dichloromethane diffuses down through the FC-72 to the bottom phase more rapidly due to its higher solubility, while the DBE diffuses up more slowly due to its lower solubility. This results in a decrease in volume of the top phase and an increase in volume of the bottom phase. But since only the solvents are exchanging, the dye (insoluble in FC-72) remains in the top phase.

During this first "solvent preequilibrium" stage, the density of the top phase starts to increase because DCM is leaving and DBE is arriving. Sometime before 40 h, a critical point is reached when the density of the top phase near the interface with the fluorous phase equals and then gradually exceeds the FC-72 phase. During this second "extraction" phase, DCM/DBE droplets break off from the upper phase and creep down the walls to the lower phase, extracting the dye with them. This process gradually accelerates over 16 h until the remaining top phase and its dye sink through the middle fluorous phase into the bottom phase.

If this analysis is correct, then the density of the creeping droplets should be approximately equal to the density of the FC-72 phase. To test this hypothesis, we removed several droplets containing dye with a microliter syringe and determined their content by GC analysis to be about 80 mol % of DCM and 20 mol % of DBE. The calculated density[4] of this mixture is 1.56 g/mL, which is indeed very close to the density of FC-72 saturated with DCM and DBE (1.65 g/mL).

We conclude that reactions such as the oxidation of alkyl phenyl sulfide shown in Figure 1[3] occur by a similar extractive mechanism. After an initial preequilibrium of the DCM and DBE phases by diffusion of the solvents (not the reagents) through FC-72, a reaction stage begins as DCM/DBE droplets begin to break off from the top phase and thereby extract the alkyl phenyl sulfide to the bottom phase. Here it meets the mCPBA and is oxidized.

This extractive mechanism predicts that it should be possible to reduce the time of the initial solvent preequilibrium stage simply by adding some DBE to the top DCM phase to make it more dense. Likewise, it predicts that the bottom phase should vanish into the top if a solvent ratio is used such that the density of the final combined DCM/DBE phase is less than 1.65 g/mL (the density of FC-72 saturated with DCM/DBE). Both predictions were verified by experiments.

Three experiments were conducted similar to those above, except that the top DCM phase was doped with DBE to give densities of 1.4, 1.5, and 1.6 g/mL.[4,5] The experiment with pure DCM ($d = 1.33$ g/mL) was also repeated as a control. As before, the dye was placed in the top phase. The initial solvent preequilibrium phase for these three mixtures was significantly shortened, and one phase was formed in order of increasing top phase density (see the Supporting Information).

To induce the bottom phase to vanish, we overlaid 0.5 mL of DBE with 1.5 mL of FC-72 and 3.2 mL of DCM. Now the density of the combined organic phase (estimated

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[4] Ratha, D. C.; Samal, K. *Acoust. Lett.* **1988**, *12*, 29−34.

[5] Extreme care is needed to make the latter two three-phase mixtures because of the similarities of the densities of the top and middle phases. The times for phase disappearance depend on the stirring rate, so care was taken to ensure that this was as similar as possible for the three reaction mixtures.

at 1.41 g/mL[4]) is considerably less than FC-72. Since we expected the bottom phase to vanish, we added the dye there. After about 12 h, there were still three phases, but the volume of the bottom phase had increased significantly. There was no color in the top phase. After about 1 d, the upper organic phase was lightly colored and the lower organic phase was beginning to creep up the walls of the test tube through the FC-72 phase. After 1.5 d, the colored organic phases had merged to float on the clear FC-72 phase. In this case, the DCM is extracted down through the FC-72 to the DBE. As the DBE is diluted with DCM, the density of the bottom phase decreases and it begins to rise through the FC-72 to vanish as it meets the top phase.

In summary, all the experiments point to an extractive process for these phase vanishing reactions. The extraction is induced by solvent diffusion, which changes the densities of the organic phases and thereby induces one to rise or the other to sink. Like the original diffusive process, the new extractive process is, in effect, a slow addition without an addition funnel or a syringe pump.

However, the similarities end there. Diffusive processes are limited to reagents or reactants that are soluble in FC-72. However, the extractive process is driven by the solvents, not the reactants, so in principle any reagent that is insoluble in fluorous solvents but has suitable solubility in the two organic solvents can be subjected to this slow addition process. In contrast, the diffusive process possesses separation features that the extractive process does not. For example, in a diffusive process, a reagent containing an impurity less soluble in FC-72 than itself can be purified by diffusion through FC-72. But in the extractive process, all the components of both organic phases ultimately end up together, just as they would if an addition funnel were used to mix the two phases.

The potential generality of the extractive process recommends it whenever a slow addition process is needed (for control of heat evolution, to maintain low concentrations, etc.). The current process with DCM/DBE is limited by the extraction rate, which starts off slow and gradually accelerates to become relatively rapid. However, the rate of extraction can presumably be controlled by altering the solvent composition, volume, and area, so this early procedure should not be regarded as optimal.

Coupled with the mechanistic insights that have emerged from this work, the many possible combinations of organic reagent and solvent densities and solubilities in fluorous solvents provide broad opportunities for developing both diffusive and extractive phase vanishing reactions.

Acknowledgment. We thank the National Institutes of Health for funding this work.

Supporting Information Available: GC analysis details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0499248