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Availability and Reactivity of Concentrated Dimethyldioxirane Solutions in Solvents Other Than Acetone[1]

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Abstract: Four to five-fold increase in concentration or the possibility of isolation in "acetone-free" medium has become possible for dimethyldioxirane solutions in CH_2Cl_2, $CHCl_3$, CCl_4 and $CFCl_3$ by employing a simple work-up procedure which involved washings with phosphate buffer. This procedure allowed the kinetics of the epoxidation of *cis*-stilbene to be studied and which were shown to follow a simple second order rate law for all solvents studied. The relative reaction rates were as follows: acetic acid > $CHCl_3$ > acetone > CCl_4 > toluene > ethyl acetate. © 1997 Elsevier Science Ltd.

Despite the advantages of dimethyldioxirane (DMD) as an oxidation reagent in organic synthesis, *i.e.* ease of preparation and manipulation, high reactivity under neutral and mild conditions, feasibility of performing chemoselective transformations and simple work-up procedures, which account for the numerous synthetic applications described to date, its use in solution still presents some important drawbacks, particularly for large scale operations.[2] For instance, poor conversion yields are obtained in the generation of DMD from caroate and acetone in buffered medium, and the acetone solutions isolated following the distillation procedures reported so far are within the 80 mM concentration range.[3,4] Often, these solutions are too diluted for working at the multigram scale. Moreover, the distillation procedure makes it difficult to control the water contents of the DMD solution, which entails the use of drying procedures which are not always compatible with the stability of the oxidation reagent (*i.e*, use of molecular sieves [5]).

On the other hand, Adam et al. reported the isolation of "ketone free" TFMD solutions by means of the dilution of the TFMD distillate with CCl_4 or CH_2Cl_2 followed by water washings, which enabled the study of the thermal or photochemical initiated radical chain decomposition of this dioxirane. A similar methodology permitted the identification of the impurity present in the 1,1,1-trifluoroacetone (TFA) used for the generation of TFMD and which was responsible for the decomposition of this dioxirane.[6] Recently, Cerré et al. reported a related procedure for increasing the DMD concentration by using $CHCl_3$ as organic cosolvent and successive water washings to achieve 0.15 M solutions in 3:1 $CHCl_3$:acetone mixtures.[7] The different results obtained for DMD and TFMD could be explained by the better solubility of acetone in organic solvents and the higher propensity of TFA to form the corresponding hydrate.

In this context, we reported a preliminary communication regarding the obtention of more concentrated and "acetone-free" DMD solutions in chlorinated solvents starting from the DMD solution isolated by distillation. In contrast with the above procedures, we devised a strategy based on the higher lipophilicity of DMD with respect to acetone.[8] In the present paper, full experimental details on the above methodology, which

has been extended to other organic solvents, are presented. Furthermore, results on the kinetics of a DMD promoted oxidation, *i.e.*, the epoxidation of *cis*-stilbene, in solvents other than acetone, are reported for the first time.

Results and Discussion

The extraction of the DMD distillate (80 mM), after dilution with the same volume of water, with small amounts of CH_2Cl_2, $CHCl_3$, CCl_4, or $CFCl_3$, led to the quantitative incorporation of DMD into the organic fraction with a concomitant increase in its concentration (0.14-0.18 M, see Table 1). It is worth noting that the first CCl_4 extract exhibited a four-fold increase in DMD concentration (0.3 M), and that after two extractions, DMD concentration in either $CHCl_3$ or CCl_4 was over 0.2 M with recoveries higher than 65%. However, these solutions still contained a high amount of acetone (approx. 8-9 M). The extraction was less efficient for the case of $CFCl_3$ (approx. 55% overall recovery for the first two extracts).

Table 1. Concentration values of DMD and acetone after successive extractions into different halogenated solvents [a].

Solvent	Extract	DMD [b]		Acetone [c]
		Conc. (mM)	Recovery (%) [d]	Conc. (M)
CH_2Cl_2 [e]	$1^{st} + 2^{nd}$	193 ± 15	59.0 ± 3.5	8.5 ± 1.3
	3^{rd}	116 ± 3.8	27.1 ± 1.9	8.0 ± 1.2
	4^{th}	59.0 ± 2.1	11.4 ± 1.5	7.4 ± 0.9
$CHCl_3$	1^{st}	257 ± 34	28.9 ± 1.0	10 ± 0.5
	2^{nd}	179 ± 21	40.7 ± 1.0	9.4 ± 0.3
	3^{rd}	114 ± 31	21.8 ± 2.0	9.1 ± 0.1
	4^{th}	73 ± 30	10.8 ± 1.0	8.5 ± 0.3
CCl_4	1^{st}	307 ± 40	37.3 ± 2.9	9.3 ± 0.3
	2^{nd}	221 ± 40	29.0 ± 1.7	9.6 ± 0.1
	3^{rd}	151 ± 26	20.3 ± 2.1	8.3 ± 0.5
	4^{th}	101 ± 15	13.3 ± 1.1	7.9 ± 0.3
$CFCl_3$	1^{st}	226 ± 4	26.0 ± 1.0	n.d.
	2^{nd}	164 ± 8	29.5 ± 0.5	n.d.
	3^{rd}	132 ± 0	21.0 ± 0	n.d.
	4^{th}	95 ± 8	15.0 ± 1.0	n.d.

[a] For details see Experimental Section. Values are given ± s.d. (n = 3 for CH_2Cl_2, $CHCl_3$ and $CFCl_3$ and n = 4 for CCl_4). [b] Determined by iodometry. [c] Determined by ^1H NMR. [d] Calculated with respect to the DMD contents of the initial distillate. [e] In this case the first extract could not be separated and it was collected together with the second one.

At this point, our next objective was the isolation of "acetone-free" DMD solutions; *i.e.*, solutions where DMD concentration would be higher than that of acetone. The simple washing of the organic extracts with phosphate buffer [9] afforded the desired results (Table 2). Thus, in all cases lower acetone than DMD concentrations were obtained in the organic extract after a number of washings which depended upon the

solvent. The lowest number of washings corresponded to the CCl_4 and $CFCl_3$ extracts as expected from their lipophilicity, whereas the highest DMD concentration values were found in the CH_2Cl_2 extract (close to 0.35 M). Another interesting feature from data of Table 2 is that acetone concentration in the organic extracts only accounted for 1-2% with respect to its contents in the original DMD distillate. Moreover, the DMD fraction that had gone into the water washings could be easily recovered by reextraction.[10]

Table 2. Concentration values of DMD and acetone in different halogenated solvent extracts after washing with 0.01 M phosphate buffer (pH 7) [a].

Solvent	Initial DMD (mM)	Initial Acetone (M)	Washes with buffer (N)	DMD[b]		Acetone[c]
				Conc. (mM)	Recov.[d] (%)	Conc. (mM)
CH_2Cl_2	135 ± 7.0	8.0 ± 1.1	10	346 ± 30	45 ± 7.3	288 ± 32
$CHCl_3$	160 ± 20.5	9.2 ± 0.3	15	220 ± 31	37 ± 8.3	158 ± 73
CCl_4	199 ± 18.5	8.8 ± 0.3	3	268 ± 20	41 ± 7.0	155 ± 82
$CFCl_3$	148 ± 9.0	n.d.	3	231 ± 29	55 ± 2.0	170 ± 57

[a] For details see Experimental Section. Values are given ± s.d. (n = 3). [b] Determined by iodometry. [c] Determined by ^1H NMR. [d] Calculated with respect to the DMD contents of the initial distillate.

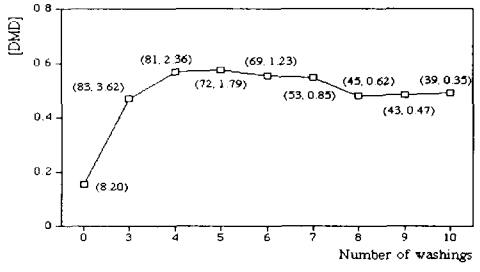


Figure 1. DMD Concentration obtained after successive washings of a CH_2Cl_2 extract (0.15 M) with 0.01 M phosphate buffer, pH 7. The percentage of DMD recovery and the corresponding molar acetone concentration remaining in the extract are given in parentheses.

Figure 1 shows the results obtained during the successive washings of the CH_2Cl_2 extract. These data can serve as an orientation for selecting the best DMD solution in view of the reaction where it is going to be employed. For instance, five phosphate buffer washes would afford DMD solutions close to 0.6 M (still over 70% DMD recovery), with acetone contents reduced to ca. 1.8 M, which can be suitable enough for a wide number of synthetic applications.

As anticipated, the drying of concentrated DMD solutions was easier and more reproducible than that observed for the 80 mM solutions in acetone. Furthermore, they exhibited a stability comparable to the conventional diluted ones, with the exception of those obtained in $CHCl_3$, due to the oxidation suffered by this solvent on storage for long periods of time.

On the other hand, the availability of DMD solutions in solvents other than acetone makes possible, for instance, the direct NMR monitoring of reactions in $CDCl_3$, which was formerly impractical due to the large presence of acetone. In this context, new spectroscopy data of the "acetone-free" DMD solution in CCl_4 could be registered; thus, subtraction of the absorption due to the residual acetone afforded the full IR spectrum of DMD, *i.e.*, 3006, 2979, 2937, 1448, 1382, 1350, 1328, 1243 and 1126 cm^{-1} (cf. data from ref. 2). The same procedure allowed the obtention of the UV-VIS spectrum, which showed a maxima at 302 nm (ε = 1850), with a tail extended up to 490 nm.[11]

Conversely, when the above washing procedure was assayed for DMD extracts in non-halogenated solvents, results were less encouraging. Either poor DMD recoveries or the impossibility of obtaining washed extracts with DMD concentrations higher than those of acetone (at the expense of losing most of the DMD),

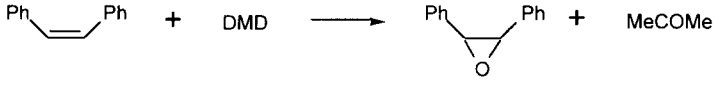
were systematically observed. An alternative approach involved the use of the $CFCl_3$ washed extracts; in this case, dilution of these extracts with the same amount of the selected non-halogenated solvent followed by elimination of the freon under vacuum at low temperatures afforded the desired DMD solutions (Table 3). As shown, the DMD concentration remained higher than that of acetone (for instance 174 to 19 mM for ethyl acetate), although part of the initial DMD was still lost, and low recovery yields were obtained for the case of acetic acid.

Table 3. Concentration values of DMD in different non halogenated solvents after dilution of a $CFCl_3$ washed extract with the desired solvent and further elimination of the freon by evaporation under vacuum [a].

Solvent	DMD		Acetone	$CFCl_3$
	Conc. (mM)[d]	Recovery (%)[c]	(mM)[b]	(mM)[c]
Toluene	155	42	70	38
Ethyl acetate	174	49	19	217
Acetic acid	82	29	60	93

[a] For details see Experimental Section. [b] Determined by ^1H NMR. [c] Determined by ^{19}F NMR. [d] Determined by iodometry. [e] Calculated with respect to the DMD contents of the initial distillate.

The availability of the above "acetone free" DMD solutions offered the possibility of studying solvent specific effects in the kinetics of DMD reactions in systems different from acetone or 1:1 acetone:solvent mixtures. It should be remarked that the kinetic studies on DMD previously reported had been carried out in acetone.[12-14] On the other hand, Murray and Gu studied the solvent influence in DMD promoted epoxidations by employing 1:1 acetone:solvent mixtures.[15] In our case, the epoxidation of *cis*-stilbene was chosen as the model reaction and the kinetics were performed in the halogenated and non-halogenated solutions described above, as well as in acetone for comparison purposes.



The kinetic data were obtained at 2°C under pseudo-first order conditions in which either DMD or *cis*-stilbene were in excess (5, 10, 15 and 20:1 molar ratios), by using $CHCl_3$, CCl_4 or acetone as solvents. For the cases of toluene, etyl acetate and acetic acid, only the study using DMD excess was carried out. For assays with excess of DMD, concentration of *cis*-stilbene was determined by HPLC analyses of an aliquot quenched by addition of a tributylphosphine excess. For experiments performed with excess of *cis*-stilbene, DMD concentration was monitored indirectly by HPLC determination of the remaining methyl phenyl sulfide after addition of a known excess of this compound to an aliquot of the crude reaction mixture (under the conditions used DMD reacts with this thioether to give only the corresponding sulfoxide). In both cases, nitrobenzene was employed as HPLC internal standard. Reactions were monitored until a 40% of conversion with a minimum of 12 aliquots well distributed to follow accurately the concentration changes. Plots of $\ln([\text{reagent.}] / [\text{reagent}]_0)$ *versus.* time gave straight lines with regression coefficients better than 0.99. The slopes of these lines corresponded to k_{obs} values and the plot of these k_{obs} *versus* the concentration of the reagent in excess also

afforded straight lines with regression coefficients better than 0.995. As representative examples, figure 2 shows the regression lines obtained for the kinetics in $CHCl_3$.

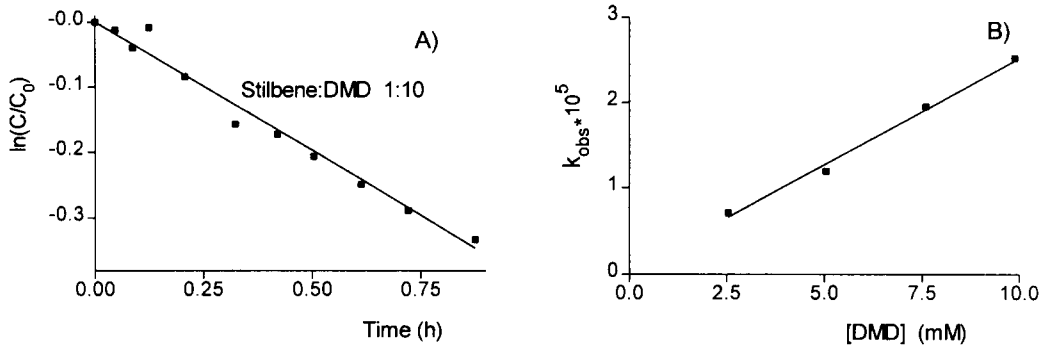


Figure 2. Kinetics of the DMD promoted epoxidation of *cis*-stilbene in $CHCl_3$ at 2 °C. a) Plot of ln ([*cis*-stilbene]/[*cis*-stilbene]$_o$) *vs.* time for the reaction with 10 fold excess of DMD, and b) plot of k_{obs} *vs.* [DMD] for the pseudo first order kinetics with different DMD excesses.

The experimental bimolecular rate constant values (k_2) derived from the above procedure are shown in Table 4. The satisfactory first order and k_{obs} plots obtained in the pseudo-first order kinetics for either DMD or *cis*-stilbene indicated that the epoxidation reaction followed simple second order kinetics (first order in each reagent). This assumption was reinforced by calculating the k_2 values using a second order equation to fit the experimental data for the case of moderate reagent excesses (5:1 molar ratios, data not shown).

Table 4. Second-order rate constants calculated from the pseudo-first order conditions with excess of DMD (k_2) or excess of substrate (k'_2) corresponding to the epoxidation of *cis*-stilbene by DMD in different solvents [a].

Solvent	k_2 $M^{-1}s^{-1}$ (x 10^3)	k'_2 $M^{-1}s^{-1}$ (x 10^3)
Acetone[b]	5.74	5.48
$CHCl_3$[b]	25.1	26.4
CCl_4[b]	1.75	1.91
Toluene[b]	0.94	n.d.
Ethyl acetate[b]	0.89	n.d.
Acetic acid[c]	189	n.d.
Acetone[c]	21.7	n.d.

[a] For details see Experimental Section. [b] Reactions were carried out at 2 °C. [c] Reactions were carried out at 20 °C.

However, the determination of the k_2 values for the cases where acetone was used as solvent was initially troublesome. Thus, the rate constant values obtained for the kinetics performed at 2 °C were significantly different, being $k'_2 > k_2$. These results suggested that a more complex process was occurring and that the use of acetone dried over 4A molecular sieves could be responsible for the above discrepancy. When the molecular sieves were replaced by drierite, consistent rate constant values were obtained. From these observations it can

be inferred that molecular sieves could induce acid catalysed reactions or decomposition of DMD and this effect could not be eliminated by simple filtration of the drying agent (cf. ref. 5). In this sense, the higher (although within the same order) value of k_2 for the epoxidation of *cis*-stilbene with DMD in acetone reported by Baumstark and Vasquez (40×10^{-3} $M^{-1}s^{-1}$, 23 °C),[12] with respect to that observed in our case (21.7×10^{-3} $M^{-1}s^{-1}$, 20 °C), could be attributed to the presence of acid or water traces.

The relative reaction rates derived from Table 4 are congruent with those reported by Murray and Gu[15] using 1:1 acetone:solvent mixtures, but with increased reactivity ratios. This difference is an obvious consequence of the absence of acetone in our case, which made possible the observation of the full solvent effect. In this context, as Murray and Gu concluded, it seems that the solvent property with the most influence on the kinetics of the DMD promoted epoxidation of *cis*-stilbene is its hydrogen bond donor capability (cf. acetic acid and $CHCl_3$ cases).

In summary, a simple work-up procedure has been developed for obtaining more concentrated solutions of DMD in solvents other than acetone. These results broaden the field of DMD application by facilitating, for instance, operations at larger scales or reactions in the presence of water sensitive reagents or products. Furthermore, the possibility of isolating pure dioxiranes can be envisaged if appropriate extraction solvents are used. On the other hand, the availability of these DMD solutions permitted the study of the solvent effect in a DMD promoted epoxidation. The results obtained showed that solvents with hydrogen bond donor capability increase the rate of this oxidation reaction. From this point of view, $CHCl_3$ could be considered the solvent of choice for DMD epoxidations; however, when the reaction rate is not a major problem, the concentration values obtained, the ease of dryness and the stability of the solutions make CH_2Cl_2 the solvent recommended for performing DMD oxidations.

Experimental Section

The IR spectra were recorded in film layer with a Bomen model MB120 apparatus. The NMR spectra (^1H, 300 MHz; ^{13}C NMR, 75 MHz) were recorded with a Varian Unity 300 spectrometer; they were performed in neutralized $CDCl_3$ solutions and chemical shifts are given in ppm downfield from tetramethylsilane for ^1H and deuteriochloroform for ^{13}C. The HPLC analyses were performed with a modular system formed by two Waters 510 pumps, a Merck column (LiChrospher 100 RP-18, 5 μm, 12.5 x 0.4 cm), and an Model 783 Applied Biosystems detector-gradient controller (UV detection).

Solvents used in the DMD preparation, extraction and kinetic studies were of analytical quality. All glassware and solvents used for the extraction and further washing operations were maintained in the freezer (-20°C) for 15 min before proceeding with the corresponding operation.

Extraction of DMD into halogenated solvents. The freshly distilled DMD solution (180 ml, 80 mM in acetone), prepared as described elsewhere,[3] was diluted with the same volume of water and extracted at 5 °C with the corresponding halogenated solvent (CH_2Cl_2, $CHCl_3$, CCl_4, or $CFCl_3$, 4 x 9 mL) using a thermostatized mechanical mixer. Extraction assays were performed in triplicate for the case of CH_2Cl_2, $CHCl_3$ and $CFCl_3$ and in quadruplicate for CCl_4. For the case of CH_2Cl_2, the first extract could not be separated and it was collected together with the second one. The DMD concentration was measured by iodometry and acetone concentration was determined by ^1H NMR using 1,1,2,2-tetrachloroethane as internal standard. Results obtained are shown in Table 1.

Washing of DMD-acetone extracts. Washes were performed at 5 °C by using 1.5 volumes (referred to the extract volume to be washed) of a 0.01M phosphate buffer, pH 7.0. The number of washings varied with each case (cf. Table 2 and figure 1). Assays were carried out by triplicate, and DMD and acetone concentrations were determined as above.

Extraction of DMD into non-halogenated solvents. A solution of the "acetone free" $CFCl_3$ extract (10 mL) was diluted with the same volume of the desired non-halogenated solvent (toluene, ethyl acetate or acetic acid), and the mixture was evaporated under vacuum at low temperature. For the cases of toluene and ethyl acetate, distillation started at a bath temperature of -35 °C (20 Torr). When the $CFCl_3$ concentration was approximately 0.7 to 1 M, the bath temperature was raised up to -20 °C until nearly all the halogenated solvent was removed (25 h overall time). For the case of acetic acid, the distillation started at 5-7 °C (195 Torr) and it was raised up to 14-16 °C to force the elimination of the halogenated solvent (40 h overall time). Results obtained are shown in Table 3.

Kinetic assays. Solvents were purified and dried as described in the literature.[16] Briefly, acetone was dried and distilled over drierite®. $CHCl_3$ and CCl_4 were distilled over P_2O_5. DMD solns. in acetone were pre-dried over $MgSO_4$ and then over drierite®, whereas DMD solns. in $CHCl_3$ and CCl_4 were dried over $MgSO_4$. *cis*-Stilbene used was freshly distilled. The reactions were carried out in at least duplicated runs at 2 °C (reaction bulk temperature) under argon atmosphere and they were monitored by HPLC (acetonitrile:water 60:40, 1 ml/min, λ=254 nm) using nitrobenzene as internal standard. For the experiments with excess of DMD, solutions containing 5, 10, 15 and 20 fold molecular excess of DMD over *cis*-stilbene were prepared (conc. of *cis*-stilbene and nitrobenzene were maintained constant in all cases). A 100 µl aliquot was taken periodically from the reaction flask and quenched by addition onto a 3 fold excess (with respect to the initial DMD) of tributylphosphine. The unreacted *cis*-stilbene was quantified by HPLC using a previously obtained relative response curve. A similar procedure was used for the kinetic experiments with excess of *cis*-stilbene, but in this case the reaction aliquot (100µl) was quenched by addition of a mixture of a known excess of methyl phenyl sulfide (600%) and the internal standard (nitrobenzene), followed by HPLC determination of the non-reacted sulfide.

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Notes and References

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9. Actually, water could be also used to wash the organic fractions, but phosphate buffer afforded better phase separations, particularly when working with CH_2Cl_2.
10. An assay was carried out by extracting a TFMD solution (9 ml, 0.52 M) with 1 ml CCl_4 portions. The results obtained for the three successive extracts, expressed as molar concentration of TFMD, percentage of TFMD recovery and molar concentration of the remaining TFA, were: i) 1.44, 27%, 2.18; ii) 0.29, 7%, 0.22; iii) 0.05, 1%, 0.15, respectively. Thus, the first extract was highly concentrated in TFMD although with low recovery yields; also interesting, most of the initial TFA could be removed concomitantly, which was not the case for the DMD extractions. This procedure, which is susceptible of optimization, could be particularly useful for specific studies, *i.a.*, reaction monitoring in NMR tubes.
11. The NMR absorptions of DMD in $CDCl_3$ were in agreement with previously published data (see Adam et al., *J. Org. Chem.*, **1987**, *52*, 2800). ^1H NMR: δ, 1.68 (s, 6 H). ^{13}C NMR: δ, 101.2, 22.8 ppm.
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