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UTILIZATION OF SULFOXIDES CONTAINING PYRIDINE NUCLEI AS A NEW TYPE OF PHASE TRANSFER CATALYSTS: IV.[1]

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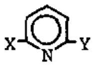
Abstract - Several sulfoxides containing pyridine nuclei were synthesized and their pKa values were determined. These sulfoxides were found to be good phase transfer catalysts which can promote alkylation reactions of phanylacetonitrile and benzyl methyl ketone with alkyl halides, and also can mediate the transport of alkali metal cations such as Li^+, Na^+, K^+, through the liquid-liquid membrane system.

Recently, a number of phase transfer catalyzed reactions have been widely utilized as a new useful procedure for various organic syntheses.[2] Generally, onium salts and crown ethers or cryptands have been used as the effective catalysts for these reactions in the two phase system. Meanwhile, t-amine,[3] t-amine oxides,[4] and a few sulfoxides,[5] have also been found to be neutral effective catalysts which promote such reactions as alkylation and the Michael type addition in the liquid-liquid or solid-liquid bi-phase system. Recently, we have found that some simple sulfoxides bound to pyridine nuclei can serve as good phase transfer catalysts which accelerate S_N2 type reactions of alkyl halides with several nucleophiles in the liquid-liquid or the solid-liquid two phase system.[1] These results suggest that these sulfoxides bound to pyridine nuclei can coordinate toward metal cations by both sulfinyl oxygen and nitrogen atoms of pyridine, thus dissolving the corresponding nucleophiles into the organic phase. Though the association constants or stability constants of these complexes between the sulfoxides and alkali metals, cannot be estimated quantitatively, one may conceive the pKa values of these sulfoxides[6] to represent roughly stabilities of the complexes of the sulfoxides with the metal cations, since there is a good correlation between the pKa values of the sulfoxides and their affinities toward metal cations. In order to estimate further the apparent stabilities of pyridylsulfoxides-metals complexes, Scheme 1



(I) X=H, Y=$S(O)CH_3$ (II) X=H, Y=$CH_2S(O)CH_3$
(III) X=Y=$CH_2S(O)CH_3$ (IV) X=H, Y=$CH_2S(O)CH_2Py$-2
(V) X=Y=$CH_2S(O)CH_2CH_2CH_2S(O)CH_3$
(VI) X=Y=$CH_2S(O)CH_2CH_2CH_2S(O)CH_2CH_2CH_2S(O)CH_3$

Table 1

X	Y	calcd. pKa	obs. pKa
H	H	---	5.25
H	CH_2SCH_3	---	5.40
H	$CH_2S(O)CH_3$	---	3.10
CH_2OCH_3	CH_2OCH_3	3.29	3.50
CH_2SCH_3	CH_2SCH_3	5.19	4.19
$CH_2S(O)CH_3$	$CH_2S(O)CH_3$	0.37	1.53

ion transfer experiments were carried out to confirm the chelating abilities of sulfoxides bound to pyridine.[7] Since these sulfoxides would have phase transfer catalytic activities, alkylation reactions of active methylene compounds with alkyl halides were carried out in the liquid-liquid two phase system in the presence of a small amount of sulfoxides (I)-(IV). This paper describes some physical properties and the catalytic activities of these sulfoxides containing pyridine nuclei in the alkylation of active methylene compounds.

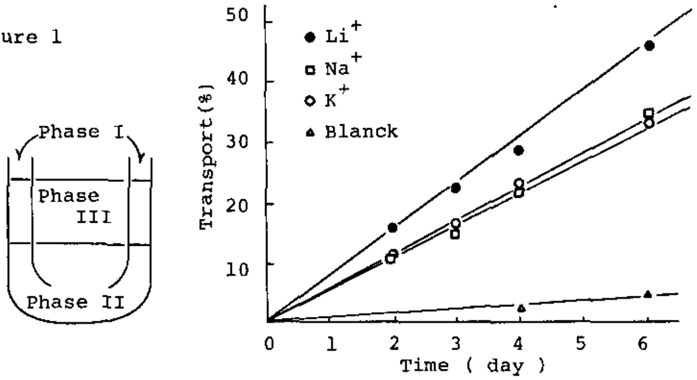
pKa Values of several pyridine derivatives having sulfenyl and sulfinyl moieties attached to either 2-, or 2,6-positions in the pyridine nuclei were determined by the ordinary UV spectral method in water at 25°C, as summarized in Table 1, together with the calculated values.[8] The observed pKa value of 2,6-bis(methylthiomethyl)pyridine is lower than the corresponding calculated value. This is considered to be due to a large steric effect of 2,6-bis(methylthiomethyl) groups which hinder the approach of proton to the nitrogen atom of pyridine ring. Although the steric bulkiness of 2,6-bis(methylsulfinylmethyl) groups should be higher than that of the corresponding methylthiomethyl groups, the observed pKa value of 2,6-bis(methylsulfinylmethyl)pyridine is larger than the corresponding calculated one. This is considered to be due to the powerful hydrogen-bonding ability of two sulfinyl groups and the nitrogen atom of pyridine, which would also chelate the alkali metal cations such as Li^+, Na^+, K^+. Both sulfinyl oxygen and pyridine nitrogen atoms are known to coordinate with these hard alkali cations. Meanwhile, the ion transfer experiments were carried out using alkali metal picrates mediated by sulfoxide (III) through an organic liquid membrane at 20°C. The apparatus used for this investigation is a double cyrindrical glass cell in which the outer aqueous phase I and inner aqueous phase III were separated by a methylene chloride solution containing sulfoxide (III) as shown in Figure 1. The amount of the cation transfer was determined by measuring the UV absorption of the picrate at 357 nm for both phases I and III by taking out 200 µl of solution by a microcyringe at proper time intervals. The result shown in Figure 1 clearly indicates that the sulfoxide (III) can mediate the transfer of metal picrates, since in the absence of the sulfoxide, the rate of transfer of Li^+ was immeasurably low. The cation selectivity of the sulfoxide (III) was also determined by comparing the amount of each of these metal cations extracted in phase III. Lithium cation was found to be transfered faster than sodium or potassium cation, revealing clearly that sulfoxide (III) can transfer preferentially such a relatively small cation as lithium.

Then liquid-liquid two phase alkylation reactions of active methylene compounds such as phenylacetonitrile and benzyl methyl ketone, and alkyl halides in 50% sodium hydroxide aqueous solution were carried out in the presence of (I)-(IV) to test the activities of these phase transfer catalysts. A few typical results thus obtained are shown in Table 2. Since the chelating effect would increase as the number of sulfinyl group increase (Octopus effect), pyridine derivatives having polysulfinyl groups attached at 2,6-positions have been synthesized[9] and their catalytic activities were also tested by the same reactions in the two phase systems. The results are shown in Table 3.

Inspection of the data in Tables 2 and 3 reveals the following characteristic features concerning for the reactions. 1) Although the reaction of phenylacetonitrile with methyl iodide proceeds without any of these catalysts, the yield of methylated product was only 12% after 24 hrs. Whereas several simple sulfoxides i.e., (I)-(IV), even in the 10 mol% amount, can promote this alkylation markedly affording the corresponding products in high yields. Therefore, such simple sulfoxides can be used as good phase transfer catalysts. 2) The reactions with several alkyl halides gave only the mono-alkylated products selectively.

3) Apparently, the catalytic activities of both sulfoxides (II) and (IV) are higher than that of either sulfoxide (I) or sulfoxide (III). 4) As we anticipated

Figure 1



Phase I : Tris Buffer, pH=8.33(5 ml), [Metal Picrate]=2×10^{-4}M

Phase II : methylene chloride(10 ml), [Sulfoxide(**III**)]=2×10^{-2}M

Phase III : Tris Buffer, pH=8.33(5 ml)

Table 2 Liquid-liquid two phase alkylation catalyzed some sulfoxides containing pyridine nuclei

$$PhCH_2X + R\text{-}I \xrightarrow[\text{50\%-NaOHaq., r.t.}]{\text{Catalyst}^{a)}} PhCH(R)X + NaI$$

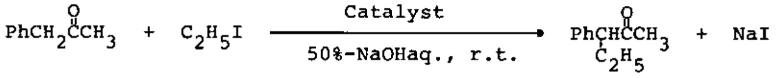
X	R-I	Cat.	Time(h)	Yield(%)[b)]	X	R-I	Cat.	Time(h)	Yield(%)[b)]
CN	CH_3I	**I**	24	73[c)]	$COCH_3$	CH_3I	**I**	2	96
"	"	**II**	24	79[c)]	"	"	**II**	2	96
"	"	**III**	24	70[c)]	"	"	**III**	2	93
"	"	**IV**	24	83[c)]	"	"	**IV**	2	100
"	C_2H_5I	**I**	24	85	"	C_2H_5I	**I**	3	83
"	"	**II**	24	93	"	"	**II**	3	97
"	"	**III**	24	73	"	"	**III**	3	75
"	"	**IV**	24	90	"	"	**IV**	3	95
"	C_4H_9I	**I**	24	54	"	C_4H_9I	**I**	7	77
"	"	**II**	24	88	"	"	**II**	7	89
"	"	**III**	24	70	"	"	**III**	7	63
"	"	**IV**	24	89	"	"	**IV**	7	91

a) 10 mol% Amount of sulfoxides were used.

b) by g.l.c. analysis

c) 5-10% Yield of dialkylated product was detected.

Table 3 Comparison of numbers of sulfinyl groups attached to pyridyl 2,6-positions using two phase alkylation



$$\mathrm{PhCH_2\overset{O}{\overset{\|}{C}}CH_3} + \mathrm{C_2H_5I} \xrightarrow[\text{50\%-NaOHaq., r.t.}]{\text{Catalyst}} \mathrm{Ph\underset{C_2H_5}{CH}\overset{O}{\overset{\|}{C}}CH_3} + \mathrm{NaI}$$

Catalyst	(mol%)	Time(h)	Yield(%)[a]
III	10.0	3.0	75
V	5.0	2.0	92
VI	5.0	1.5	94
VI	1.0	4.0	92

a) by g.l.c. analysis

pyridine derivertives having polysulfinyl chains attached to 2,6-positions have higher catalytic activities than those of sulfoxides (I)-(IV). Especially, sulfoxide (VI) is the most effective catalyst, since when only 1.0 mol% amount of this sulfoxide was used as catalyst, the reaction finished within 4 h at room temperature, affording mono-alkylated product selectively and quantitatively. One advantage of these sulfoxides bound to pyridine is that they can be recovered very easily and quantitatively by shaking with any mineral acid. Therefore, these sulfoxides can be used as new phase transfer catalysts, and are useful in organic syntheses.

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8. The calculated pKa values were obtained by using the Taft's equation, namely $pka=\rho\Sigma\sigma^*$ in where σ^* values were determined by plotting the known pKa values of 2-substituted pyridines. Thus, ρ is -4.4 and σ^* values are CH_3OCH_2-, +0.241; CH_3SCH_2-, 0.001; $CH_3S(O)CH_2$-, +0.521; respectively.
9. (**V**): mp 130-140°C; IR(KBr) 1043 cm^{-1}(S→O); ^{1}H-NMR($CDCl_3$) δ 2.08-2.66(4H, m, 2xCH_2C), 2.58(6H, s, 2xCH_3), 2.68-3.10(8H, m, 4xCH_2S), 4.08 and 4.19(4H, J_{AB}=12 Hz, 2xCH_2Py), 7.26(2H, d, J=8 Hz, 2xβ-H), 7.66(1H, t, J=8 Hz, γ-H).

   (**VI**): mp 132-143°C; IR(KBr) 1040 cm^{-1}(S→O), ^{1}H-NMR($CDCl_3$) δ 2.08-2.66(8H, m, 4xCH_2C), 2.58(6H, s, 2xCH_3), 2.68-3.08(16H, m, 8xCH_2S), 4.08 and 4.19(4H, J_{AB}=12 Hz, 2xCH_2Py), 7.26(2H, d, J=8 Hz, 2xβ-H), 7.66(1H, t, J=8 Hz, γ-H).

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