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TETRAZOLES.

20.* TETRAZOLIUM SALTS IN INTERPHASE CATALYSIS

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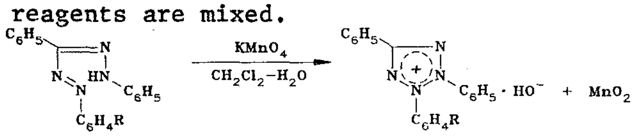
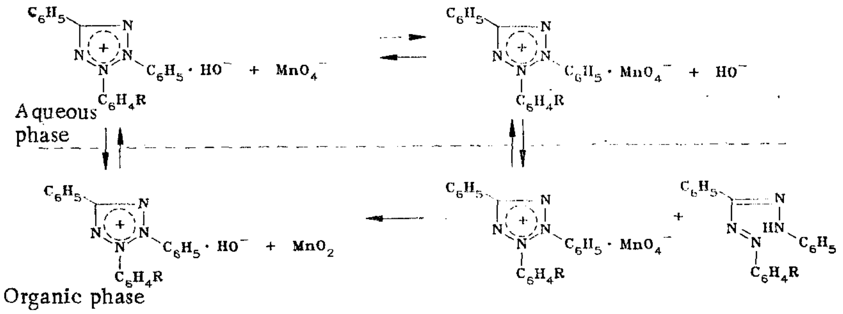
Oxidation of substituted triaylformazanes by potassium permanganate in a two-phase organic solvent—water system in the presence of catalytic amounts of tetrabutylammonium bromide gives the corresponding tetrazolium salts, which are interphase transfer catalysts in oxidation, alkylation, and esterification. From distribution coefficient data it is concluded that 2,3,5-triphenyltetrazolium chloride has less catalytic activity than 2,5-diphenyl-3-(m-nitrophenyl)-tetrazolium bromide.

The substantial interest in tetrazolium salts in recent years is related to their use in medicine [2, 3] and in new silver-free photographic materials [4]. The principal method for synthesizing tetrazolium salts is the oxidation of formazanes. In the numerous variants of this method the oxidants are alkyl nitrites [5], lead tetracetate [6], silver nitrate [7], bromine [8], and other reagents [9]. Nevertheless because of the unsatisfactory reproducibility of the results it is difficult to give preference to any of those oxidants. It was therefore of interest to study formazane oxidation by interphase catalysis. For this purpose substituted arylformazans were chosen to be oxidized at 25° by potassium permanganate in a two-phase organic solvent—water system in the presence of tetrabutylammonium bromide. Under these conditions formazane oxidation is rapid and is finished within 15-20 min after the reagents are mixed.





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*Communication 19, see [1].

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TABLE 1. Distribution Coefficients of Tetrazolium Salts in Organic Solvent—Water System, 25°

Organic solvent	$c_{tot} \cdot 10^3$ mole/liter	$c_o \cdot 10^3$ mole/liter	$c_w \cdot 10^3$ mole/liter	$K_d \cdot 10^2$
	2,3,5-Triphenyltetrazolium chloride			
Methylene chloride	1,037	0,018	1,022	1,50
	1,655	0,031	1,624	1,90
	1,896	0,037	1,859	1,96
	2,980	0,073	2,907	2,51
	8,607	0,415	8,192	5,10
	12,22	0,600	11,620	5,16
Chloroform	1,850	0,049	1,801	2,72
	2,212	0,062	2,150	2,88
	3,209	0,101	3,108	3,25
	3,780	0,129	3,651	3,53
	5,743	0,240	5,503	4,36
	8,001	0,401	7,600	5,28
	1,5-Diphenyl-3-(m-nitrophenyl)tetrazolium bromide			
Methylene chloride	1,186	0,073	1,113	6,9
	3,479	0,459	3,020	15,3
	6,328	1,237	5,091	24,4
	6,690	1,358	5,332	25,5
	8,709	2,071	6,638	31,3
	9,811	2,501	7,310	34,2

Later it will be shown that triarylformazane oxidation in a two-phase organic solvent—water system proceeds in the absence of an interface transfer catalyst (tetrabutylammonium bromide) and the yields of tetrazolium salts are not changed. Evidently in this case the oxidation proceeds as follows. First, as a result of reaction at the interface a small amount of tetrazolium salt forms, which then fills the role of interphase transfer catalyst (see scheme).

The following facts support this assumption. When a formazane suspension is stirred with aqueous potassium permanganate for 6-8 h, no reaction occurs. But when methylene chloride, chloroform, or any other water-immiscible solvent that will dissolve formazane is added to the reaction mixture, formazane oxidation is complete in 15-20 min. Another important demonstration of the ability of tetrazolium salts to transfer inorganic ions from the aqueous phase to the organic phase is the formation of a so-called raspberry-colored solution of methylene chloride. When 2,3,5-triphenyltetrazolium chloride is added to a two-phase methylene chloride—aqueous potassium permanganate system, the previously colorless methylene chloride turns a raspberry color, because of the transfer of permanganate anion from the aqueous phase to the organic. The solution of 2,3,5-triphenyltetrazolium permangante thus obtained can be used as an efficient reagent for the oxidation of various organic substrates. E. g., in the oxidation of benzyl alcohol by potassium permangante at 25° in a methylene chloride—water system in the presence of catalytic amounts of 2,3,5-triphenyltetrazolium chloride, benzaldehyde is formed in 93% yield within 1 h after the reagents are mixed.

It should also be noticed that triaryltetrazolium salts show catalytic activity in other interphase reactions. For example, in a methylene chloride—1% aqueous sodium hydroxide system at 25° no reaction occurs between 5-phenyltetrazole and methyl iodide. But when catalytic amounts of 2,3,5-triphenyltetrazolium chloride are added, the isomeric 1-methyl- and 2-methyl-5-phenyltetrazoles form in 50% yield within 3 h. However under the same conditions ethyl benzoate forms from benzoic acid and ethyl bromide at a much slower rate; according to TLC data the reaction is complete at room temperature only after 4 days. Thus it is evident that tetrazolium salts can catalyze reactions that take place at an interface. But for a broader estimate of the catalytic activity of tetrazolium salts, additional information is needed concerning the behavior of these compounds in organic solvent—water systems.

It is known [10] that to a first approximation the efficiency of an interphase transfer catalyst can be estimated from its distribution coefficient between organic and aqueous phases. On the other hand it must be kept in mind that the distribution coefficient is an indirect index of catalyst efficiency in any reaction. In a stricter approach it is necessary to consider the distribution coefficient of the ion pair $Q^+ Nu^-$, where Q^+ is the quaternary cation catalyst and Nu^- is the anionic substrate. In the present work the efficiency of tetrazolium salts as interphase transfer catalysts was estimated with 2,3,5-triphenyltetrazolium chloride

TABLE 2. 2,5-Diphenyl-3-(R-phenyl)tetrazolium Salts

R	Anion	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %*
			C	H	N		C	H	N	
p-CH_3	ClO_4^-	290—292	58,1	4,0	13,8	$C_{20}H_{17}ClN_4O_4$	58,2	4,2	13,6	50 (MC)
H	Cl^-	237—238	67,7	4,9	16,4	$C_{19}H_{15}ClN_4$	68,2	4,5	16,7	62 (C)
p-Br	ClO_4^-	236—237	47,5	3,3	12,0	$C_{19}H_{14}BrClN_4O_4$	47,8	2,9	11,7	61 (MC)
p-Cl	ClO_4^-	270—273	52,9	3,5	13,2	$C_{19}H_{14}Cl_2N_4O_4$	52,7	3,3	12,9	53 (MC)
m-NO_2	Br^-	228—229	53,8	3,4	16,5	$C_{19}H_{14}BrN_5O_2$	53,8	3,3	16,5	45 (C)
p-NO_2	ClO_4^-	264—266	51,8	3,2	16,1	$C_{19}H_{14}ClN_5O_6$	51,4	3,2	15,8	39 (MC)

*Organic phase: MC, methylene chloride; C, chloroform.

(I) and 2,5-diphenyl-3-(m-nitrophenyl)tetrazolium bromide (II). Distribution coefficients were determined for I in the methylene chloride—water and chloroform—water systems, and for II in methylene chloride—water. Tetrazolium salt concentration was determined in water by UV spectrophotometry. The electron spectra of I and II in water contain distinct absorption maxima at 247 (ε = 25,600) and 249 (ε = 31,100) respectively. Thus the concentration of the test compounds can be determined with a high degree of precision. Our data are shown in Table 1.

As Table 1 shows, the distribution coefficient $K_d = c_o/c_w$ (where c_o is the concentration of all forms of salt in the organic solvent, and c_w is the concentration of all forms of salt in water) of these tetrazolium salts depends significantly on the total salt concentration in the system (c_{tot}), and there is a linear relationship between log K_d and log c_{tot}. The corresponding linear regression equations are

$$\log K_d = (0.54\pm0.03)\log c_{tot} - (0.23\pm0.08) \qquad (1)$$
$$(r=0.99,\quad n=6,\quad s=0.03),$$

$$\log K_d = (0.45\pm0.03)\log c_{tot} - (0.34\pm0.08) \qquad (2)$$
$$(r=0.99,\quad n=6,\quad s=0.02),$$

$$\log K_d = (0.76\pm0.01)\log c_{tot} + (1.06\pm0.01) \qquad (3)$$
$$(r=0.99,\quad n=6,\quad s=0.01).$$

In the general form such relationship are typical of salts that dissociate in both aqueous and organic phases, but for organic solvents with low dielectric constants the salt dissociation in the organic phase can be neglected. In that case, from the dependence of $\sqrt{c_o}/c_w$ on K_d we can estimate the dissociation constant of the salt in water [11]. Indeed there is a linear relationship between $\sqrt{c_o}/c_w$ and K_d, but at a salt concentration in the organic phase of $\sim 10^{-3}$ M and less (Table 1) there is significant deviation from linearity. The reason is that at low concentrations, salt dissociation in the organic phase must not be neglected. Therefore such data were not taken into account in the calculations. The respective linear regression equations are:

$$\sqrt{c_o}/c_w = (-30.96\pm5.80)K_d + (3.87\pm0.21) \qquad (4)$$
$$(r=0.95,\quad n=5,\quad s=0.19),$$

$$\sqrt{c_o}/c_w = (-36.90\pm5,81)K_d + (4,50\pm0,23) \qquad (5)$$
$$(r=0.97,\quad n=5,\quad s=0.11),$$

$$\sqrt{c_o}/c_w = (-1.47\pm0.20)K_d + (7.32\pm0.06) \qquad (6)$$
$$(r=0.97,\quad n=5,\quad s=0.03).$$

The dissociation constants of 2,3,5-triphenyltetrazolium chloride in water calculated by Eqs. (4) and (5) are $8.51\cdot10^{-3}$ and $6.04\cdot10^{-3}$, respectively; the dissociation constant of 2,5-diphenyl-3-(m-nitrophenyl)tetrazolium bromide in water, according to Eq. 6, is $9.29\cdot10^{-2}$.

Thus from the distribution coefficient data it can be concluded that 2,5-diphenyl-3-(m-nitrophenyl)tetrazolium bromide ought to be a more efficient interphase catalyst than 2,3,5-triphenyltetrazolium chloride. However it should be noted that catalyst efficiency in interphase reactions is also determined by other factors, and for a complete evaluation of the catalytic activity of tetrazolium salts, additional studies are necessary.

EXPERIMENTAL

UV spectra were obtained on a SF-16 spectrophotometer; analytical concentration of tetrazolium salts, $1 \cdot 10^{-5}$ M.

2,3,5-Triphenyltetrazolium Chloride (I). To a solution of 1 g (3.5 mmole) of triphenylformazane in 35 ml of chloroform was added a solution of 0.54 g (3.5 mmoles) of potassium permanganate in 35 ml of water at 25°. The reaction mixture was stirred for 20 min, 20 ml of 5% HCl was added, and stirring was continued for another 30 min. Manganese dioxide was filtered off and washed on the filter with water (2 × 10 ml); the washings were combined with the filtrate and the aqueous layer was separated. The chloroform layer was extracted with water (2 × 10 ml), the extracts were combined with the water layer, and the water was evaporated in vacuum. The residue was recrystallized from 10% CHl.

2,5-Diphenyl-3-(m-nitrophenyl)tetrazolium bromide (II) was obtained analogously to I. To isolate the salt the aqueous solution was evaporated to 10 ml and treated with a solution of 0.4 g of potassium bromide in 5 ml of water. The precipitate of II was filtered off and recrystallize from 50% ethyl alcohol.

2,5-Diphenyl-3-(p-bromophenyl)tetrazolium perchlorate was obtained analogously to I. To isolate the salt, 1 ml of 70% perchloric acid was added to the aqueous solution. The precipitated tetrazolium salt was filtered off and washed on the filter with boiling water (3 × 50 ml).

Other tetrazolium salts were obtained analogously (Table 2).

Determination of Distribution Coefficients. Experiments were carried out in a thermostated reactor (25 ± 0.1°) equipped with a turbine stirrer at a constant rpm (700 $\min^{-1}$). Equal volumes (20 ml each) of organic solvent and an aqueous solution of tetrazolium salt were stirred for 30 min. After the layers separated the concentration of tetrazolium salt was determined in the aqueous layer as the average of 3-5 replicate measurements. The data were treated by the methods of mathematical statistics [12].

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