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Hydrotropes as effective reaction Media for the Synthesis of Rafoxanide

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ABSTRACT

The paper describes the synthesis of Rafoxanide. It is used as anthelmintics that expel parasitic worms (Helminthes) from the body or kill them. A traditional remedy of this type is often called a vermifuge. The synthesis of Rafoxanide was carried out using four different hydrotropes. The effect of various hydrotropes on yield, rate constant and activation energy at various temperatures and concentrations are studied.

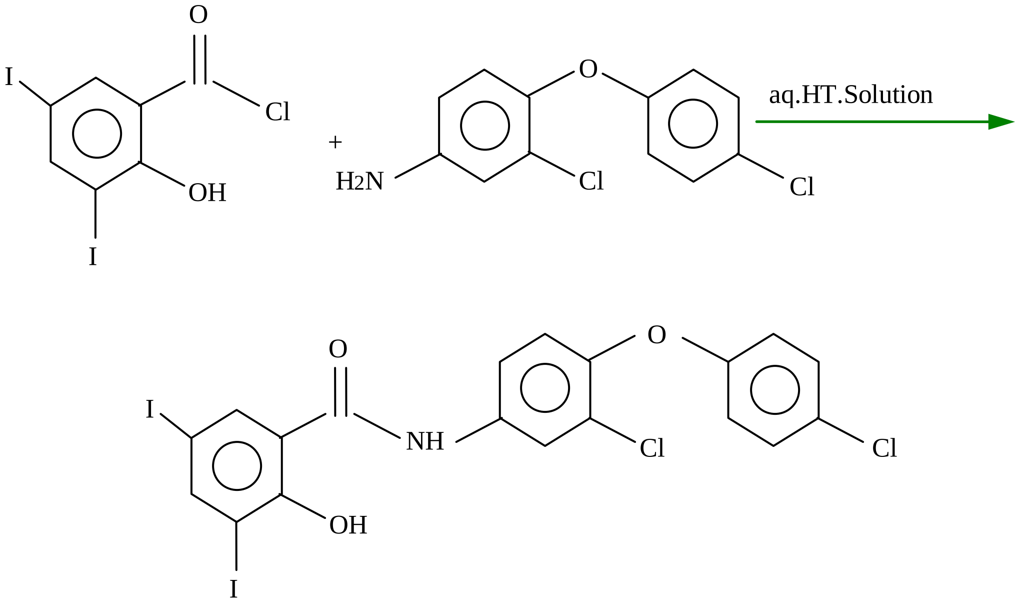
Keywords: Hydrotropes, Xylene sulfonic acid (XSA), Cumene sulfonic acid (CSA), (n-BBSA): n-Butyl benzene sulfonic acid (n-BBSA), Isobutyl benzene sulfonic acid (I-BBSA), ^{1}H NMR, IR.

INTRODUCTION

Carl Neuberg conceptualized one such area in the form of hydrotropy almost a century ago. This exciting field sprung back into the chemical limelight, after a dormancy period of about eight decades and today is regarded as one of the frontiers in the field of applied organic chemistry. The pioneer Carl Neuberg baptized this phenomenon as Hydrotropes or Hydrotropism[1,2]. It is enhancement in the solubility of organic molecules in water, which otherwise are sparingly soluble or totally insoluble[3,6]. Hydrotropes or hydrotropic agents are defined as the compounds which possess the property of solubility enhancement of other compounds. Hydrotropes are surface active, highly water soluble organic salts, which when present at high concentration, can solubilise the otherwise insoluble or sparingly soluble organic compounds in water. Hydrotropes can be differentiated from common surfactants in terms of their hydrofobicity i.e. hydrotopes are poorly hydrophobic as compared to surfactants. The performance of hydrotropic solutions was found to be efficient, usually at higher concentration ranging from 0.2M to 1.0M. At concentration above 1.0M 'salting out effect' is observed.

In the present study the researchers intend to study the aromatic hydrotropes, especially the aromatic sulphonates which are considered to be superior to the aliphatic counterparts as they are thermally stable and have higher affinity. Hydrotrops are readily biodegradable in water under areobic conditions studies with cummene , tolune and xylene[7]. This ecofriendly methodology where Hydrotropes demonstrate a low level of toxicity on aquatic life Xylene and cumene sulfonates (ammonium , calcium and sodium salts) have no acute toxicity towards fish and invertebrates at concentrations tested (> 318 mg/L)[7].One of the great advantage of Hydrotopes is the reusability of solvent media without operations such as distillation etc. there by reducing operation cost, Hence it is an alternate media to organic solvents include water, ionic liquids, supercritical solvents ,hydrotropic solutions etc[8-11]. Hydrotropic solutions are non toxic shows no hazards of flammability hence consider as safer solvents. The compatibility of aqueous hydrotropic solutions as safer solvents for microwave assisted reactions has been studied[12]. Bromohexine Hydrochloride is an oral mucolytic agent used in the treatment of resperator disorders associated with viscid or excessive mucus[13]. So there is now a realization that more benign chemical synthesis is required as an integral part of developing sustainable technologies[14]. Efforts have been made to carry out studies on hydrotropes as effective reaction media for the certain organic reactions.

Reaction Scheme:



Synthesis of N-[3-chloro-4-C4-chlorophenoxy) phenyl]-2-hydroxyl -3, 5 - diiodbenzamide

The reaction of 3, 5–Diiodosalicylolyl chloride with 4–amino–2–Chloro–4–chlorodiphenyl ether in aqueous hydrotropic solutions yields the titled product. Hydrotropes used are: 1) (XSA): Xylene sulfonic acid, 2) (CSA): Cumene sulfonic acid, 3) (n-BBSA): n-Butyl benzene sulfonic acid, 4) (I-BBSA): Isobutyl benzene sulfonic acid

MATERIALS AND METHODS

In a 250 cm^3 3-necked flask fitted with a stirrer, thermo well and an addition funnel were added (0.01 moles) of 3, 5–diiodosalicylolyl chloride at room temperature followed by the addition of (0.01 moles) of 4-amino–2–Chloro–4–chlorodiphenyl ether was dissolved in aqueous hydrotropic solution of Xylene sulfonic acid. The reaction mixture was stirred at 303K and 323K for 8 hours. The progress of the reaction was monitored by TLC for the completion of reaction.

On cooling at room temperature the product precipitated out from the reaction medium and was washed with demineralised water in order to make it free from the traces of the hydrotropic solution adhering to it. The product was then purified and dried in a vacuum drier. The qualitative estimation of the product was done by TLC using the following system. Chloroform: Methanol (9:1)

The product was found to be pure without the traces of either of the starting materials. This is because of the selective solubilization of the reactants which helps to maintain them in the hydrotropic medium. The product N–[3–Chloro–4–(4–Chlorophenoxy) phenyl]–2–hydroxy–3, 5–Diiodobenzamide has a melting point of 168 - 170°C. Similar reactions were carried out using other Hydrotropes such as Cumene sulfonic acid, n-Butyl benzene sulfonic acid and Isobutyl benzene sulfonic acid. The concentration range utilized for these Hydrotropes was from 0.2 Mol/dm^3 to 1.0 Mol/dm^3. Higher concentrations of Hydrotropes were avoided due to the salting out of the Hydrotropes from the water which is an inherent property of these salts.

Characterization Data:

^{1}HNMR δppm	δppm.
^{1}HNMR (CD3OD, 300MHz) δppm	6.8 - 8.4 (m, Ar - H).
IR υ max cm-^{1}.	**IR values cm-^{1}.**
IR (KBr) υmax cm-^{1}	3361 (- OH, - NH), 1622 (> C = 0), 1535, 1481 (Ar - H), 810, 784 (Cl, I).

Melting Range = 168 - 170°C., ***rf*** = 0.6 (Chloroform: Methanol (9:1)). Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Varian s pectrometer and IR spectra on a Shimadzu FT/IR-4200 instrument.

Column chromatography: For column chromatography 100 – 200 mesh Acme grade silica gel was used. The crude reaction mixture was concentrated under reduced pressure to yield crude mass which was preadsorbed on silica gel and purified by column chromatography with increase in concentration of Ethyl acetate in Petroleum ether. The fractions having similar 'R_f" values were pooled together, concentrated and subjected for characterization using various spectroscopic techniques.

Thin layer chromatography: TLC plates were prepared using silica gel G (ACME, BOMBAY). Pet. Ether: EtOAc (85 : 15) was used as the solvent system.

Radial chromatography: The circular glass plates of thickness 1 mm were prepared by using silica gel (PF254, E. MERCK, 50 g) in cold distilled water (105 ml). For elution, gradually increasing concentrations of EtOAc in pet ether were employed.

RESULTS AND DISCUSSION

The effect of hydrotrope concentration and temperature on the yield of N – [3 – Chloro –4 – (4 – Chlorophenoxy) phenyl] – 2 – hydroxy – 3,5– diiodobenzamide (Rafoxanide)was depicted in Table IX a-d.

Table - IX a. (Hydrotrope Used: XSA)

Hydrotropes Concentration Mole/dm^3	% Yield Obtained & Time in hours	
	303 K (8hrs)	323 K (8hrs)
0.2	11	17
0.4	13.3	19.1
0.6	16.6	23
0.8	30	36
1.0	50.7	58

Table - IX b.(Hydrotrope Used: CSA)

Hydrotrope Concentration Mole/dm^3	% Yield Obtained & Time in hours	
	303 K (8hrs)	323 K (8hrs)
0.2	14	20
0.4	18	22.7
0.6	20.7	25.1
0.8	34	39.2
1.0	55.7	68.8

Table - IX c.(Hydrotrope Used: n-BBSA)

Hydrotropes Concentration Mole/dm^3	% Yield Obtained & Time in hours	
	303 K (8hrs)	323 K (8hrs)
0.2	14	21.2
0.4	22.4	28.7
0.6	35	41.7
0.8	47.7	55
1.0	68.7	74.7

Table - IX d. (Hydrotrope Used: I-BBSA)

Hydrotrope Concentration Mole/dm^3	% Yield Obtained & Time in hours	
	303 K (8hrs)	323 K (8hrs)
0.2	21	29.7
0.4	25.1	31
0.6	32	38.5
0.8	55.7	63
1.0	74	80

Similarly the effect of hydrotrope concentrations on the rate constants (k_1, k_2) and activation energies (Ea) was listed in Table IX e to Table IX h.

Table - IX e. (Hydrotrope Used – XSA)

Hydrotropic Concentration Moles/dm^3	K_1 x 10^{-4} (303 K)	K_2 x 10^{-4} (323 K)	E_a x 10^4 Cal/gm-mol/k
0.2	0.0404	0.0647	1.9163
0.4	0.0495	0.0736	1.6143
0.6	0.0630	0.0907	1.4829
0.8	0.1238	0.1549	0.9119
1.0	0.2455	0.3012	0.8320

Table - IX f. (Hydrotrope Used – CSA)

Hydrotropic Concentration Moles/dm^3	K_1 x 10^{-4} (303 K)	K_2 x 10^{-4} (323 K)	E_a x 10^4 Cal/gm-mol/k
0.2	0.0523	0.0774	1.5950
0.4	0.0689	0.0894	1.0604
0.6	0.0805	0.1003	0.8974
0.8	0.1442	0.1727	0.7339
1.0	0.2827	0.3341	0.3341

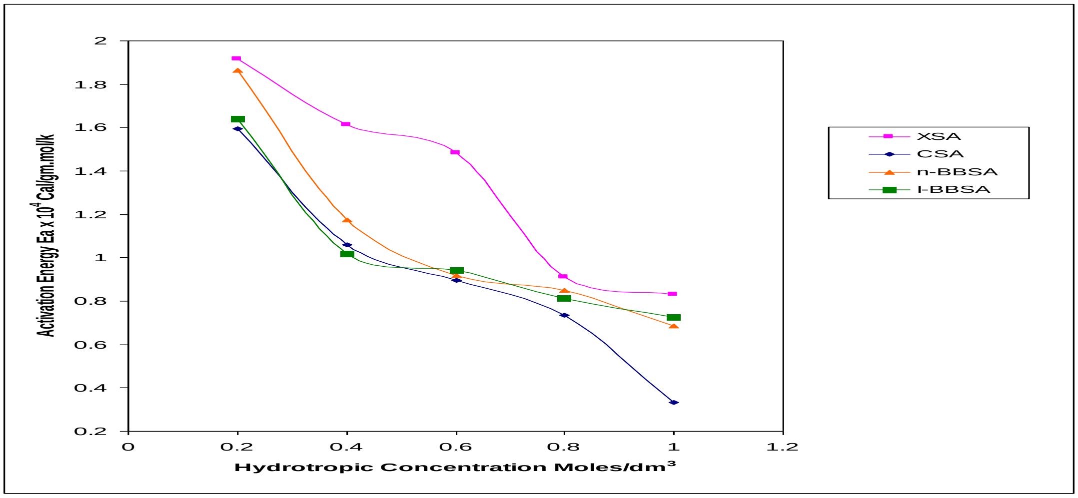
Table - IX g. (Hydrotrope Used - n-BBSA)

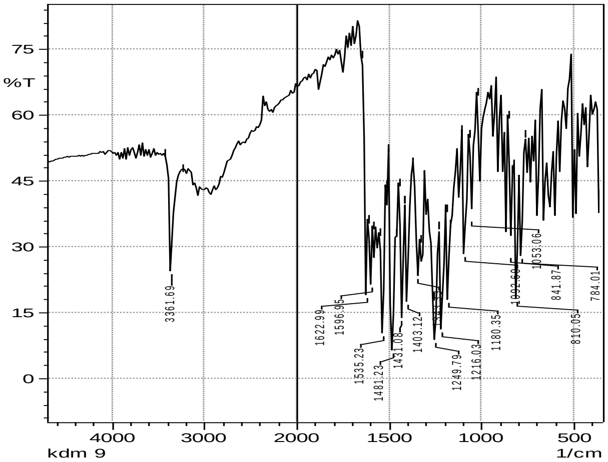
Hydrotropic Concentration Moles/dm^3	K_1 x 10^{-4} (303 K)	K_2 x 10^{-4} (323 K)	E_a x 10^4 Cal/gm-mol/k
0.2	0.0523	0.0827	1.8646
0.4	0.0880	0.1174	1.1729
0.6	0.1495	0.1873	0.9172
0.8	0.2250	0.2772	0.8503
1.0	0.4033	0.4772	0.6852

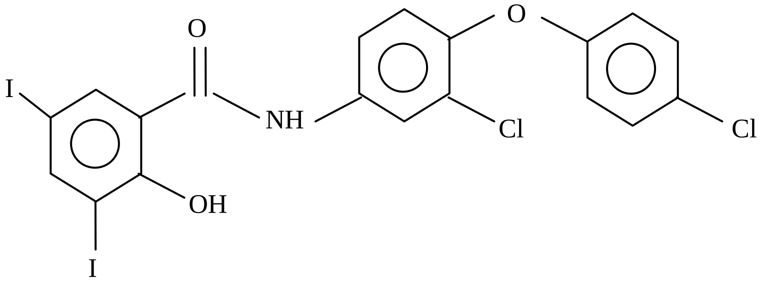
Table - IX h. (Hydrotrope Used - I-BBSA)

Hydrotropic Concentration Moles/dm^3	K_1 x 10^{-4} (303 K)	K_2 x 10^{-4} (323 K)	E_a x 10^4 Cal/gm-mol/k
0.2	0.0818	0.1223	1.6366
0.4	0.1003	0.1288	1.0176
0.6	0.1339	0.1688	0.9428
0.8	0.2827	0.3452	0.8135
1.0	0.4677	0.5588	0.7248

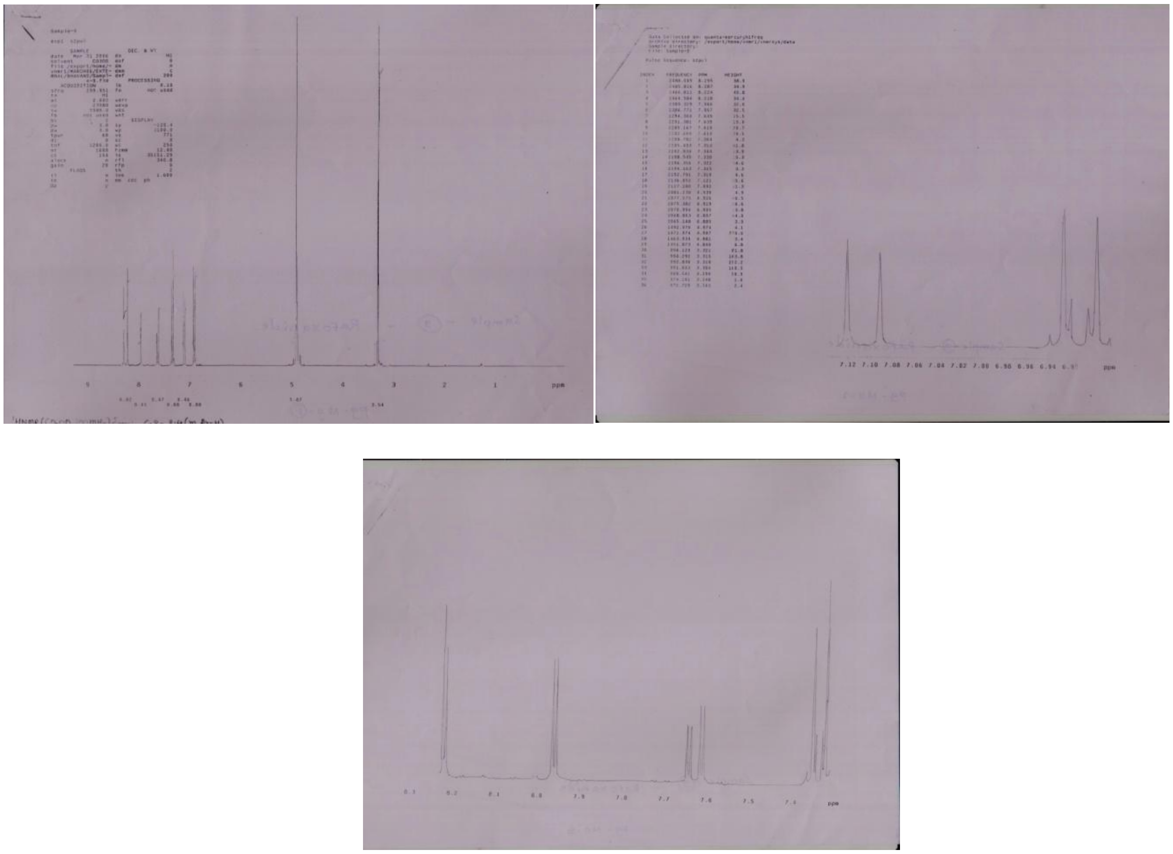
The graphical Representation of effect of Hydrotrope Concentrations on Energy of activation (Ea) was summarized below





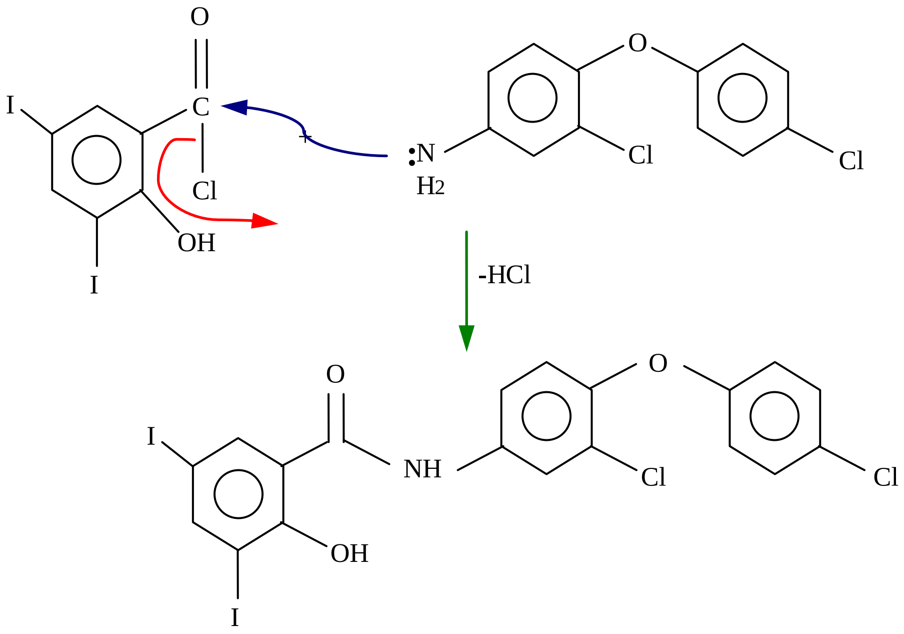


IR Spectra for Rafoxanide



NMR Spectra for Rafoxanide

The reaction of 3, 5–diiodosalicylolyl chloride with 4–amino–2–Chloro–chlorodiphenyl ether in presence of hydrotropic solutions. The proposed mechanism for this reaction is as follows:



This scheme involves the amidation of 3, 5–diiodosalicylolyl chloride. The lone pair of electrons presents on nitrogen of the amine attacks the carbonyl radical in the form of HCl giving the desired amide. In this molecule the halogen atoms are present in meta position to both the reacting situ in the reactants.The phenomenon of the hydrotropy was applied to this synthesis and its effect on yield and reaction kinetics was studied. The hydrotropes used are Xylene sulfonic acid (XSA), Cumene sulfonic acid (CSA), n-Butyl benzene sulfonic acid (n-BBSA) and Isobutyl benzene sulfonic acid (I-BBSA).

The percentage yield obtained for all the four hydrotropes was tabulated in tables IX(a) to IX(d) respectively. It was observed that the percentage yield increased from 11% to 50.7% at 303K and from 17% to 58% at 323K for hydrotrope XSA. It was further increased from 14% to 55.7% at 303K and 20% to 68.8% at 323K. For the hydrotrope n-BBSA the percentage yield increased from 14% to 68.7% at 303K and from 21.2% to 74.7% at 323K. For the hydrotrope I-BBSA the percentage yield increased from 21% to 74% at 303K and from 29.7% to 80% at 323K.

These were in accordance with the fact that the hydrophobicity of I-BBSA was more than that of XSA, CSA and n-BBSA and reactants are soluble to a greater extent in I-BBSA.The kinetics of this reaction was studied and the rate constant K_1 and K_2 for temperature 303K to 323K was calculated for all the hydrotropic solutions. The values of K_1 and K_2 obtained are recorded in tables IX(e) to IX(h) respectively. For the hydrotrope XSA the values of K_1 and K_2 increased from 0.0404 to 0.2455 at 303K and from 0.0647 to 0.3012 at 323K. Similarly for CSA the values of K_1 and K_2 are from 0.0523 to 0.2827 at 303K and from 0.0774 to 0.3341 at 323K.

For the hydrotrope n-BBSA the values of rate constants were more than that of XSA, CSA and these are from 0.0523 to 0.4033 at 303K and from 0.0827 to 0.4772 at 323K. Similarly increased in values of rate constants observed for the hydrotrope I-BBSA than n-BBSA are from 0.0818 to 0.4677 at 303K and from 0.1223 to 0.5588 at 323K. From the above data it was observed that the rate constant went on increasing as concentration of hydrotropes increased from 0.2 Mol/dm³ to 1.0 Mol/dm³.

The activation energy for various concentrations of the hydrotropes was tabulated in IX(e) to IX(h). The activation energy dropped from 1.9163 to 0.8320 for hydrotrope XSA and similarly from 1.5950 to 0.3341 for the hydrotrope CSA. For n-BBSA the activation energy dropped from 1.8646 to 0.6852 and for I-BBSA the activation energy decreased from 1.6366 to 0.7248 as the concentration of Hydrotropes increased. Therefore this decrease in Activation energy as hydrotrope concentration increased suggest that these hydrotropes also provide some catalytic assistance in shifting the equilibrium towards the product.

APPLICATIONS

The synthesis of Rafoxanide was carried out by using four different hydrotropes.

CONCLUSIONS

It is evident from the above scheme that at lower hydrotrope concentration the solubility of organic solutes is less thereby yielding less product. At lower hydrotropic concentration the quantity of water is substantially large thereby the reactions are not favorable also resulting in less yields. At higher concentration of hydrotrope the quantity of water is less and the reaction solubility is more and hence the yields are much better. It is also seen in the above experiment that lower hydrotrope concentrations the time required for the completion of all reaction is more than the time required for a higher hydrotrope concentration.

ACKNOWLEDGMENTS

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