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Characterization and spectral studies of the ion-pairs of the drugs: ketotifen, dequalinium, oxybutinin and dextromethorphan with phosphomolybdate, phosphotungstate, reineckate and tetraphenylborate anions

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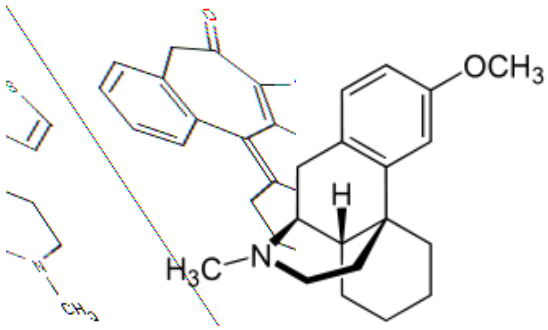
Summary. The interaction of several drugs with some anions was studied where solid ion-pairs are formed. The ion-pairs of ketotifen, dequalinium, oxybutinin and dextromethorphan with phosphomolybdate (PM), phosphotungstate (PT), tetraphenylborate (TPB) and reineckate $[Cr(SCN)_4(NH_3)_2]^-$ were prepared in the solid state. The produced ion pairs were subjected to elemental analysis, IR spectra and thermo- gravimetric analysis to elucidate their molecular structures. The TG plots of the ion-pairs showed multistep decomposition in the temperature range 200-800 ^oC. The calculation of the reaction order for decomposition of the ion-pairs showed that they follow first order kinetics. The thermo- dynamic parameters ΔE, ΔH, ΔG, ΔS for the thermal decomposition of the ion pairs were caculated from the TG plots. The thermal behaviour was studied by simultaneous TGA, DTG and DTA techniques indicating thermal stability of the ion-pairs up to 300^oC.

Introduction

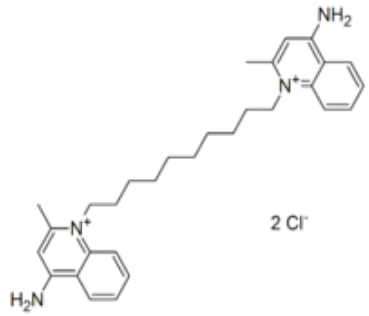
Most of the pharmaceutical compounds form ion pairs with the heteropolyacids such as phosphomolybdic (PM) acid, phosphotungstic (PT) acid and with sodium tetraphenylborate TPB and with ammonium reineckate.The drug ion-pairs are used as electroactive modifier (ion exchanger) for the ion selective electrodes[1-6]. The drug ion pairs can be incorporated into ion sensitive membranes to produce PVC membrane electrodes capable of measuring the concentration of the specific drug in solution.This experimental technique is considered as a useful application for the drug analysis [7-11]. In the present work, four important

pharmaceutical compounds were used: **Dequalinium** salt is the active ingredient of several drugs used as an antiseptic and disinfectant while **Ketotifen** fumarate is antihistamine which is used in treating allergies. **Oxybutinin** is an anticholinergic drug used to relieve urinary and bladder difficulties. **Dextromethorphan** is an antitussive (cough suppressant) drug used for pain relief and for psychological applications.

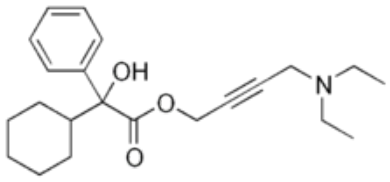
The aim of the present work is to characterize and determine some physical properties and molecular structure of the solid ion-pairs formed between the above mentioned drugs including ketotifen, dequalinium, oxybutinin and dextromethorphan (Fig. 1) and some anions. These anions include two heteropolyacid radical $[PMo_{12}O_{40}]^{3-}$, $[PW_{12}O_{40}]^{3-}$, tetraphenyl borate (TPB) and reineckate $[Cr(SCN)_4(NH_3)_2]^-$. The characterization of the produced solid ion-pairs was done using elemental analysis, IR spectra and thermogravimetric analysis.



Ketotifen



Dextromethorphane



Oxybutynin

Deqalinium

Fig 1 : Molecular structures of the drugs under investigation.

Experimental

All chemicals used in this work are analytical grade reagents. Ketotifen hydrochloride ($C_{19}H_{19}NOS.2HCl$; MW 382) was provided from Novartis Pharm. Co.(Egypt). Dequalinium hydrochloride ($C_{30}H_{40}N_4.2HCl$; MW 527) was provided from Memphis Co.(Egypt). Oxybutinin HCl ($C_{22}H_{31}NO_3.HCl$; MW 537) was provided from Egyptian Co. for Chemicals & pharmaceuticals. Dextromethorphan HBr ($C_{18}H_{25}NO.HBr$; MW 352) was provided from EIPICO (Egypt). Ammonium reineckate was Aldrich product ; the water used is always twice distilled from an all-glass apparatus. The solid ion pairs were prepared as reported [12].

Preparation of the drug ion pairs

All the ion-pairs were prepared by adding 50 mL of 0.01 M of the above mentioned drug hydrochloride (except ketotifen fumarate) solution to 50 mL 0.01 M sodium tetraphenylborate NaTPB /or ammonium reineckate solution. Similarly, the ion pairs with phosphomolybdate PM and phosphotungstate PT were prepared using 0.0033 M of PM / or PT acid respectively in molar ratio 3:1. In all cases the reaction mixture was left overnight then filtered and washed with distilled water (till free from chloride ions) then the product was dried in air at room temperature. The elemental analytical results and molar ratio are shown in Table 1.

Analysis and physical measurements

All the ion-pairs prepared in this work were subjected to elemental analysis using automatic CHN analyzer (Perkin-Elmer model 2400) in the Microanalytical Center of Cairo University.

The infrared absorption spectra were obtained by applying KBr disc technique using Jasco 4100 FTIR spectrophotometer.

The TG analysis was carried out using Shimadzu-50 thermal analyzer from ambient temperature to 1000^{o}C under heating rate of 10^{o}C per min.

Results and discussion

The ion-pairs of the drugs were prepared as described before [12,13] and subjected to elemental analysis, infrared spectral measurement, and thermal analysis for elucidation of their molecular structures. The reactions of association of drug cations with different anions proceed as the follows:

Drug cation + Anion ——————— Ion-Pair

R^+ + $[P\,Mo_{12}O_{40}]^{3-}$ ——————— R_3 [PM] (varied ratios)

R^+ + $[P\,W_{12}O_{40}]^{3-}$ ——————— R_3 [PT] (varied ratios)

R^+ + $[Cr(SCN)_4(NH_3)_2]^-$ ——————— R [reineckate] (1:1 ratio)

R^+ + $(C_6H_5)_4\,B^-$ ——————— R [TPB] (1:1 ratio)

Chemical composition of the ion pairs

All the results of the elemental analysis for C, H, N (Table 1) are in good agreement with the suggested formulae of the ion-pairs. Some ion-pairs have 1:1 molar ratio and some others have 1:2, 3:1 and 3:2 molar ratio (drug : anion) depending on the type of ion pairing species (Table1).

Infrared spectral measurements

The infrared spectroscopy has been proved as a good method for elucidating the molecular structure and to detect the presence of several function groups in the molecules. This discussion is an attempt to elucidate the molecular structure and type of interaction occurring in the formation of the ion-pairs under investigation. Tables 2, 3 and 4 comprise the important IR bands of the drugs ion-pairs, together with their assignment. Some new bands are observed in the spectra of ion-pairs.

A strong band is observed in 2070-2080 cm^{-1} region in the spectra of the ion-pairs containing reineckate anion $[Cr(SCN)_4(NH_3)_2]$ which is assignable to $\nu_{(SCN)}$ [14,15]. The appearance of this new band is an evidence for the formation of ion pairs consistent with the results obtained from elemental analysis. Ketotifen ion-pairs spectra show a strong band at 1630-1650 cm^{-1} which is assigned to ketonic C=O group. The CH_3 band at 2990 and 1470 cm^{-1} are assignable to $\nu(CH_3)$ stretching and $\delta(CH_3)$ bending vibration. In the IR spectra of dequalinium reineckate, a new band appeared at 2077 cm^{-1} is assignable to ν(SCN) which is absent in spectra of other dequalin ion-pairs. Two bands at 3418-3448 and 3325-3349 cm^{-1} are assigned to vibration of NH_2 group in dequalin rings. The spectra of oxybutinin ion-pairs contain three IR bands assignable to ν(OH), ν(C≡C) and ν(C=O ester) which are absent in the spectra of dextromethorphan ion-pair. On the other hand, the spectra of dextromethorphan ion pair contain two bands at 1040 and 1240 cm^{-1} assignable to ν(C-O-C) sym. and assym. vibrations, respectively. These two bands are absent in the spectra of oxybutinin ion-pairs.

TG sudies of the solid drug ion pairs

The thermal behaviour of the investigated drug ion-pairs was studied by TGA and DTA analysis shown in the plots presented in Fig 2.

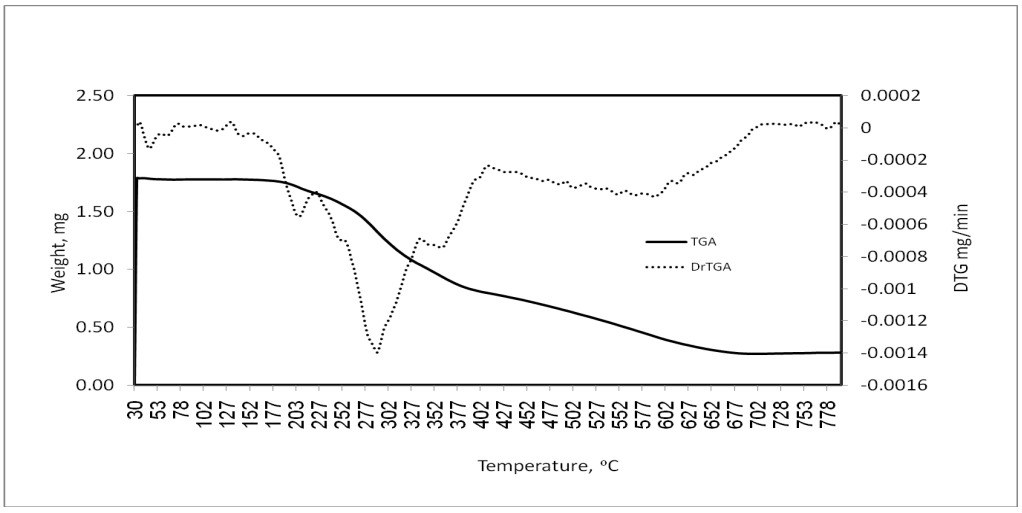


Fig. 2 TGA and DTG of Oxybutynin reineckate ion-pair.

The thermal decompositions of the solid ion-pairs are not simple as they occur in multistep process. No stable intermediates were found due to complexity of the degradation processes. The thermal decomposition of all ion-pairs continues with mass loss to Cr_2O_3 (from reineckate ion-pair) and MoO_3 (from molybdate ion-pair) and WO_3 (from tungstate ion-pair). The thermogravimetric data which agree with the proposed molecular formula of the ion-pairs are summarized in Table 5.

Thermodynamics of the thermal decomposition of the ion-pairs

The values of the thermodynamic parameters ΔS, ΔH and ΔG caculated from Coats-Redfern equation[16, 17], are listed in Table 6 for the first and second steps (and third step in case of dequalin PM). The negative sign of entropy ΔS of activation implies increased ordaining and slow decomposition of the drug ion-pair. The activation energies E* of the decomposition in the range 30-356 $kJmol^{-1}$ reflect a moderate thermal stability of the ion-pairs. Generally, oxybutinin ion pair is thermally more stable than ketotifen ion pair as reflected from comparing their activation energies E* (Table 6). All DTA curves display two peaks, the first one is exothermic peak at 300-400^oC represents the thermal decomposition of the drug. The second one is endothermic peak at 500-700^oC represents the decomposition of the inorganic part of the ion-pair.

TG of oxybutinin reineckate 1:1

The thermal decomposition of oxybutinin ion-pair occurs in two steps. The first step occurs at 286^oC which corresponds to the removal of the organic part (53%). In the second step, the reineckate anion starts to decompose at 400^oC and converts at 700^oC to Cr_2O_3 (11%) as a final product (metallic residue). The results indicate the thermal stability of this ion-pair up to 200^oC and formation of unstable intermediate.

$$\text{Drug- reineckate} \xrightarrow[400^oC]{286^oC} \text{reineckate}$$

$$[Cr(SCN)_4(NH_3)_2] \longrightarrow Cr_2O_3$$

TG of ketotifen phosphomolybdate 3:1

This ion-pair is decomposed in two steps. The first step (up to 400°C) represents the decomposition of ketotifen drug which is 34% of the solid ion-pair. The phosphomolybdate PM anion remains stable until 700°C then decomposes sharply to MoO_3 (61%). These results indicate the thermal stability of ketotifen ion-pair up to 350°C.

$$\text{Drug- phosphomolybdate} \xrightarrow{> 350^oC} \text{phosphomolybdate PM}$$

$$\text{PM } (P_2O_5(MoO_3)_{12}) \xrightarrow{700^oC} MoO_3$$

$$MoO_3 \xrightarrow{750^oC} MoO_2$$

TG of oxybutinin phosphomolybdate 3:1

This oxybutinin ion-pair has a different thermal behaviour. During the first step till 400°C, the mass loss 37% indicates the decomposition of oxybutinin drug. Then the phosphomolybdate anion decomposes gradually with unstable intermediate which decomposes to MoO_3 residue at 630°C then converted to MoO_2 as follows :

$$\text{Oxybutinin- PM} \xrightarrow{300^oC} \text{intermediate}$$

$$\text{Intermediate} \xrightarrow{630^oC} MoO_3 \quad (60\%)$$

$$MoO_3 \xrightarrow{760^oC} MoO_2 \quad (53\%)$$

TG of dequalin phosphomolybdate 3:2

The thermal decomposition of dequalin PM takes place in two steps. The first broad one occurs at 200-400°C with a mass loss of 27 % . This mass loss corresponds to the elimination of dequalin drug from the ion-pair. The second step 500-700°C is the conversion of phosphomolybdate $[PMo_{12}O_{40}]$

to another form e.g. Mo_7O_{24} near 500-600^oC. This conversion is followed by the final decomposition of heptamolybdate to MoO_3 near 650^oC with mass loss 32 % then MoO_2 as a final product at 800^oC.

$$\text{Dequalin-PM} \xrightarrow{350^oC} \text{intermediate}$$

$$\text{Intermediate} \xrightarrow{500\text{-}600^oC} Mo_7O_{24}$$

$$Mo_7O_{24} \xrightarrow{650^oC} MoO_3$$

$$MoO_3 \xrightarrow{800^oC} MoO_2$$

Conclusion

The solid ion-pairs of the studied drugs with different anions have varied ratio 1:1, 1:2, 3:1 and 3:2. Their IR spectra display all functional groups of the prepared ion-pairs. The IR spectra of the reineckate ion-pairs show a new band assignable to $\nu_{(SCN)}$ group while the spectra of ketotifen ion- pairs contain the ketonic C=O band. On the other hand, the thermal decomposition of the ion-pairs occur through multistep process as shown by the inflections in the TG curve. The thermal decomposition of the organic drug occurs at first and is followed by conversion of phospho- molybdate to MoO_3 residue (with exothermic peak) then to MoO_2 (with endothermic peak in DTA curves). It could be concluded that the thermal stability of the ion- pairs varies depending on both the drug type and the anions present.

Table (1) : Elemental analytical results of the studied solid ion-pairs

Ion pair	formula	MW	ratio	Calc %		Found %	
				C	H	C	H
Ketotifen-PM	$(C_{19}H_{19}NO_5)_3$ $[PMo_{12}O_{40}]$	2738	3:1	25	2.1	25.8	2.5
Ketotifen-PT	$(C_{19}H_{19}NO_5)_3$ $[PW_{12}O_{40}]$	3804	3:1	18	1.5	19.1	2.1
Ketotifen-TPB	$(C_{19}H_{19}NO_5)$ $[B(C_6H_5)_4]$	628	1:1	82.2	6.2	81.2	6.0
Dequalinium-PM	$(C_{30}H_{40}N_4)_3$ $[PMo_{12}O_{40}]_2$	4220	3:2	21.6	2.4	22.1	3.0
Dequalinium- PT	$(C_{30}H_{40}N_4)_3$ $[PW_{12}O_{40}]$	4245	3:1	25.4	2.8	25.0	3.1
Dequalin TPB	$(C_{30}H_{40}N_4)$ $[B(C_6H_5)_4]_2$	1094	1:2	85.5	7.3	86.0	6.9
Dequalinium-Reineckate	$(C_{30}H_{40}N_4)$ $[Cr(SCN)_4(NH_3)_2]$	774	1:1	52.7	5.9	52.0	5.4
Oxybutynin-Reineckate	$(C_{22}H_{31}NO_3)$ $[Cr(SCN)_4(NH_3)_2]$	675	1:1	46.2	5.5	45.9	5.2
Oxybutynin-PM	$(C_{22}H_{31}NO_3)_3$ $[PMo_{12}O_{40}]$	2882	3:1	27.5	1.1	28.0	1.4
Dextromethor-phan-TPB	$(C_{18}H_{25}NO)$ $[B(C_6H_5)_4]$	590	1:1	85.7	7.6	85.7	7.2

Table (2) IR band assignment of some of the prepared ion-pairs

Assignment	TPB	PM	PT	Reineckate
Ketotifen ion-pairs				
νCH arom.	3049	3060	3063	
νCH_3 sym.	2990	--	2970	
δCH_3	1474	1465	1473	
νC=O ketonic	1630	1642	1649	
νC=C	1400	1401	1402	
Dequalin ion-pairs				
νNH_2 asym	3446	3348	--	3418
νNH_2 sym	3345	3349	3349	3325
νCH arom	3120	---	3121	3154
CH_2 sym.	2853	2850	2852	2853
CH_2 asym	2926	2923	2924	2925
S-C≡N	---	---	----	2077
δNH_2	1635	1640	1650	1641
CH_2 bend	1479	1486	1490	1488
νN-C arom	1263	1311	1313	1251
C-H arom	7307	799	760	760
Oxybutinin ion-pairs				
νOH		3469		3460
νCH arom.		3055		3158
νCH_3 sym		2928		2928
C≡C		2356		2360
S-C≡N		---		2080
C=O ester		1730		1734
νC=C		1449		1442
νC-O-C asym		---		---
νC-O-C sym		---		---
Arom CH bend		805		772
Dextromethorphan IP				
νOH	---			
νCH arom	3060			
νCH_3 sym	2929			
C≡C	---			
S-C≡N	---			
C=O ester	---			
νC=C	1463			

νC-O-C asym	1240
νC-O-C sym	1040
Arom CH bend	710

Table (3) : The thermogravimetric data of the solid drug ion-pairs.

Ion-pair	Ratio	Decomp. temp.^{o}C	Wt loss %	eliminated species	Residue
Oxybutynin	1:1	286	53	Oxybut.	
Reineckate		400	36	$NH_3 + C_2N_2$	Cr_2O_3
Ketotifen PM	3:1	300	34	Ketotifen	
		700	61	P_2O_5	MoO_2
Oxybutynin PM	3:1	160	37	Oxybut.	
		600	60	P_2O_5	MoO_2
Dequalin PM	3:2	300	27	Dequal.	
		600	32	P_2O_5	MoO_2

Table (4) Thermodynamic data of thermal decomposition of the ion pairs

Ion pair	Ts ^{o}C	Decomp. start ^{o}C	E* kJ mol^{-1}	S* J mol^{-1}	H* kJ mol^{-1}	G* kJ mol^{-1}
Oxybutinin	202	286	124	2	120	119
Reineckate	287	400	68	-155	63	150
KetotifenPM	390	300	61	-125	55	139
	784	700	356	64	347	279
OxybutinPM	206	160	61	-143	57	126
	728	600	30	-83	22	105
DequalinPM	414	300	65	-178	60	182
	552	450	148	-115	141	236
	787	600	181	-102	173	281

PM : phosphomolybdate

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