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Chemistry of Drug Interactions: Characterization of Charge-Transfer Complexes of Guaifenesin with Various Acceptors Using Spectroscopic and Thermal Methods[1]

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Abstract—The present study deals with the complexation properties of Guaifenesin with two types of acceptors: σ-acceptor (i.e., iodine) and π-acceptors (i.e., dichlorodicyanobenzoquinone, chloranil and picric acid). All the prepared complexes were characterized stoichiometrically and structurally using various spectral techniques, as well as elemental analyses. Thermal decomposition behavior of complexes was studied, and their thermodynamic parameters were calculated using Coats–Redfern and Horowitz–Metzger equations. It has been found that the complexation with PA and CHL acceptors increases the values of enthalpy and entropy, while the complexation with DDQ and iodine acceptors decreases the values of these parameters compared with the free GU donor.

Keywords: guaifenesin, drug-acceptor interaction, σ-acceptor, π-acceptor, TG, DTG

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INTRODUCTION

Guaifenesin [GU, R,S-3-(2-methoxyphenoxy)-propane-1,2-diol] (Fig. 1), is a constituent of guaiac resin from the wood of *Guajacum officinale* [1]. It is a widely used expectorant drug, and usually is taken orally to assist the bringing up of phlegm from the airway in acute respiratory tract infections and can be used for treatment sinusitis, pharyngitis, and bronchitis [2–6]. It is termed an expectorant since it is believed to alleviate cough discomfort by increasing sputum volume and decreasing its viscosity (hydration hypothesis), thereby promoting effective cough. Based on the interesting results obtained for the complexation properties of drugs with acceptors, in this research, as a continuation of our work in this field [7–19], the interactions of guaifenesin with two types of acceptors (σ- and π-acceptors) were investigated. First, the CT complexes of GU with iodine, DDQ, CHL and PA acceptors were obtained. Then, the formed complexes were stoichiometrically and structurally characterized by elemental and spectral data. The formation constant (K_{CT}), molar extinction coefficient (ε_{CT}) and other spectroscopic data were calculated using the 1 : 1 and 1 : 2 Benesi–Hildebrand equations. The thermal decomposition behavior of the reported complexes was discussed. Additionally, the thermodynamic properties of these complexes were determined using Coats–Redfern and Horowitz–Metzger equations.

EXPERIMENTAL

Elemental analyses for the C, H and N content were performed by the microanalysis facility at Cairo University, Egypt, using a Perkin–Elmer CHN 2400 instrument. All of the electronic absorption spectra were recorded in methanol or chloroform over a wavelength range of 200–800 nm using a Perkin–Elmer Lambda 25 UV-Vis double-beam spectrophotometer at Taif University, Saudi Arabia. The instrument was fitted with a quartz cell with a path length of 1.0 cm. The infrared spectra of the solid CT complexes (as KBr discs) were acquired at room temperature using a Shimadzu FT-IR spectrophotometer in the range of 4000–400 cm^{-1} for 30 scans at a 2 cm^{-1}

[1] The text was submitted by the authors in English.

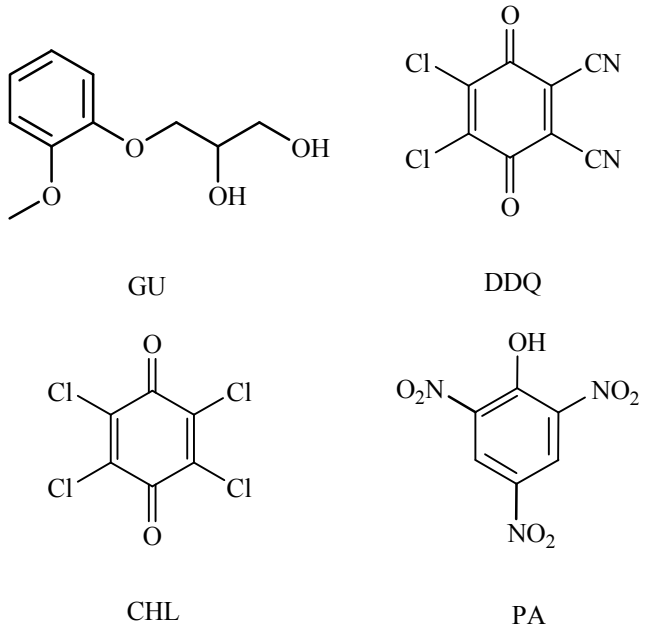

Fig. 1. Chemical structure of guaifenesin (GU) and the acceptors.

resolution. ^{1}H NMR spectra were collected by the Analytical Center at King Abdul Aziz University, Saudi Arabia, on a Bruker DRX-250 spectrometer operating at 250.13 MHz with a dual 5 mm probe head. The measurements were performed at ambient temperature using DMSO-d_6 as a solvent and TMS as an internal reference. Thermogravimetric experiments (TG and DTG) were performed under nitrogen atmosphere in 25–800°C range at a heating rate of 10°C/min using a Shimadzu TGA–50H thermal analyzer at the Central Lab at Ain Shams University, Egypt.

Guaifenesin (purity >98%) used in this study was purchased from Aldrich. The electron acceptors iodine, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), chloranil (CHL) or picric acid (PA) (Fig. 1) and spectroscopic grade solvents were obtained from Aldrich and Merck and were used without purification. Standard stock 5.0×10^{-3} M solutions of GU and acceptors were freshly prepared prior to each series of measurements and were kept protected from light. Solutions for spectroscopic measurements were made by mixing appropriate volumes of GU and acceptor stock solutions with the solvent immediately before recoding the spectra.

Preparation of CT **complexes.** To obtain the solid CT complexes, a methanol or chloroform solution of GU (1 mmol) was stirred with a solution of each acceptor (1 mmol) in the same solvent for ca. 30 min on a magnetic stirrer at room temperature. A change in color developed, and the volume of the solution was reduced to one-half by evaporation on a water bath, resulting in the precipitation of the solid CT complexes. The formed complexes were filtered off and washed twice thoroughly with the minimum amount of appropriate solvent to obtain the pure products. The solid products were then dried in vacuo for 48 h. These complexes were characterized by spectroscopy (IR, ^{1}H NMR, and UV-Vis) elemental and thermal analysis. Strong change in colors was observed upon mixing solutions of the donor with any of the acceptors. These observed new colors were brown for GU–I_2 and GU–CHL, reddish-brown for GU–DDQ and yellow for GU–PA reaction mixtures. These changes in colors represent strong evidence of the CT interactions between the donor and each of the acceptors. Elemental analysis: (GU–I_2) (705.82); Calculated, %: C 17.0; H 1.98. $C_{10}H_{14}O_4I_4$. Found, %: C 17.05; H 2.1. (GU–DDQ) (425.22); Calculated, %: C 50.80; H 3.29, N 6.59. $C_{18}H_{14}Cl_2N_2O_6$. Found, %: C 50.84; H 3.32, N 6.63. (GU–CHL) (444.1); Calculated, %: C 43.23; H 3.15. $C_{16}H_{14}Cl_4O_6$. Found, %: C 43.27; H 3.18. (GU–PA) (427.32); Calculated, %: C 44.93; H 3.98, N 9.83. $C_{16}H_{17}N_3O_{11}$. Found, %: C 44.89; H 3.95, N 9.87.

The elemental analysis data were in satisfactory agreement with the calculated values. The stoichiometry of the interaction between the donor and the acceptors was found to be 1 : 2 for the iodine acceptor and 1 : 1 for the DDQ, CHL, and PA acceptors.

Spectrophotometric measurements. To determine the stoichiometry of the GU–acceptor interactions, various molar ratio were examined by spectrophotometric titration measurements. These titrations monitored the detectable CT bands during the reactions of I_2, DDQ, CHL or PA with GU. Briefly, 0.25, 0.50, 0.75, 1.00, 1.50, 2.0, 2.50, 3.00, 3.50 or 4.00 mL aliquot of a standard solution (5.0×10^{-4} M) of the appropriate acceptor in methanol or chloroform was added to 1.00 mL of 5.0×10^{-4} M GU solution in the same solvent. The final volume of the mixture was 5 mL. The concentration of the donor (C_d) was maintained at 5.0×10^{-4} M, whereas the concentration of the acceptor (C_a) varied from 0.25×10^{-4} M to 4.00×10^{-4} M to produce solutions with a (donor: acceptor) molar ratio that varied from 4 : 1 to 1 : 4. The absorbance of each complex was plotted against the volume of the added acceptor.

Calculations of the spectroscopic data. Calculation of K and ε. The formation constant (K) and the molar extinction coefficient (ε) were determined spectrophotometrically using the 1 : 1 Benesi–Hildebrand equation [Eq. (1)] [20] for the (1 : 1) CT complexes (with DDQ, CHL and PA acceptors) or the 1 : 2 modified Benesi–Hildebrand equation [Eq. (2)] [21] for the (1 : 2) CT complexes (with iodine acceptor). C_a and C_d are the initial concentrations of the acceptor and donor, respectively, and A is the absorbance of the CT band. By plotting the $(C_a\ C_d)/A$ values for the 1 : 1 CT complex as a function of the corresponding $(C_a + C_d)$ values or $(C_a)^2C_d/A$ values against C_a $(4C_d + C_a)$ values for the 1 : 2 CT complex, a straight line is obtained with a slope of $1/\varepsilon$ and an intercept at $1/K\varepsilon$.

$$(C_aC_d)/A = 1/K\varepsilon + (C_a + C_d)/\varepsilon, \quad (1)$$

$$(C_a)^2C_d/A = 1/K\varepsilon + 1/\varepsilon\ C_a\ (4C_d + C_a). \quad (2)$$

Calculation of E_{CT}. The energy values (E_{CT}) of the $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ interactions between the donor and the acceptor was calculated using the equation derived by Briegleb [Eq. (3)] [22], where λ_{CT} and ν_{CT} are the wavelength and wavenumber of the complexztion band of the formed complex, respectively.

$$E_{CT} = (h\nu_{CT}) = 1243.667/\lambda_{CT}\ (\text{nm}). \quad (3)$$

Calculation of f. The oscillator strength (f) is a dimensionless quantity used to express the transition probability of the band. From the absorption spectra, f can be obtained using an approximate equation (4) [23]. $\int\varepsilon_{CT}d\nu$ is the area under the curve of the extinction coefficient of the absorption band in question plotted as a function of the frequency. To a first approximation, f can be calculated using Eq. (5). ε_{CT} is the maximum extinction coefficient of the CT band, and $\nu_{2/2}$ is the full width at half maximum in cm^{-1}.

$$f = 4.319 \times 10^{-9}\int\varepsilon_{CT}\,d\nu, \quad (4)$$

$$f = 4.319 \times 10^{-9}\,\varepsilon_{CT}\,\nu_{1/2}. \quad (5)$$

Calculation of μ. The transition dipole moments (μ) were calculated using Eq. (6) [24]. The transition dipole moment (μ) can be employed to determine if a particular transition is allowed. The transition from a bonding π orbital to an antibonding π^* orbital is allowed because the integral that defines the transition dipole moment is nonzero.

$$\mu(\text{Debye}) = 0.0958(\varepsilon_{CT}\nu_{2/2}/\nu_{max})^{1/2}. \quad (6)$$

Calculation of ΔG^0. The values of the standard free energy change (ΔG^0) were calculated from the formation constants using Eq. (7) [25]. ΔG^0 is the standard free energy change of the complexes (kJ/mol), R is the gas constant (8.314 J mol^{-1} K^{-1}), T is the absolute temperature in Kelvin, and K is the formation constant of the complex (L/mol) at room temperature.

$$\Delta G^0 = -2.303RT\log K_{CT}. \quad (7)$$

Calculations of the Kinetic–thermodynamic data. Calculation using Coats–Redfern method. The Coats–Redfern equation [26], which is a typical integral method, can be represented using Eq. (8). For convenience, the lower limit T_1 is usually taken as zero. After integration, this equation can be represented using Eq. (9). α is the fraction of the sample decomposed at time t, T is the derivative peak temperature, A is the frequency factor, R is the gas constant, E^* is the activation energy, and φ is the linear heating rate. A plot of the left-hand side (LHS) against $1/T$ was constructed. E^* is the activation energy in kJ/mol and was calculated from the slope. The A (s^{-1}) value was calculated from the intercept. The entropy of activation, ΔS^*, in (J mol^{-1} K^{-1}) can be calculated using Eq. (10). k is the Boltzmann constant, h is Planck's constant, and T_s is the DTG peak temperature.

$$\int_{0\rightarrow\infty} d\alpha/(1-\alpha)^n = (A/\varphi)\int_{T_1\rightarrow T_2} e^{-E^*/RT}dT, \quad (8)$$

$$\ln[-\ln(1-\alpha)/T^2] = -E^*/RT + \ln[AR/\varphi E^*], \quad (9)$$

$$\Delta S^* = R\ln(Ah/kT_s). \quad (10)$$

Calculation using Horowitz–Metzger method. The Horowitz–Metzger equation [27] can be represented using Eq. (11). $\theta = T - T_s$, $w_\gamma = w_\alpha - w$, w_α is the mass loss at the completion of the reaction, and w is the mass loss at time t. The plot of log [log (w_α/w_γ)] vs. θ was constructed and was observed to be linear, and E^* was calculated from its slope. The pre-exponential factor, A, was calculated from Eq. (12). From the TG curves, the activation energy, E^*, the entropy of activation, ΔS^*, the enthalpy of activation, ΔH^*, and the Gibbs free energy, ΔG^*, were calculated using Eqs. (13) and (14).

$$\log[\log(w_\alpha/w_\gamma)] = E^*(\theta)/2.303RT_s^2 - \log 2.303, \quad (11)$$

$$E^*(\theta)/RT_s^2 = A/[\varphi\cdot\exp(-E^*/RT_s)], \quad (12)$$

$$\Delta H^* = E^* - RT, \quad (13)$$

$$\Delta G^* = \Delta H^* - T\Delta S^*. \quad (14)$$

RESULTS AND DISCUSSION

UV-Vis spectroscopy. These spectra revealed the presence of the absorption bands that correspond to the CT interactions. The absorption bands appeared at 270

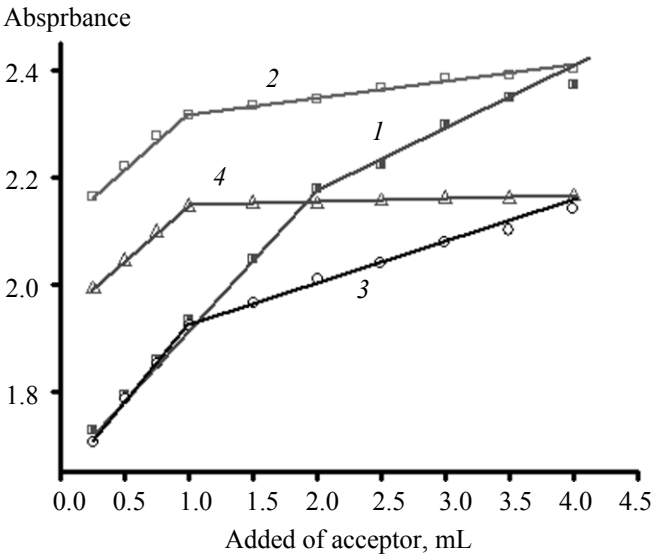

Fig. 2. Spectrophotometric titration curves for (*1*) GU-I_2, 1 : 2, (*2*) GU-DDQ, 1 : 1, (*3*) GU-CHL , 1 : 1, and (*4*) GU-PA, 1 : 1 systems.

and 350 for I_2 complex, 360 and 415 for DDQ complex, 325 and 375 for CHL complex and 320 nm for PA products, respectively, are presumably due to the GU–acceptor interactions and are indicative of the formation of a CT complex. The spectrum of the GU–I_2 complex was characterized by a strong absorption band at 270 and a weak broad band 350 nm that correspond to the GU–iodine interaction. The appearance of these two absorption bands at approximately 360 and 280 nm is well known to be characteristic of the formation of the triiodine ion (I_3^-) [28–30]. The observed electronic absorption spectrum of the iodine complex confirmed the formation of the $[GU–I]^+I_3^-$ complex. The stoichiometry of the formed CT complexes between the GU donor and the acceptors was determined by applying a varying molar ratio spectrophotometric titration method. The electronic spectra of the GU–acceptor systems were recorded with varying concentrations of acceptor and a constant GU concentration. The composition of the complexes were determined graphically by plotting the absorbance as a function of the volume of acceptor (in mL). Representative spectrophotometric titration plots based on the characterized absorption bands are shown in Fig. 2. The results show that the largest interaction between GU donor and each acceptor occurred at a GU: acceptor ratio of 1 : 2 for iodine acceptor and of 1 : 1 for DDQ, CHL and PA acceptors. The structures of the new formed CT complexes were formulated to be $[GU–I]^+I_3^-$, [(GU)(DDQ)], [(GU)(CHL)], and [(GU)(PA)]. These structures and stoichiometries agree quite well with the elemental analyses of the formed solid complexes.

Spectroscopic data. The values of both K and ε are thus determined and are given in Table 1 along with the other spectroscopic data (f, μ, E_{CT}, and ΔG^0) calculated as described above. The obtained data of these CT complexes led to the following observations:

(1) In general, the 1 : 2 complexes exhibit high values for the formation constants (K). The GU–I_2 complex shows higher K value compared with the other 1 : 1 complexes. This high K value indicates a strong interaction between the GU–I_2 pairs and confirms a high stability of the prepared complex.

(2) The complex stability is strongly dependent on the nature of the used acceptor including the type of electron withdrawing subsitituents to it such as nitro and halo groups. The complex containing the DDQ acceptor exhibits a higher K value compared with the other 1 : 1 complexes, which reflects the relatively higher powerful electron acceptance ability of DDQ. The DDQ acceptor has two cyano and two chloro

Table 1. Spectral properties of the GU–acceptor CT complexes at 298 K

Property	Complexes			
	GU–I_2	GU–DDQ	GU–CHL	GU–PA
λ_{max}, nm	270	415	375	320
Formation constant; K, L/mol	4.25×10^7	25.84×10^4	11.50×10^4	10.87×10^4
Extinction coefficient; ε_{max}, L mol^{-1} cm^{-1}	460×10^4	13.9×10^4	17.6×10^4	13.3×10^4
Energy value; E_{CT}, eV	4.61	3.32	2.99	3.88
Oscillator strength; f	79.6	20.13	15.18	5.73
Dipole moment; μ	6.76	4.0	3.65	1.97

groups between two carbonyl groups. This causes high delocalization leads to a great increase in the Lewis acidity of the acceptor, and hence the higher value of K for its complex compared with the others. The observed high value of K suggest that the formed CT complex is strongly bound and highly stable.

(3) The stability of the 1 : 1 complexes decreases in the following order: GU–DDQ > GU–CHL > GU–PA.

(4) The GU–DDQ complex also exhibits higher values of both f and μ, which indicates a strong interaction between the MZ–DDQ pairs with relatively high probabilities of CT transitions.

(5) All of the ΔG^0 values are negative. These negative values indicate that the interaction between the GU donor and the acceptors is spontaneous.

(6) The ΔG^0 values of the complexes in decreasing order for the different acceptors are as follows: I_2 > DDQ > CHL > PA.

IR spectroscopy. The IR spectra of the free donor and of its solid CT products were recorded. The peak assignments for the important peaks are reported in Table 2. The results indicated that the shifts in position of some of the peaks could be attributed to modifications of the symmetry and electronic structure in both the donor and acceptor units in the complexes relative to the free molecules.

The IR spectrum of the free GU donor shows the following distinguished absorption bands: (1) a very strong broad band of ν(O–H) at 3240 cm^{-1}; (2) band at 3010 cm^{-1} assigned to ν(C–H) aromatic vibrations; (3) bands at 2937, 2885, 2843, and 2752 cm^{-1} assigned to the vibration of $–CH_2–$ groups; (4) stretching C=C vibration at approximately 1593 cm^{-1}; (5) bending deformation vibrations of δ(C–H) appearing at 1514–1460 cm^{-1}; (6) intensive absorption band at 1254, which is characteristic of the O–H in-plane bending vibration and (7) sharp strong band at ~741 cm^{-1}, assigned to δ_{rock}(C–H) vibrations.

Iodine complex. The stretching vibrational of ν(O–H) absorption band of free GU donor is appeared at 3240 cm^{-1} and under complexation this band was shifted to higher frequency (3390 cm^{-1}) and become more broadening. The observed shift in the ν(O–H) band upon complexation clearly indicated that the –OH moiety of the donor participated in the CT bonding with iodine. Such shifts suggest electron transfer from the O atom of the donor to the iodine molecule to form the corresponding triiodide complex. The observed UV-Vis spectrum of this system confirmed the formation of the $[GU–I]^+I_3^-$ complex. A general mechanism can be proposed for the formation of the $[GU–I]^+I_3^-$ complex as follows [31–34]: the drug initially forms an outer complex with iodine in a fast step, followed by its transformation into an inner complex, followed by a fast reaction of the resulting inner complex with another mole of iodine to form a triiodide (I_3^-) ion, as depicted below.

$$GU + I_2 \overset{\text{fast}}{\rightleftharpoons} GU–I_2 \text{ (outer complex)},$$

$$GU–I_2 \overset{\text{slow}}{\rightleftharpoons} [GU–I]^+I^- \text{ (inner complex)},$$

$$[GU–I]^+I^- + I_2 \overset{\text{fast}}{\rightleftharpoons} [GU–I]^+I_3^- \text{ (triiodide complex)}.$$

DDQ complex. When CHL acceptor complexed with the GU donor, the vibration frequency of the ν(O–H) for GU existed at 3240 cm^{-1} were still unshifted, this meaning that O–H group is not participated in the CT complexation. Instead, the bands that results from the ν(C≡N) vibration of the free DDQ acceptor were changed in frequencies and decrease in intensities upon CT compexation. Free DDQ shows two ν(C≡N) vibration at 2250 and 2331 cm^{-1}, while in its complex it occur at 2222 cm^{-1}. The cyano group (C≡N) is an electron-withdrawing group that exists in DDQ in a conjugated bonding system. The CN groups in DDQ withdraw electrons from the aromatic ring, and such a process will make the aromatic ring an electron-accepting region. Instead, GU donor contains high electron density over the aromatic ring. So, because of the electron-withdrawing process and the conjugated electron system in the DDQ acceptor, and the good electron-donating ability of the GU donor, the interactions mode (GU→DDQ) occur through π→π* charge migration via the aromatic ring of the GU donor and the aromatic ring of the DDQ acceptor [35–40]. The group of bands observed at 2919 and 2849 cm^{-1} in this complex were assigned to ν_s(C–H) + ν_{as}(C–H) vibrations with different position wave-numbers compared with the free GU.

CHL complex. When CHL acceptor complexed with the GU donor, the stretching vibrational of ν(O–H) absorption band of free GU donor appeared at 3240 cm^{-1} was shifted to higher frequency (3346 cm^{-1}). The observed shift in the ν(O–H) band upon complexation clearly indicated that the –OH moiety of the donor participated in the CT bonding with CHL. This

Table 2. Summary of TG and DTG studies of the GU and its CT complexes

GU donor	Acceptor			Complexes				Vibrational assignments
	DDQ	CHL	PA	iodine	DDQ	CHL	PA	
3240	–	–	3416	3390	3246	3346	3327	ν(O–H)
3010	–	–	3103, 2980	3066	–	3012	3103	ν(C–H); aromatic
2937, 2885, 2843, 2752	–	–	–	2931, 2881, 2839	2919, 2849	2948, 2935, 2843	2929	ν_s(C–H) + ν_{as}(C–H); CH_2+CH_3
–	–	–	–	–	–	2633, 2584	2667, 2578	ν(OH···O), hydrogen bonding
–	2250, 2231	–	–	–	2222	–	–	ν(C≡N); DDQ, complex
–	1673	1685	–	–	1736	1664	–	ν_{as}(C=O); CHL, DDQ
–	1552	1567	–	–	1635	1576	–	ν_s(C=O); CHL, DDQ
–	–	–	1632, 1608	–	–	–	1623	$\nu_{as}(NO_2)$; PA
1593	–	–	–	1593	1593	1516	1535	ν(C=C) (in–ring), aromatic
1514, 1460	–	1257, 1232	1529, 1432	1506, 1456	1547, 1504	1462	1445	δ(C–H) deformation
–	1451	–	–	–	1454	–	–	ν(C=N)
1379	–	–	1343, 1312	1329	1408	1381, 1336	1342	δ_{rock}, CH_2, $\nu_a(NO_2)$; PA
1254	–	–	–	1254, 1223	1252, 1223	1250, 1227	1257	O–H in–plane bending
1120	–	–	–	1180, 1124	1180, 1124	1115	1136	ν(C–O)
1032	–	–	1150, 1086	1026	1024	1055	1094, 1080	δ(C–H) in–plane bending
987, 924	–	–	829, 781	833, 877	934,	1033	1032, 924	δ(C–H) out–of–plane bending
–	893, 800	903, 709	–	–	872, 824	918	–	ν(C–Cl); CHL, DDQ
835	–	–	–	825	–	837	835	δ(C–H) out–of–plane bending
–	–	–	732	–	–	–	771	$\delta(NO_2)$, scissoring; PA
741	–	–	703	744	744	746	735	δ_{rock}, CH_2 + $\omega(NO_2)$; PA
633	615, 457	–	652	613	611	–	–	O–H out–plane bending, Skeletal vibrations
–	–	–	522	–	–	–	534	C–NO_2 in–plane bending

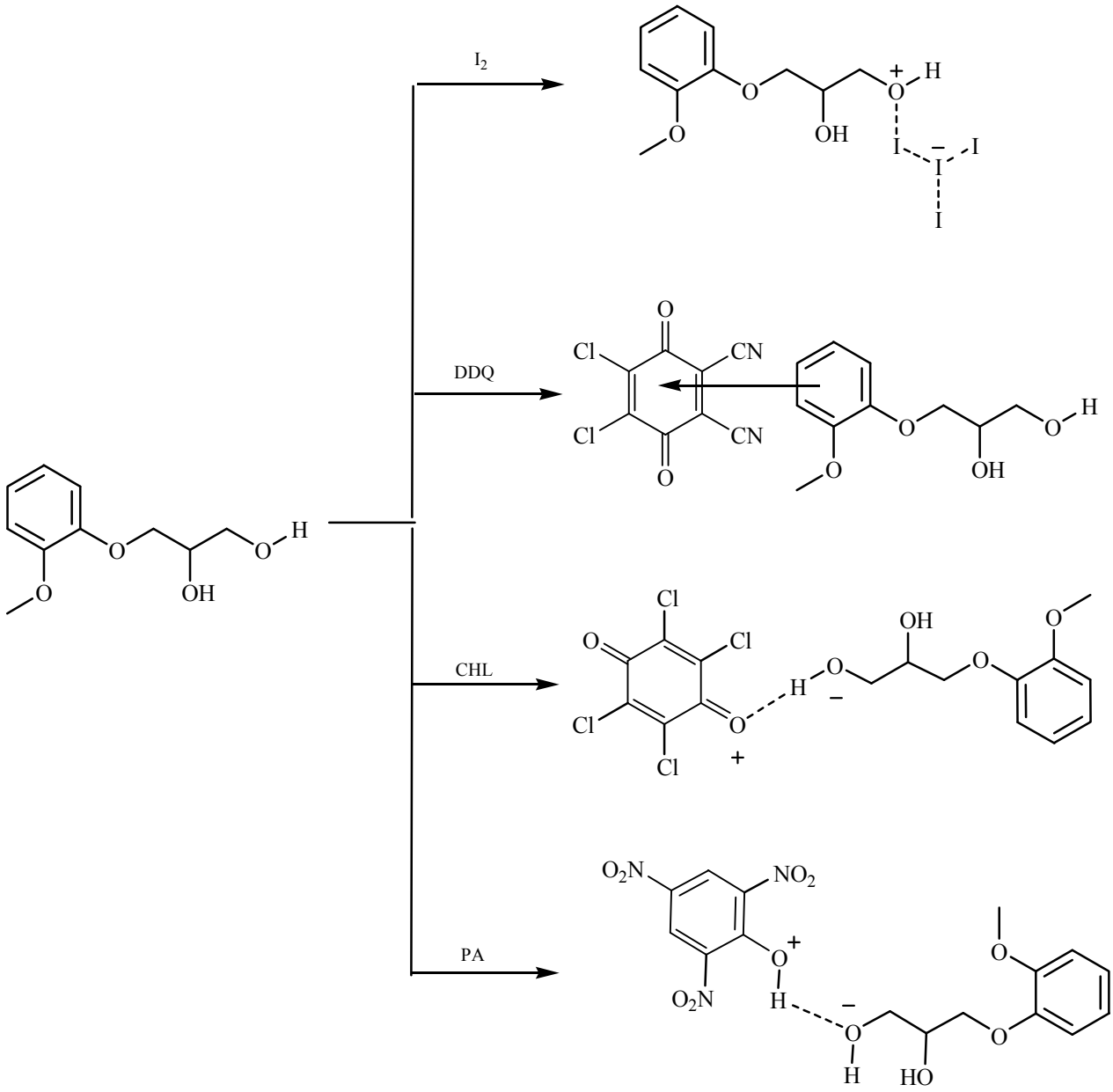

Fig. 3. Proposed structural formula of the GU CT complexes.

complex is also characterized by a weak bands appearing in the region between 2400 and 2800 cm^{-1}. These bands presence at 2633 and 2584 cm^{-1} was attributed to the stretching vibration of a proton attached to the accepting site (C=O) of the acceptor. Furthermore, the carbonyl vibration bands; ν_{as}(C=O) and ν_{as}(C=O), slightly shifted with respect to those of the free CHL acceptor; this is most likely due to intermolecular CT interactions.

PA complex. When PA acceptor was complexed with the GU donor, the characteristic bands of the free donor and acceptor were shifted and decreased in the intensities. The outlined changes in the bands of ν(O–H) (for GU donor) and ν(O–H) (for PA acceptor) upon complexation clearly supports the formation of the CT complexes between donor and acceptor. This complex is also characterized by a medium bands appearing in the region between 2400 and 2800 cm^{-1}. These bands

Table 3. Summary of TG and DTG studies of the GU and its CT complexes

Compound	Stages	TG range, °C	DTG_{max}, °C	TG mass loss, %		Lost species
				found	calculated	
GU donor	I	115–280	220	99.46	100.0	$3C_2H_2 + 4CO + 4H_2$
$[GU–I]^+I_3^-$	I	125–300	223	88.50	88.92	$2I_2 + 4CO + 4H_2$
	II	300–600	–	10.91	11.05	$3C_2H_2$
[(GU)(DDQ)]	I	55–350	209, 259	53.28	53.38	DDQ
	II	350–800	–	29.54	29.63	$4CO + 7H_2$
	Residue	–	–	16.79	16.93	6C
[(GU)(CHL)]	I	125–500	213	99.67	100.0	GU + CHL
[(GU)(PA)]	I	110–450	226	99.75	100.0	GU + PA

presence at 2667 and 2578 cm^{-1} was attributed to the stretching vibration of a proton attached to the accepting site (C=O) of the acceptor and forming $^+$OH group. All these observations indicates that the complexation occurs through the formation of intermolecular H-bonding between the donor and the acceptor [41-48]. Furthermore, the nitro vibration bands; $\nu_{as}(NO_2)$, $\nu_{as}(NO_2)$, and $\delta(NO_2)$, slightly shifted with respect to those of the free acceptor; this is most likely due to intermolecular CT interactions.

^1H NMR spectroscopy. The positions of chemical shift (δ) of the different types of protons were expected to be shifted based on the changes in the electronic environment around the protons attached to the groups which contain the site of donation and involvement in the complexation. The reaction of GU donor with PA acceptor yielded a new CT complex, which produced signals at δ = 3.45 s (3H, CH_3), 3.74–3.93 m (7H, $2CH_2$, CH, and 2OH groups, $OC\underline{H_2}C\underline{H}O\underline{H}C\underline{H_2}O\underline{H}$), 5.96 s (2H, picric acid protons), 6.88–6.92 m (4H, Ar–H), 8.60 s (1H, Hydrogen bonded picric acid OH). The peak at δ =11.94 ppm, which is assigned to the ($^-$OH) proton of free picric acid [49], is absence in the spectrum of this complex. Instead, the peak appeared at 8.60 ppm, is assigned to $^+$OH proton. It is clearly obvious that the formation of this new signal indicating the involvement of (–OH) group of donor and (–OH) group of acceptor in chelating through the deprotonation from the PA to the GU. The intensities and chemical shifts of the aromatic signals were significantly affected by the existence of the (O^+–H) charge-transfer interaction between the donor and the acceptor molecules. The results of elemental analyses, UV-Vis, IR, and ^{1}H NMR spectral data are in agreement with each other to support the predicted structures of the obtained CT complexes. The suggested complexation mechanism of the CT complexes between GU donor with different acceptors is illustrated by Fig. 3.

Thermal methods. TG and DTG data. To confirm the composition and structures of the formed solid CT complexes, Thermal analyses (TG and DTG) were carried out for the GU donor and its complexes with I_2, DDQ, CHL, and PA acceptors. The measurements were carried out under nitrogen atmosphere in the temperature range of 25–800°C. The possible thermal degradation patterns for these compounds are collected in Table 3. Fairly close values of the calculated and experimental percentage of the moieties expelled from these complexes strongly support the experimentally determined stoichiometry of the complexes.

Kinetic-thermodynamic data. The Kinetic-thermodynamic parameters [i.e., the activation energy (E^*), the frequency factor (A), the enthalpy of activation (H^*), the entropy of activation (S^*) and the Gibbs free energy of activation (G^*)] associated with the GU donor and its CT complexes were evaluated graphically by employing the Coats–Redfern and Horowitz–Metzger methods, previously described, and the evaluated data are listed in Table 4. The obtained data led to the following observations:

(1) The kinetic-thermodynamic data obtained from the two methods are comparable and can be considered in good agreement with each other.

(2) The activation energy (E^*) of the complexes is expected to increase with the increasing thermal stability of complexes. Therefore, the E^* value for the [(GU)(PA)] complex is higher compared to the other

Table 4. Kinetic parameters determined using Coats–Redfern (CR) and Horowitz–Metzger (HM) methods

Complex	Method	Parameters					r
		E^*, kJ/mol	A, s^{-1}	ΔS^*, J mol^{-1} K^{-1}	ΔH^*, kJ/mol	ΔG^*, kJ/mol	
GU	CR	1.45E+05	6.10E+08	–8.44E+01	1.40E+05	2.00E+05	0.99688
	HM	1.50E+05	6.37E+09	–6.50E+01	1.51E+05	2.06E+05	0.99345
$[GU–I]^+I_3^-$	CR	1.17E+05	1.41E+06	–1.30E+02	1.12E+05	2.11E+05	0.98549
	HM	1.25E+05	7.95E+06	–1.17E+02	1.21E+05	2.12E+05	0.98140
[(GU)(DDQ)]	CR	1.28E+05	6.11E+06	–1.20E+02	1.21E+05	2.13E+05	0.99544
	HM	1.44E+05	1.71E+08	–9.43E+01	1.45E+05	2.16E+05	0.99196
[(GU)(CHL)]	CR	1.59E+05	6.80E+09	–6.41E+01	1.62E+05	2.00E+05	0.99816
	HM	1.70E+05	8.30E+10	–4.30E+01	1.72E+05	2.03E+05	0.99813
[(GU)(PA)]	CR	1.60E+05	7.71E+09	–6.32E+01	1.55E+05	2.12E+05	0.99617
	HM	1.74E+05	8.11E+10	–4.30E+01	1.68E+05	1.89E+05	0.99553

complexes, which indicates the higher thermal stability of the [(GU)(PA)] complex.

(3) By comparing the E^* values for the main decomposition stage of the complexes, we observed the following trend for the different acceptors: PA > CHL > DDQ > Iodine. These differences may be due to the reactivity of the complexes and the electronic configuration of the acceptor when complexed with the GU donor.

(4) The negative values of the ΔS^* indicate that the activation complexes have more ordered structure than the reactants.

(5) The ΔS^* values of the complexes occur in a decreasing order for the different acceptors as follows: PA > CHL > DDQ > Iodine.

(6) A linear relationship obtained between ΔH^* and ΔS^* (Fig. 4) for all complexes.

(7) It has been found that the complexation with PA and CHL acceptors increases the values of enthalpy and entropy, while the complexation with DDQ and iodine acceptors decreases the values of these parameters compared with the free GU donor.

CONCLUSIONS

Four new GU–acceptor complexes with iodine, DDQ, CHL, and PA acceptor were synthesized. Elemental analyses and spectrophotometric titration methods conclude that the complexes are formed based on a 1 : 1 stoichiometric ratio, except for iodine acceptor (1 : 2 ratio). Significant changes in the UV-Vis spectra were observed and may be attributed to the formation of the CT complexes. UV-Vis experimental data suggests that the interaction between the drug and iodine acceptor is characterized by the formation of the antisymmetric triiodide ion. Thermal experimental data suggests that the formation of the complexes was stable, exothermic and spontaneous. Our study provides a basis to understand the mechanism of the interaction of Guaifenesin with different σ- and π-acceptors.

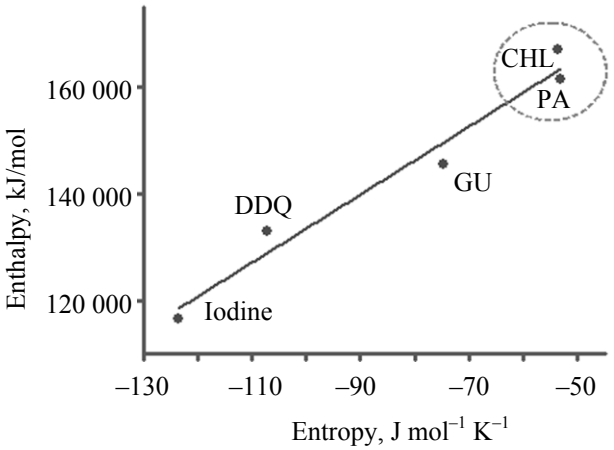

Fig. 4. Linear correlation between enthalpy and entropy of the GU and its CT complexes.

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