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ANTHRACENE ANALOG ADDUCTS

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A considerable number[1] of physiological processes depend on electron transfer from a donor to an acceptor molecule. In drugs[2] with electron donor properties such as those based on the phenothiazines, phenoxathiin and carbazole, profound interest attaches to the unambiguous assignment of the donor site.

We wish to report on the synthesis of a series of new tricyclic heteroaromatic adducts of the type shown in Fig. 1 with Q and R variously replaced by N,O,S,-CH_2-CH_2-, as listed in Table 1 with a series of electron acceptors such as BF_3, Br_2, I_2 and SO_2. We also wish to report on the donor sites in the heteroaromatics.

All compounds were of reagent grade purity. Adducts involving gaseous acceptors were prepared by condensation of the gas at liquid nitrogen temperature in an inert atmosphere. Warming of the interaction product to room temperature evaporated excess acceptor. I_2 adducts were generally prepared by grinding the compounds together in 1:2 donor-acceptor molar ratio to allow for possible stoichiometric variation[3] and excess I_2 evaporated at room temperature with a stream of nitrogen.

Adduct stoichiometry was determined by Byrd's method,[4] supplemented by conventional KI_3 redox titrations in the case of SO_2 adducts. Infrared spectra were recorded with a Beckman IR12 spectrometer with the adducts studied as KBr pellets, NaCl sandwiches or in Nujol with a cold cell[5] where necessary. Charge transfer bands were observed with a Cary 14 spectrometer while electron spin resonance scans of the adducts in sealed tubes were effected at room temperature with a spectrometer similar to a Varian 4502 EPR.

In all cases intensely colored 1:1 adducts were obtained which yielded the original components upon mild evacuation. The compounds formed interaction products with characteristics of molecular complexes generally dative in the ground state. Some spectroscopic data is given in Table 1. Portions of the IR spectra of some I_2- adducts are shown in Fig. 2.

The infrared spectra of the donors singly closely resembled the superimposed spectra of

those in adduct form, but all the fused tricyclic aromatic donors with a 5- or 6-membered central ring showed a new band (sometimes a doublet) in the 1600 cm^{-1} aromatic absorption region or an intensity increase of a band already present in this frequency range, irrespective of acceptor species used.

Changes in bondlengths and angles accompany electron-donor acceptor interactions and thus dipole moment changes leading to changes in the infrared spectra[6] of the components may be expected. Vibrational assignments of aromatic molecules are generally incomplete. Bridge substituted halogen-, cyano-,[7] and deutero-anthracenes[8] exhibit an intensity increase of bands near 1630 cm^{-1} compared with anthracene. Polarization vector studies[9] of the latter compound show this absorption to be caused by a dipole moment change in the direction of the bridge atoms in the plane of the molecule, i.e., in the Z-direction, Fig. 1. As the bridge atoms are progressively altered from C in anthracene to N in phenazine,[10] the relative intensity of this absorption is again increased. Complexation also[11] causes changes in absorptions of the 1600 cm^{-1} region, a view which supports the relative intensity enhancement of these bands in our adducts. The presence of a distinct new infrared doublet in several of the adducts with a 6-membered central ring indicates absorptions arising from parallel and anti-parallel stretching vibrations of the carbon pairs of the central ring. Such vibrations are not possible in the non-fused compounds, diphenylamine, triphenylamine, and the seven-membered central ring compounds iminodibenzyl and imipramine since these permit twisting of the aromatic rings and consequently exhibit no infrared intensity enhancement in this region. Consensus[12] exists that the intensification of the aromatic absorption at lower frequency (about 1580 cm^{-1}) is a positive indication of increased external conjugation, and this is observed in several of the fused ring adducts. It is unlikely that the intensification is due to a conjugated or polymeric species of the kind previously[13] suggested for phenothiazine adducts. These involved aromatic substitutions which must induce extensive changes in the CH out-of-plane bending pattern in the region 800-1000 cm^{-1} contrary to our observation Studies involving a large number of polynuclear aromatics[14], and conjugated heterocycles[15] suggest that π-electron donation causes a shift in CH out-of-plane bending absorptions to higher frequencies which is not a feature of our spectra. Hence, the electron donation in the heterocycles studies herein is of the π-type. From which it follows that the position occupied by the acceptor in these adducts is in the Y-Z plane, probably near the atom with the lower ionization potential.

Charge transfer complex formation depends on the ionization potential of the donor,

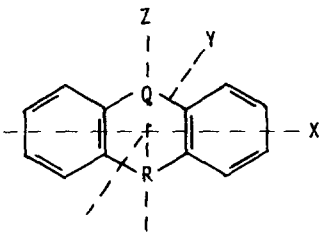

Fig. 1.

Fig 2

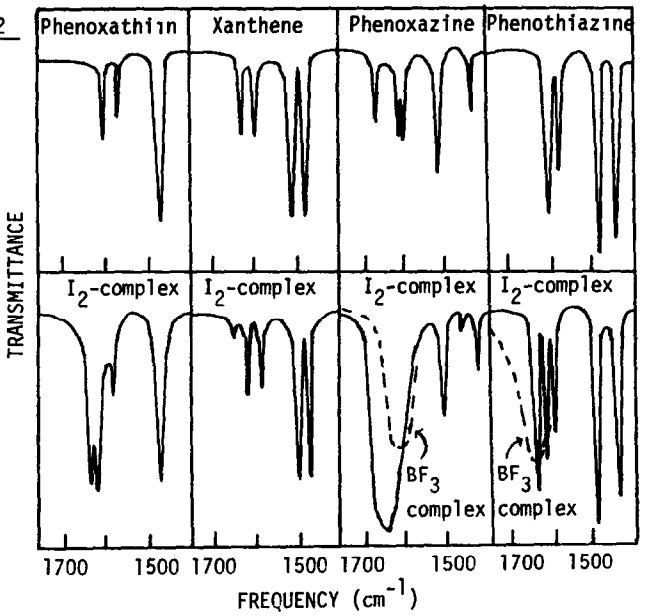

Table 1 Some Properties of Adducts

Donor \ Acceptor	Charge transfer band in $CHCl_3$ (m) SO_2	Br_2	esr intensity (referred to Pitch = 1) SO_2	BF_3	%ir intensity increase compared to parenthesized aromatic absorption as 100% internal standard (cm^{-1}) SO_2	Br_2	SO_2 Solubility (in SO_2)	Stability
Xanthene	395	**Obs.	0	0	no change	no change	Insoluble	Dissociates rapidly
Thianthrene	395	"	0 01	0	"	"	"	"
Carbazole	"	"	0 003	0.06	"	1605*30%(1630)	"	"
Iminodibenzyl	"	472	0	0.048	"	1560*	Red. Soln	"
Imipramine HCl	400	Obs.	0	0	"	no change	"	"
Diphenylamine	398	"	0.001	0 01	"	"	"	"
Triphenylamine	420	"	0	0.01	"	"	"	"
Phenazine	Obs	"	0.13	1.96	1630·60%	1630·200%(1550)	Insoluble	Dissociates slowly
Phenoxazine	420	590	0.28	4 5	1630·20% 1580·10%	1630.10%,1580·10% 1570*400%(1595)	Red. Soln.	"
Phenothiazine	430	468 525 570	0.32	6.2	1575:250%	1575 500%(1605)	"	"
N-methylphenothiazine	410	475 775	0.08	0.9	1610 60%	1610.20% 1575·200%(1600)	"	"
Chlorpromazine-HCl	405	540	0.005	0 1	1610 10%	1610 20%(1575 30%(1590)	Red oil	Stable
Ethopropazine-HCl	405	Obs	0 14	17	1640 50% 1570·10%	(1605)	"	"

* new band **Obs. = Obscured

electron affinity of the acceptor and steric factors which affect the proximity of the components in the adduct This is borne out by the comparative esr signal of the adducts. For instance, BF_3 is a stronger acceptor than SO_2 and induces a larger signal in the adducts. The donors containing bridge N and S, N and O, N and N generally exhibit the stronger of the adduct signals Chlorpromazine, as a thiazine derivative, might have been expected to show a strong signal, but of these derivatives it shows the weakest, suggesting that the side-chain may be a moderating influence. Nevertheless, our results support the contention that anthracene analog drugs which act physiologically in charge transfer capacity most likely do so initially via the central ring and as π-donors.

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