Charge-Transfer Complexes in Medicinal Chemistry. I. Correlations with the Psychotropic Activity of Piperidinol Esters and Related Compounds[1]

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Charge-transfer complex stabilities and quaternization rate constants of the benzoates of three piperidinols, quinuclidinol, ψ-granotoline, and tropine, were compared with their psychotropic activity as characterized by three different tests. The availability of the nonbonding electron pair of the hetero-N atom, influenced by molecular configuration and conformation, was found to correlate directly with the psychopharmacological activities.

Charge-transfer (CT) complex formation is one of the intermolecular forces presumably playing an important part in the drug–receptor binding process as well as in subsequent reactions. The rapidly growing interest of the physical chemist in CT phenomena is reflected lately in some data on compounds of interest to the medicinal chemist.[3]

A good opportunity to enter this field presented itself in the publication of the elegant investigations of Gabel and Abood.[4] They related the psychotropic activity of some benzilate esters of heterocyclic amino alcohols to molecular configuration and the availability of the nonbonding electron pair of the heterocyclic nitrogen. The authors, however, refrained from a quantitative determination of nucleophilicities, because of the semiquantitative nature of the pharmacological assays.

While this may be reasonable, we nevertheless deemed it worthwhile to examine exactly the nucleophilicity of the same series of compounds. Two methods seemed to be the obvious choice: CT complex formation and kinetic study of quaternization rates. Since both methods gave a good and exact indication of the "availability" of the nonbonding electron pair, they seemed to offer an opportunity to check the validity of Gabel and Abood's interesting hypothesis. The separate comparison of CT complex stabilities and quaternization rates with known[4] pharmacological activities promised also to reveal binding forces, if any, other than those due to nonbonding electrons (*e.g.*, π complexes of the aromatic acyl moiety).

Experimental Section

Synthesis.—Quinuclidinol and tropine were obtained commercially. N-methyl-3-piperidinol,[5] N-methyl-4-piperidinol,[6] N-methyl-ψ-granatoline,[7] and 1,2,2,6,6-pentamethyl-4-piperidinol[8] were obtained by known methods or their trivial modification.

The benzoates of the amino alcohols were prepared by heating them in excess benzoyl chloride until the usually exothermic reaction started. It was moderated by cooling if necessary and then completed by heating again to 100°. The ester hydrochlorides were isolated by crystallization from EtOH–Et_2O or EtOH alone, and the ester base was prepared just before use.

Melting points, analyses, and spectra of all compounds were in agreement with literature values or as expected.

Charge-Transfer Complex Formation.—A Beckman DK-2A recording spectrophotometer with a time-drive attachment was used to record absorption spectra. Chloranil (Matheson Coleman and Bell) served as acceptor, a fresh solution being prepared daily. All complexes were formed in a solution containing a 1:1 molar ratio of donor to acceptor in the following way: 2.6 ml of the donor solution was placed into a 1-cm quartz cuvette, the four concentrations used being 0.6, 0.8, 1.0, and 1.2×10^{-3} M, respectively. To this 0.26 ml of a 0.6, 0.8, 1.0, and 1.2×10^{-2} M chloranil solution was added, to keep the time required for mixing to a minimum. The formation of the complex was followed for 20 min at 550 mμ at all four concentrations. Each concentration was run three times and the deviations did not exceed $\pm 0.8\%$.

The solvent used throughout the series was 90% THF mainly for solubility reasons. To assure reproducibility in this rather capricious solvent, stringent purification procedures were established. The THF (Fisher Scientific Co., certified) was distilled from $LiAlH_4$ and the middle fraction was kept in a dark bottle equipped with a drying tube. To this 10% H_2O was added and used within a week.

To calculate complex stabilities and complex molar extinction coefficient, the Benesi-Hildebrand equation[9] was used and the calculation was done for every minute of the 20-min run, on an IBM 1620 computer. Because the stability constant changes with time, we show the median value from 4 to 20 min, since the change is most rapid and somewhat erratic in the first few minutes.

Quaternization Rate Measurements.—An equimolar mixture of the tertiary base and MeI was prepared from 0.1 M stock solutions in 95% dioxane. This was incubated at 25 ± 0.5° and 5-μl. samples were withdrawn from the solution (centrifuged to avoid crystals in the microsyringe). These samples were injected immediately into a Microtek 2000-R gas chromatograph. The following parameters gave excellent separation of the MeI from the dioxane and H_2O: column, 1 m × 3 mm methyl silicon rubber SE-30; inlet temperature, 240°; column temperature, 70°; He flow, 30 cc/min. The disappearance of MeI was followed as a function of time for 90 min, when even the slowest reaction was 10–15% completed. Since the CH_3I peaks are very sharp, the peak heights rather than areas were compared, the reading at the time of mixing being considered as 0.05 M. The deviation of parallel runs was ±1%. The rate constants were calculated in the usual way for a bimolecular second-order reaction.

Results and Discussion

With chloranil all six compounds used gave a broad CT band in the 530–550-mμ region not shown by either

(1) Presented in part at the III[ème] Rencontre International de Chimie Thérapeutique, Paris, July 1967.

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TABLE I

No.	Benzoate of	BDI[4]	Anti-cholinergic[4] ED_{50}, mg/kg	Complex stability $K_{4-20\,min}$ l. mole^{-1}	Quaternization rate constant $K_1 \times 10^{-3}$ l. mole^{-1} sec^{-1}
1	3-Quinuclidinol	16.2	70	4.5	1453
2	N-Methyl-4-piperidinol	15.8	300	23.0	118
3	N-Methyl-3-piperidinol	11.8	300	20.6	88
4	ψ-Granatoline	11.6	350	9.9	20
5	Tropine	10.0	350	10.6	64
6	Pentamethyl-4-piperidinol	7.4	100	6.7	9
	Saline	5.7			

compound alone. This develops fully within 6 to 10 min, after which time the increase in absorbance is very slow. The only exception was the N-methyl-benzoyl-ψ-granatoline, where the complex starts to disappear slightly after about 15 min and, probably due to fast secondary reactions, the absorbance decreases.

Other interesting phenomena, some photochemical in nature, were also observed and will be discussed in a future paper, since they shed light on the whole redox reaction of which the CT is only the first step.

Our results are shown in Table I and are compared to pharmacological data,[4] most notably to the behavioral disturbance index (BDI). This is a composite of activity cage, swim maze, and "peak" test results. The anticholinergic activity, as given by Gabel and Abood,[4] does not seem to be of great significance since it shows poor correlation with stereochemical considerations, BDI values, and also our own data.

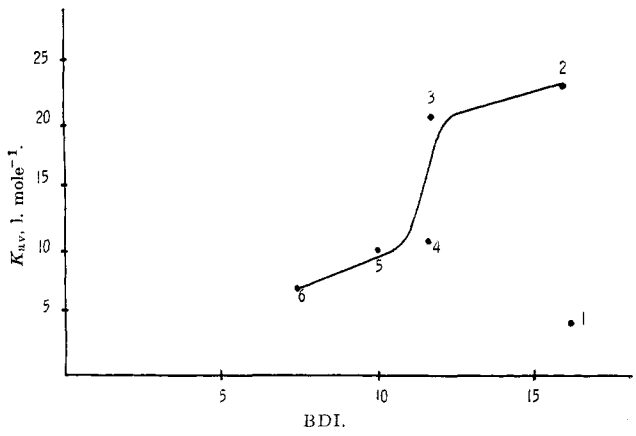

Figure 1.—Correlation of behavior disturbance index (BDI) with complex stability constant (K_{av}).

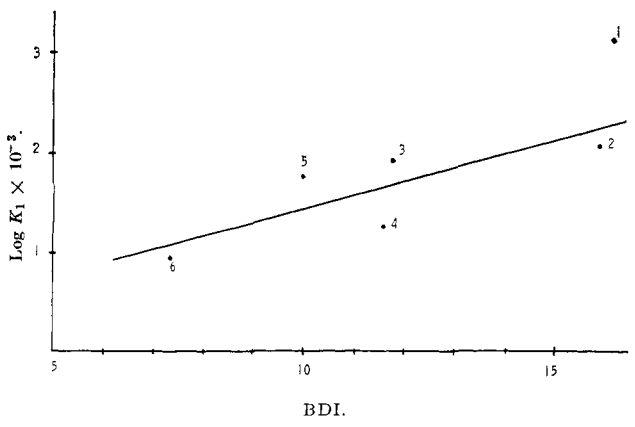

Figure 2.—Correlation of behavioral disturbance index (BDI) with quaternization rate constant.

The CT complex stability constants show a reasonable semiquantitative agreement with the BDI, with two notable exceptions: the value for benzoyloxyquinuclidine is the lowest in the series instead of being the highest, and the ψ-granatoline ester and benzoyltropine are in a slightly reversed order if compared to the sequence established on the basis of BDI data.

The reason for the first discrepancy could be the increased rate of secondary ionic reactions in the relatively polar solvent. We have some indications on the high rate of these reactions. Since this uses up the primary CT complex, the apparent stability constant may seem lower than it really is. This argument is strengthened by the extremely high quaternization rate constant (which is in a reasonably good agreement with literature data).[10] The second slight deviation from the order of activities established by Gabel and Abood is corroborated by quaternization rate data in a rather striking way.

The correlation of CT complex stability constants and quaternization rates with BDI is shown graphically in Figures 1 and 2. The deviation from strict linearity could probably be explained by two factors. First of all, we compare a very complex biological system (BDI) with a model chemical reaction, which may be an oversimplification. Secondly, Gabel and Abood used benzilic acid esters, whereas we used benzoates. However, we set out to investigate the "availability" of the nonbonding electron pair on the heteroatom. Since only the carbonyl part but not the aryl groups of the ester can interact with the electron pair, as already pointed out by Gabel and Abood,[4] the exact nature of the acyl part may be neglected justifiably in model systems, as long as any ester carbonyl is present and no adsorption or receptor fitting is involved (where size, shape, and hydrophobic interactions may play a role).

It may be concluded that the availability of the nonbonding electron pair of heterocyclic amino esters, measured by CT complex formation and quaternization rate studies, correlates quite well with established psychotropic activities, as far as the present series is concerned. The attractive hypothesis of Gabel and Abood could therefore be upheld in the light of our studies in molecular pharmacology.

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