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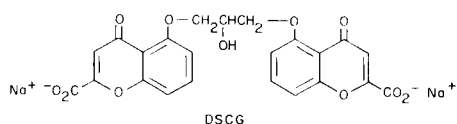
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The reaction of disodium cromoglycate with five cationic dyes: crystal violet, Janus green, methylene blue, methyl green, and safranin, was investigated. Spectroscopic shifts indicated that at low concentration (0.01 mM) all these dyes were able to form complexes (ion pairs) with the cromoglycate anion. In addition, the complexes formed by crystal violet and Janus green were extractable into chloroform.

J. Heterocyclic Chem., **16**, 845 (1979).

Disodium cromoglycate (DSCG) is an antiasthmatic drug which has received much scientific attention in the last ten years (1,2). A principal disadvantage of the drug is its poor absorption from the gastrointestinal tract, necessitating administration by inhalation. Gastrointestinal absorption of ionic drugs is partly a function of their lipid solubility (3), which is negligible in the case of DSCG. The absorption of isopropamide, a quaternary ammonium salt, was improved by replacing its iodide anion with trichloroacetate, which forms an ion pair extractable into organic solvents (4). A brief report on DSCG itself claimed enhanced buccal absorption when the drug was administered as an ion pair with a benzalkonium cation (5). We have observed that DSCG can form complexes with several cationic dyes and have investigated the ability of these dyes to solubilize the cromoglycate anion in chloroform.



The dyes used in this study are listed in Table I, and the results obtained with a detergent, benzyldimethylpentadecylammonium chloride (BDPAC), are given for comparison. At all concentrations employed, both crystal violet and Janus green formed complexes (ion pairs) with cromoglycate which could be extracted into chloroform. At the highest cation concentrations used, the efficiency of crystal violet as an extractant was greater than that of BDPAC; that of Janus green was lower. At high drug concentrations methylene blue, methyl green, and safranin all showed spectral evidence of complexation with cromoglycate (see below). However, these complexes could not be extracted from the aqueous solution. The extractability of the dye-drug complexes paralleled that of the dyes themselves. That is, 0.04 mM aqueous crystal violet and Janus green solutions without DSCG could be 90 and 73% extracted, respectively, but the other dyes remained almost totally in the aqueous layer. As the solubility of ion pairs in chloroform is an indication of their ability to be absorbed from the gastrointestinal tract (4), the results here suggest that substitution of the sodium ions of DSCG by certain large organic cations may render oral administration of the drug more feasible. The spectral effects observed upon reaction of DSCG with the dyes are also of interest. In all cases the peak of the dye in the visible region undergoes a bathochromic shift, probably because of π -electronic interaction between the dye and benzopyran ring systems. These shifts are listed in Table I. The large displacements in the case of Janus green reflect the superior ability of this dye to complex the cromoglycate anion and its extensive chromophoric system.

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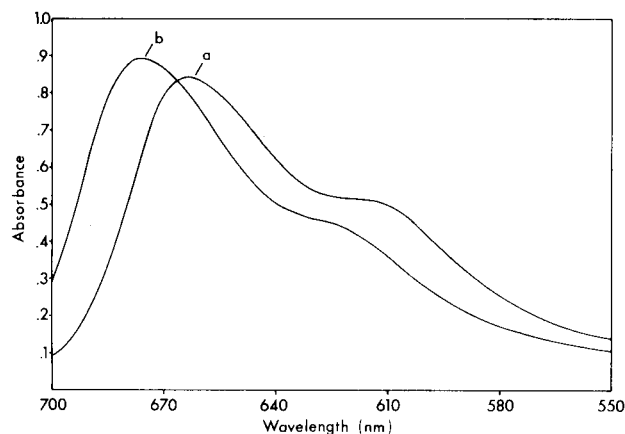


Figure 1. Absorption spectrum of 0.01 mM methylene blue in water in the absence (a) and presence (b) of 8 mM DSCG.

Figure 1 shows the changes induced by 8 mM DSCG in the spectrum of methylene blue. Here not only does a bathochromic shift occur, but the shoulder-to-peak absorbance ratio increases. © HeteroCorporation

Table I
Spectral and Extraction Results for Dye-Cromoglycate Complexes

Dye	Spectral Shifts (Nm) (a)		Extraction	
	0.025 mM	8 mM DSCG	Dye:Cromoglycate Mole Ratio	Partition Coefficient (b)
Crystal Violet	0.5	5	0 0.4 0.8 2.0	0 0.18 0.45 3.5
Janus Green	10	108	0.4 0.8 2.0	0.13 0.27 1.6
Methylene Blue	1	13 (c)	0.4 0.8 2.0	-0
Methyl Green	1.5	11 (c)	0.4 0.8 2.0	-0
Safranin	0.5	18 (c)	0.4 0.8 2.0	-0
BDPAC			0.4 0.8 2.0	0.19 0.48 2.1

(a) 0.01 mM Dye. (b) [Cromoglycate] in organic phase/[cromoglycate] in aqueous phase. (c) The complex formed in this mixture (dye:cromoglycate mole ratio = 0.00:25) was not extractable into chloroform.

ance ratio decreases by about 40% (6). The peak corresponds to the monomeric form of the dye, and part of the shoulder corresponds to the dimer (7). Therefore, it is possible that complexation with cromoglycate leads to dissociation of the dye dimer. Such an interpretation must be made with caution, however, because part of the

spectral shoulder is a component of the monomeric dye (7). A similar, though less pronounced, effect was observed with crystal violet, which also exhibits self-association and has a spectrum very close in shape to that of methylene blue (8). Further study of these phenomena may provide clues to reactive sites on the cromoglycate anion.

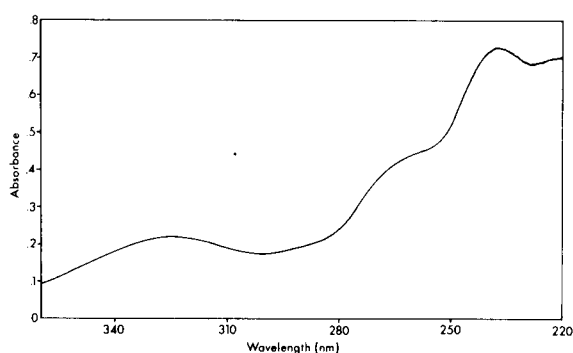


Figure 2. Absorption spectrum of 0.015 mM DSCG in water.

EXPERIMENTAL

DSCG was a gift from Fisons, Ltd., Bedford, Mass. Its purity was verified by paper chromatography in several different ethanol-water mixtures. BDPAC was a gift from A. E. Soria of Sterling-Winthrop Research Institute. Methylene blue was crystallized from ethanol and crystal violet and methyl green from water. Janus green was crystallized from isopentyl alcohol and washed with benzene. The safranin used was the commercial 0.25% solution, appropriately diluted. Triply distilled water and "analytical reagent" chloroform were used throughout.

Spectral scans were made with a Bausch and Lomb Spectronic 505 spectrophotometer. Absorbance readings for the extraction experiments were made with a Gilford model 240 spectrophotometer. One-cm quartz cuvettes were used.

Extractions were carried out by combining DSCG and dye (or BDPAC) so that the final concentration of the former was 0.025 mM and those of the latter were 0, 0.01, 0.02, and 0.05 mM. Five ml. of the aqueous solution was then shaken with an equal

volume of chloroform for one minute at room temperature. The amount of cromoglycate extracted was determined from the loss in absorbance of the aqueous solution at 326 nm, the longest-wavelength peak in the spectrum of DSCG (Figure 2). Corrections due to residual dye were made by simultaneously monitoring the long-wavelength peak of the dye, where DSCG does not absorb. In practice these corrections were slight because, at the concentrations employed, the dye was extracted nearly quantitatively into the organic phase or not at all. For this reason also the deviations from Beer's law characteristic of many dyes made no difference. BDPAC does not absorb at 326 nm, and therefore no correction was necessary in this case.

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