Table 2. Log *SR* sums for organic radicals and functional groups.

Group	No. of atoms	Σlog SR	Group	No. of atoms	Σlog SR
CH	2	1.1288	CHO	3	1.8456
CH_2	3	1.6790	COOH	4	2.5624
CH_3	4	2.2292	COO	3	2.0122
C_2H_5	7	3.9082	CO	2	1.2954
C_3H_7	10	5.5872	$CONH_2$	5	3.0480
C_4H_9	13	7.2662	COCl	3	1.9882
C_5H_{11}	16	8.9452	NH_2	3	1.7526
C_6H_{13}	19	10.6242	NH	2	1.2024
C_6H_5	11	6.2226	NO	2	1.3690
C_6H_4	10	5.6724	NO_2	3	2.0858
C_6H_3	9	5.1222	CF_3	4	2.8577
$CH_3C_6H_4$ / $C_6H_5CH_2$	14	7.9016	CF_2	3	2.0980
			CF	2	1.3383
OH	2	1.2670	SH	2	1.1640
CN	2	1.2308	SO_3H	5	3.3144

Some suggestions are offered here as an aid to the successful application of atomic-charge data.

1) The existence of partial charges on the atoms of a molecule implies not only polarity of the bonds but also special susceptibility of the charged atoms to the electrostatic interactions with other and separate charged atoms of the same molecule, if geometry permits. The molecular geometry may therefore be an important cofactor in the behavior of the molecule.

2) Steric influences apart from the electrostatic influences just referred to may also affect the molecule's behavior.

3) Much of organic chemistry involves multiple bonds in which certain electrons are more than ordinarily mobile. Such electrons may be especially susceptible to electrostatic influences introduced by bond polarity and may tend to oppose its expected effect. Mobility of outer unshared electron pairs may also be significant.

4) The availability on an atom of electrons for chemical reaction will, in general, be expected to diminish with increasing positive charge and to increase with increasing negative charge.

5) In evaluating the electron-releasing or electron-withdrawing power of an atom or group, it is necessary to take into account not only the charges on the atoms most directly involved but also the charge capacity of these atoms as influenced by the attached atoms or groups of atoms. The latter may be regarded as reservoirs that may permit an atom to release considerable charge without becoming excessively positive or to withdraw considerable charge without becoming excessively negative.

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New Blocking Agent against the Development of LSD-25 Psychosis

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Our clinical observations on Meratran (*1*), alpha-(2-piperidyl) benzhydrol hydrochloride, followed the experimental work of Brown and Werner (*2*). It differs significantly from other central nervous system stimulants such as the amphetamines. No cardiovascular pressor reactions, no appetite loss, and little disturbance in nocturnal sleep have been observed with this compound, which may be used therapeutically in mild depressive states (*3*) as well as in narcolepsy and certain selected motor tic syndromes (*4*). Himwich and his associates (*5*) state that Meratran is not a sympathomimetic drug. They have demonstrated that the central reticular substance of the rabbit brain is stimulated by the compound, followed by cortical stimulation, and Heath (*6*) found that Meratran has a unique ability to cause rapid high-voltage activity in the septal area of the monkey electrographically.

These clinical and experimental results impressed us with the fact that other compounds of similar chemical configuration might also be of value as therapeutic agents in disorders of the central nervous system. Brown and Werner (*7*) have found that the gamma-isomer of Meratran, alpha-(4-piperidyl) benzhydrol hydrochloride, prevents or diminishes central stimulation induced in the mouse by various agents, including amphetamine, morphine, cocaine, and Meratran.

In June 1954, we began to study this gamma-isomer of Meratran clinically; thus far we find that it appears to have therapeutic value in certain dissociation syndromes, although inconsistently in the dosage range used. Some cases of acute schizophrenia, alcoholic hallucinosis, senile and arteriosclerotic hallucinosis, and, to a lesser extent, some of the more chronic schizophrenic syndromes respond to the oral administration of this drug to a degree that has encouraged us to continue our observations, which will be reported later. Because of the dramatic way in which it has cleared up hallucinated, deluded, and dissociated patients on occasion, and despite the fact that its action has not been consistent, we decided to study the possible effect of this gamma-isomer of Meratran as a blocking agent against model psychoses produced by lysergic acid diethylamide (LSD-25) ingestion (*8*). Preliminary results are reported here (*9*).

In the first experiment (*10*) two healthy male graduate students in psychology swallowed 100 μg of LSD-25 in 100 ml of distilled water on the morning of 6 Nov. 1954. Typical psychotic responses occurred. In the first student, age 25, weight 88 kg, a 5½-hr psychosis resulted. He wrote:

> The pervading feeling was that there was a gulf between me and the rest of the environment. It seemed that it would be impossible for me to communicate

with those across this gulf because I could not establish any common points of reference. Also within this state there were hallucinations and a sense of timelessness, all unusual, none of which had any real emotional tone to them.

In the second student age 22, weight 70 kg, a distressing agitated paranoid state and almost catatonic withdrawal took more than 13 hr to come to an end. His written account reads in part:

I had very little by way of visual hallucinations, but what *I* consider the important thing that—well, what's a word to describe it—dissociated, plagued, pounded, weighed—all these are inadequate to describe the horrible state I was in, all of them put together. Perhaps the central thing was suspicion and fear that you would find out about me, or perhaps think things that were not true. On and on and ON this went, and, as was no doubt obvious, I decided to do as little as possible so I wouldn't make any mistakes.

On the next day both subjects were started on the blocking agent orally. The first was given 10 mg twice daily in tablet form; the second was given 5 mg in the same manner. This dose was continued throughout the subsequent week, during which time they continued their usual academic schedules, and a final dose of 10 mg in the first case and 5 mg in the second case was given on arising on 13 Nov. 1954, the date of the second 100-μg LSD-25 ingestion. The first subject recorded his impressions as follows:

The effects were markedly different on the second Saturday. There was some slight defect of attention and I didn't feel sharp mentally, but I have experienced this same sort of feeling when a hard day's work has tired me out. I felt that I had the situation under control and that I was not dissociated at any time. There were no hallucinations. I felt that I could have gone through my normal routine that Saturday morning although I would have preferred that my work be of a passive sort.

The second subject wrote of his experience as follows:

It was quite similar, yet it was very different. Where the first time, my mind began racing and becoming tangled, eventually swallowing me up despite my efforts, the second time my efforts to fight it off were successful. In one sentence, I think it might be summed up rather adequately by saying: It was a fight both times, but the second time, I won.

The gamma-isomer of Meratran, when given orally as a premedication, did not block the visceral effects of LSD-25 as it did the psychic. Nausea, a vague feeling of numbness in the limbs, tightening of the jaws, dry mouth, conjunctival injection and sweating of the extremities were among the manifestations noted on both occasions. No significant changes in pulse, blood pressure, respiration, or pupillary size were seen on the two experimental days. A month later the first experiment using LSD-25 without premedication was repeated, and psychotic reactions of the original type recurred in both boys, but in the second case it was terminated abruptly by intravenous administration of the blocking agent.

A second type of experiment was carried out on six subjects, three female and three male. In this study the subjects were kept in doubt about the dose of blocking agent used, or whether the tablets were placebos. None of the subjects reported any subjective or objective reactions during the premedication period. On the experimental day all were given 100 μg of LSD-25 in distilled water (which is tasteless) but were not informed of the contents of the drink.

Briefly, five of the six developed no psychotic states, or only fragmentary and fleeting manifestations of them, such as attention defect (3 cases), excessive laughter (2 cases), depression of mood level (1 case), fleeting visual hallucinations and distortion of spatial relationships (1 case), and disturbing nausea (3 cases). Dosage of the blocking agent varied from 10 to 30 mg daily for a week in divided doses prior to the LSD-25 ingestion.

The sixth subject, a quiet, intelligent intern, who had received five 1-mg tablets of the blocking agent twice daily for a week prior to ingesting LSD-25, became loquacious and depersonalized in a rapturous experience of "pure unblemished happiness" in which he had visual hallucinations of amorphous swirls of color, and again of green forests, and "an almost unspoken voice arising in response to the overwhelming abundance of sensation." Because he developed this response despite the administration of 10 mg of the blocking agent daily for a week prior to swallowing LSD-25, he was asked to continue the same number of tablets and to return the following Saturday. During the interval he was given five 5-mg tablets of the gamma-isomer of Meratran twice daily instead of five 1-mg tablets of similar appearance and was not told the difference. LSD-25 was given in the same 100-μg dose after this week of premedication with 50 mg daily of the blocking agent. On the second occasion he read a book and had nothing of the poetic flight of thinking with depersonalization and dissociation, or of the hallucinatory experiences of the previous Saturday, and stated that he could have carried out his intern's duties with his usual level of efficiency.

A recent observation on two subjects in which mescaline sulfate rather than LSD-25 was used suggests that this type of model psychosis can be blocked in the same fashion.

References and Notes

1. Meratran is the trademark of the Wm. S. Merrell Co., for its brand of pipradrol.
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9. I wish to express my thanks to W. E. Hillard for assisting in the experiments, to the Sandoz Chemical Works, Inc., New York, N.Y., for supplying LSD-25, and to the Wm. S. Merrell Co., Cincinnati, Ohio, for supplying the gamma-isomer of Meratran.
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Role of Cytochrome and Pyridine Nucleotide in Algal Photosynthesis

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All known important biological oxidation-reduction catalysts, such as cytochromes, flavins, and pyridine nucleotides, show appreciable changes in the near-ultraviolet or visible region of the absorption spectrum when they undergo oxidation or reduction. If any of these catalysts take part in photosynthesis, one would expect their oxidation-reduction state to change upon illumination.

To study the changes in absorption spectrum that may occur in photosynthesizing cells, a sensitive absorption spectrophotometer was developed with which, for the first time, fast, reversible changes in absorption spectrum were observed in purple bacteria (*1–3*) and in *Chlorella* (*4*). In general the changes upon illumination and upon darkening happened within a few seconds. In purple bacteria the difference spectrum in the visible region, obtained by subtracting the absorption spectrum in the light from that in the dark, was similar to, but not identical with, the spectrum obtained by subtracting the absorption spectrum of oxidized from that of reduced cytochrome *c* (*3*).

These experiments showed that a cytochrome pigment was quickly oxidized in the light and reduced in the dark. In *Chlorella* a peak of the difference spectrum was found at 420 mμ (*4*). In analogy with our findings with purple bacteria, this peak was tentatively attributed to the oxidation in light of cytochrome *f*, a cytochrome pigment discovered by Hill and Scarisbrick (*5*), and only found in leaves and algae. However, there was also a much higher peak at 520 mμ and a smaller one at 480 mμ. Since neither of these peaks could be attributed to a cytochrome, the interpretation of the effect as a whole was uncertain. Lundegårdh (*6*), by using a modification of a flow method used by us before (*2*), measured a narrow region of the difference spectrum of *Chlorella* from 550 to 570 mμ and found, at 555 mμ, a small dip in the difference spectrum, which too, could be attributed to cytochrome *f* (and so interpreted by him).

The experiments described in this article (*7*) were performed with an apparatus similar in principle to but having a greater sensitivity and range than the original one (*1*).

Clear-cut evidence for the oxidation of a cytochrome in algae was obtained in experiments on the red alga *Porphyridium cruentum*. The difference spectrum is shown in Fig. 1. The spectrum shows a maximum at 555 mμ which occurs also in the difference spectrum of cytochrome *f*, shown in the same figure, and maximums in the blue resembling those of cytochrome *f*. This shows that in *Porphyridium* cytochrome *f*, or a cytochrome with similar absorption spectrum, becomes oxidized in the light and reduced in the dark. The spectrum of *Porphyridium* was measured after the cells had been in a closed vessel in the dark for about half a day, a treatment that was found to increase the change in absorption upon illumination without profoundly changing the shape of the spectrum in the visible region.

In contradistinction to the spectrum of *Chlorella*, the difference spectrum of *Porphyridium* did not show pronounced peaks at 480 and 520 mμ. The difference spectrum of *Chlorella* showed a peak at 420 and a small dip at 555 mμ, both of which were very probably caused by the same cytochrome pigment as the peaks at 420 and 555 mμ in *Porphyridium*. The magnitude and the time course of the absorption changes in the maximums at 420 and 520 mμ were influenced differently by changing the medium, indicating that these maximums resulted from two different substances.

The oxidation of a cytochrome in light and its reduction in dark in photosynthesizing species of widely different groups suggest an important role for this pigment in photosynthesis. In respiration, the reactions leading to the oxidation of DPNH (reduced diphosphopyridine nucleotide) are mediated by cytochrome *c*. In these reactions, ATP (adenosine triphosphate) is probably generated (*9*), and the function of the cytochrome in photosynthesis may well be that of an intermediate in processes leading to the formation of ATP, which presumably is needed to assist in the carbon dioxide reduction (*10*). Arnon *et al.* (*11*) showed that ATP can be generated by illuminated chloroplasts from added ADP (adenosine diphosphate) and inorganic phosphate.

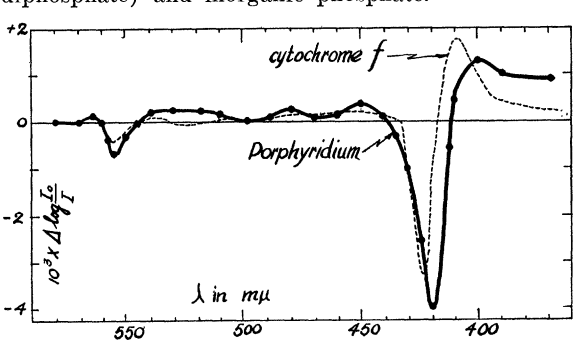

Fig. 1. Difference spectrum of *Porphyridium*, absorption spectrum in light minus that in darkness; and of cytochrome *f*, oxidized minus reduced. The latter spectrum was obtained by subtracting the spectra of reduced and oxidized cytochrome *f* measured by Davenport and Hill (*8*). The optical density of the *Porphyridium* suspension corrected for scattering was 0.46 at 680 mμ.