1 or 2, above) since (a) the induced anomalous ORD could only be detected in the region of maximum absorption for the HBABA–protein complex, (b) the ERD effect was small, and (c) no change was observed in the ORD spectrum at 233 mμ. These data, however, do not differentiate between configurationally or conformationally induced rotatory activity.

Irrespective of the mechanism of induced optical rotatory activity, these data complement the results obtained spectrophotometrically and by equilibrium dialysis and do suggest that if any structural change in the protein is involved, the change must be exceedingly small and/or occurring at the end of the polypeptide chain. Certainly, a large rearrangement of secondary structure is not involved. That a small change in structure is occurring with RSA is suggested by the displacement of the induced ORD to a longer wavelength (a 26-mμ shift) upon adding CPMPA. This shift in the induced ORD is not paralleled by a bathochromic shift of the λ_{max} at 477 mμ; *i.e.*, HBABA seems to be binding to a new site in the presence of CPMPA. Again, it is difficult to explain the unmasking of this new site without invoking the concept of allosteric transition. How general this phenomenon is and how important it may be in drug transport mechanisms remains to be seen.

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Molecular Orbital Calculations on Anticonvulsant Drugs

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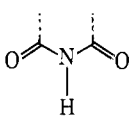
Molecular orbital calculations on a number of anticonvulsant drugs and related compounds have been completed by two methods, extended Hückel and complete neglect of differential overlap. Calculated dipole moments indicate that the latter method is more suitable for assessing net atomic charges. The calculated atomic charges at a "biologically active center" proposed by Perkow, together with those at atoms capable of forming hydrogen bonds, have been compared with observed anticonvulsant activity. The "biologically active center" does not appear to effect activity, while the hydrogen-bonding atoms, although common to all the drugs studied, are not proved responsible for variations in activity.

Widespread research on anticonvulsant drugs has led to numerous theories[1] which ascribe their CNS activity to a variety of simple physicochemical properties, but none appears to account satisfactorily for all the observed facts. A selection of anticonvulsant drugs which have proved useful clinically, together with some related compounds, is shown in Table I. These compounds all have a similar structure, and the presence of the grouping I appears to be a possible factor in their activity. Furthermore, it seems feasible that variation in the net atomic charges in this part of the molecule might change the CNS activity of the drugs by altering hydrogen-bonding behavior.



I

II

Another hypothesis has been put forward by Perkow,[2] who suggests that the net charge at a biologically active center (BAC), starred in II, is partly responsible for the type and degree of CNS activity. In this work both hypotheses have been tested by completing molecular orbital calculations on the compounds shown in Table I.

Methods

The molecular orbital calculations used were the extended Hückel theory (EHT) of Hoffmann[3] and the complete neglect of differential overlap calculation (CNDO/2) devised by Pople and Segal.[4] The original atomic parameters have been retained, except for some of the valence-state ionization potentials employed in the EHT calculations, which were averaged from atomic spectral data.[5] The values used were (in eV) H_{1s}, 13.6; C_{2s}, 20.8; C_{2p}, 11.3; N_{2s}, 26.5; N_{2p}, 13.6; O_{2s}, 33.0; O_{2p}, 16.2. The calculation of atomic charges by both methods, and of dipole moments by the CNDO/2 method, is described in the original papers. The EHT dipole moments, μ, were evaluated from expressions 1 and 2 where Q_A is the net charge on atom A, x_A is the

$$\mu_x = 4.80 \sum_{A}^{\text{atoms}} Q_A x_A - 7.337 \sum_{A}^{\text{atoms}} P(2s,2p_x)_A / Z_A \quad (1)$$

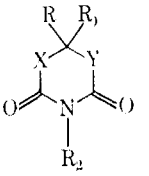
$$\mu^2 = \mu_x^2 + \mu_y^2 + \mu_z^2 \quad (2)$$

x coordinate, $P(2s,2p_x)_A$ is the bond order[4] between the 2s and $2p_x$ orbitals, and Z_A is the Slater exponent. The first term in eq 1 is the contribution from the net atomic charges, and the second is the atomic polarization contribution.[4]

Using Hoffmann's program[6] as a basis, a Fortran IV program[6] has been written which does EHT calculations for systems involving up to 96 atomic orbitals. The CNDO/2 calculations were done with a Fortran IV program[6] written by Segal, which handles a maximum of 72

(1) T. C. Butler, *Pharmacol. Rev.*, **2**, 121 (1950).
(2) W. Perkow, *Arzneimittel-Forsch.*, **10**, 284 (1960).
(3) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963).
(4) (a) J. A. Pople and G. A. Segal, *ibid.*, **43**, S136 (1965); (b) J. A. Pople and G. A. Segal, *ibid.*, **44**, 3289 (1966).
(5) (a) H. A. Skinner and H. O. Pritchard, *Chem. Rev.*, **55**, 745 (1955); (b) G. Pilcher and H. A. Skinner, *J. Inorg. Nucl. Chem.*, **24**, 937 (1962).
(6) Available from Quantum Chemistry Program Exchange, University of Indiana, Bloomington, Ind.

TABLE I



Compd	X	Y	R	R_1	R_2
Barbituric acid		CONH	H	H	H
5,5-Diethylbarbituric acid		CONH	C_2H_5	C_2H_5	H
5-Ethyl-5-phenylbarbituric acid		CONH	C_2H_5	C_6H_5	H
5-Ethylhydantoin		NH	C_2H_5	H	H
5-Phenylhydantoin		NH	C_6H_5	H	H
5-Ethyl-5-phenylhydantoin		NH	C_2H_5	C_6H_5	H
5,5-Diphenylhydantoin		NH	C_6H_5	C_6H_5	H
Succinimide		CH_2	H	H	H
1-Methylsuccinimide		CH_2	H	H	CH_3
3-Phenylsuccinimide		CH_2	C_6H_5	H	H
3-Methyl-3-phenylsuccinimide		CH_2	CH_3	C_6H_5	H
3-Ethyl-3-phenylsuccinimide		CH_2	C_2H_5	C_6H_5	H
3,3-Diphenylsuccinimide		CH_2	C_6H_5	C_6H_5	H
5,5-Dimethyloxazolidine-2,4-dione		O	CH_3	CH_3	H
3,5,5-Trimethyloxazolidine-2,4-dione		O	CH_3	CH_3	CH_3
3,5-Dimethyl-5-ethyloxazolidine-2,4-dione		O	C_2H_5	CH_3	CH_3
Glutarimide	CH_2	CH_2	H	H	H
N-Methylglutarimide	CH_2	CH_2	H	H	CH_3
β-Methylglutarimide	CH_2	CH_2	CH_3	H	H
β,β-Dimethylglutarimide	CH_2	CH_2	CH_3	CH_3	H
β-Methyl-β-ethylglutarimide	CH_2	CH_2	CH_3	C_2H_5	H
β-Methyl-β-*n*-propylglutarimide	CH_2	CH_2	CH_3	*n*-C_3H_7	H
β-Methyl-β-*n*-butylglutarimide	CH_2	CH_2	CH_3	*n*-C_4H_9	H
α-Ethyl-α-phenylglutarimide		CH_2CH_2	C_2H_5	C_6H_5	H

atomic orbitals. Input for both programs consists of atomic numbers and molecular geometries.

Since the geometries of many of the drugs considered are not known, they were obtained by averaging bond lengths and angles from similar molecules. Thus, for example, the ring geometry used for the hydantoins was based upon the known geometries[7] of cycloserine hydrochloride, succinimide, creatinine, parabanic acid, isatin, and ethylenethiourea. Minimal adjustments were made to the average bond lengths and angles to form a closed ring. The bond lengths and angles used for the substituent groups were C–C, 1.54 Å; C–C (aromatic), 1.39 Å; N–C, 1.47 Å; C–H, 1.09 Å; sp^3, 109°28′; and sp^2, 120°. The preferred orientations of the substituent groups are unknown, but EHT calculations on twelve conformations of 5-ethylhydantoin, for which results are given in Table II, show that the choice of molecular conformation is not critical. Similar results were obtained for 5-phenylhydantoin. In all subsequent calculations the conformation which allowed maximum bond staggering was used, since this procedure generally minimizes total energy.[3]

Results and Discussion

It is recognized that EHT calculations exaggerate atomic charges,[3] whereas the CNDO/2 method, judged on ability to predict dipole moments,[4,8] is close to optimum in this respect. Comparison of calculated dipole moments with known experimental values, given in Table III, further verifies these generalizations. Atomic charges calculated by the CNDO/2 method are therefore preferable, but those obtained from EHT calculations are included for comparison, since some molecules considered were beyond the capacity of the CNDO/2 program.

For all compounds except the glutarimides, the calculated charges are compared with activity against both supramaximal shock and pentylenetetrazole. The glutarimides are classified according to type of activity.

Biologically Active Center (BAC) Hypothesis.—Comparison of the charge at the BAC with anticonvulsant activity (Table IV) shows that there is no direct correlation between the two. In addition, the glutarimides, which range from anticonvulsants through to convulsants, all have a BAC charge within the anticonvulsant range. It is thus apparent that the net charge at Perkow's biologically active center does not determine the type or degree of the CNS activity exhibited by the drugs studied.

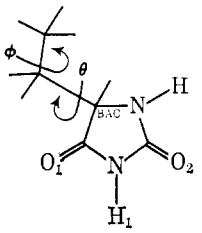
Hydrogen-Bonding Hypothesis.—The net charges at the three terminal atoms in I have been taken as a measure of hydrogen-bonding ability. This procedure is by no means rigorous, but it is not unreasonable for compounds with similar structure, such as those considered here. In cases where there are more potential bonding sites than those common to all of the drugs, it is assumed that the additional sites will only increase the number of ways in which the molecule can form hydrogen bonds, and not the strength of the bonding. The net atomic charges on the three relevant atoms are presented, to-

(7) L. E. Sutton, Ed., "Tables of Interatomic Distances," Special Publication No. 11 and 18, The Chemical Society, London, 1958 and 1965.

(8) J. E. Bloor and D. L. Breen, *J. Am. Chem. Soc.*, **89**, 6835 (1967).

TABLE II

VARIATION IN ATOMIC CHARGES AND MOLECULAR ENERGY WITH ORIENTATION OF THE ETHYL GROUP IN 5-ETHYLHYDANTOIN (EHT METHOD)



Dihedral angles, deg		Atomic charges				Rel
θ	φ	BAC	O_1	H_1	O_2	energy, eV
0	0	0.206	−1.333	0.321	−1.341	1.311
60	0	0.225	−1.332	0.321	−1.341	0.265
120	0	0.209	−1.335	0.321	−1.341	0.514
180	0	0.224	−1.335	0.321	−1.341	0.211
240	0	0.213	−1.335	0.321	−1.341	1.076
300	0	0.222	−1.335	0.321	−1.342	0.291
0	180	0.210	−1.331	0.321	−1.341	0.630
60	180	0.220	−1.329	0.321	−1.341	0.099
120	180	0.207	−1.335	0.321	−1.341	0.225
180	180	0.220	−1.335	0.321	−1.341	0.000
240	180	0.214	−1.335	0.321	−1.341	0.486
300	180	0.218	−1.335	0.321	−1.341	0.059

TABLE III

DIPOLE MOMENTS

Compound	Calcd dipole, D		Expl dipole, D
	EHT	CNDO/2	
Barbituric acid	0.43	0.61	1.04[a]
5,5-Diethylbarbituric acid	0.53	0.71	1.13[a]
5-Ethyl-5-phenylbarbituric acid	1.27		0.87[a]
Succinimide	6.40	2.05	1.47[b]
1-Methylsuccinimide	5.61	1.88	1.61[b]
3,5,5-Trimethyloxazolidine-2,4-dione	3.73	2.01	1.74[c]
3,5-Dimethyl-5-ethyloxazolidine-2,4-dione	3.73	2.05	1.69[c]
Glutarimide	9.18	3.10	2.58[b]
N-Methylglutarimide	8.46	3.03	2.70[b]
β-Methyl-β-ethylglutarimide	9.45	3.34	2.92[b]
α-Ethyl-α-phenylglutarimide	8.67		2.83[b]

[a] S. Soundararajan, *Trans. Faraday Soc.*, **54**, 1147 (1958). [b] C. M. Lee and W. D. Kumler, *J. Am. Chem. Soc.*, **83**, 4586 (1961). [c] C. M. Lee and W. D. Kumler, *ibid.*, **83**, 4596 (1961).

TABLE IV

Compound	Charge on BAC		Activity	
	EHT	CNDO/2	Electroshock[a]	Pentylenetetrazole[b]
3,5,5-Trimethyloxazolidine-2,4-dione	0.618	0.122	6.85[d]	5/1.75[d]
3,5-Dimethyl-5-ethyloxazolidine-2,4-dione	0.602	0.118	2.55[d]	5/0.80[d]
5-Ethyl-5-phenylhydantoin	0.330	0.085	0.19[e]	5/2.44[d]
5,5-Diphenylhydantoin	0.329		0.04[e]	0/1.97[e]
5-Phenylhydantoin	0.206	0.061	0.90[f]	3/2.82[d]
3-Methyl-3-phenylsuccinimide	0.065	−0.022	0.53[g]	5/0.34[g]
5-Ethyl-5-phenylbarbituric acid	0.050		0.10[e]	5/0.21[e]
5,5-Diethylbarbituric acid	0.048	−0.068	1.01[h]	
3-Ethyl-3-phenylsuccinimide	0.047		0.29[g]	5/0.32[g]
3,3-Diphenylsuccinimide	0.044		0.18[g]	0/1.97[g]
3-Phenylsuccinimide	−0.080	−0.043	1.70[g]	5/1.42[g]
Succinimide	−0.197	−0.061	>4.04[g]	0/5.05[g]
β,β-Dimethylglutarimide		0.069	Convulsant[c]	
β-Methyl-β-ethylglutarimide		0.064	Convulsant[c]	
β-Methyl-β-n-butylglutarimide		0.060	Anticonvulsant[c]	
β-Methyl-β-n-propylglutarimide		0.058	Dual action[c]	
β-Methylglutarimide		0.053	Inactive[c]	
Glutarimide		0.033	Inactive[c]	

[a] Supramaximal electroshock data. Activity is the dose (in mmoles/kg) which protects 50% of mice from the tonic extensor phase. [b] Pentylenetetrazole data. Activity is the number of rats (out of five) protected by the given dose (in mmoles/kg). [c] From A. Shulman, *Proc. Roy. Australian Chem. Soc.*, **31**, 41 (1964). [d] G. Chen, C. R. Ensor, and I. G. Clarke, *A.M.A. Arch. Neurol. Psychiat.*, **66**, 329 (1951). [e] G. Chen and C. R. Ensor, *ibid.*, **63**, 56 (1950). [f] C. R. Ensor and G. Chen, *ibid.*, **62**, 857 (1949). [g] G. Chen, R. Portman, C. R. Ensor, and A. C. Bratton, Jr., *J. Pharmacol. Exptl. Therap.*, **103**, 54 (1951). [h] G. Chen, B. Bohner, and C. R. Ensor, *Proc. Soc. Exptl. Biol. Med.*, **87**, 334 (1954).

TABLE V

Compound	Atomic charges (EHT) O_1	H_1	O_2	Atomic charges (CNDO 2) O_1	H_1	O_2	Activity Electroshock[a]	Pentylenetetrazole[b]
5-Ethyl-5-phenylbarbituric acid	−1.311	0.332	−1.343				0.10[c]	5 0.21[c]
5,5-Diphenylhydantoin	−1.317	0.322	−1.341				0 0.4[c]	0 1.95[c]
5-Ethyl-5-phenylhydantoin	−1.326	0.322	−1.341	−0.370	0.150	−0.408	0 1.9[c]	5 2.41[d]
3,5,5-Trimethyloxazolidine-2,4-dione[e]	−1.327		−1.312	−0.337		−0.361	0.85[d]	5 1.75[d]
3,5-Dimethyl-5-ethyloxazolidine-2,4-dione[e]	−1.327		−1.313	−0.337		−0.360	2.55[d]	5 0.80[d]
5,5-Dimethyloxazolidine-2,4-dione	−1.327	0.323	−1.313	−0.343	0.161	−0.366		
5,5-Diethylbarbituric acid	−1.329	0.332	−1.342	−0.324	0.156	−0.368	1.01[b]	
3,3-Diphenylsuccinimide	−1.331	0.321	−1.353				0.18[g]	0 1.97[g]
5-Phenylhydantoin	−1.335	0.322	−1.341	−0.339	0.156	−0.384	0.90[f]	3 2.82[g]
3-Methyl-3-phenylsuccinimide	−1.340	0.321	−1.352	−0.364	0.156	−0.353	0.53[g]	5 0.34[g]
3-Ethyl-3-phenylsuccinimide	−1.340	0.321	−1.352				0.29[g]	5 0.32[g]
3-Phenylsuccinimide	−1.350	0.322	−1.353	−0.360	0.160	−0.355	1.70[g]	5 1.42[g]
Succinimide	−1.353	0.321	−1.353	−0.371	0.156	−0.371	>4.0[g]	0 5.05[g]
β-Methylglutarimide				−0.323	0.143	−0.323	Inactive[c]	
Glutarimide				−0.337	0.140	−0.337	Inactive[c]	
β,β-Dimethylglutarimide				−0.340	0.139	−0.340	Convulsant[c]	
β-Methyl-β-*n*-propylglutarimide				−0.342	0.142	−0.342	Dual action[c]	
β-Methyl-β-*n*-butylglutarimide				−0.354	0.139	−0.354	Anticonvulsant[c]	
β-Methyl-β-ethylglutarimide				−0.356	0.139	−0.356	Convulsant[c]	

[a–b] See corresponding footnotes in Table IV. [c] These compounds are demethylated at N metabolically (T. C. Butler, *J. Am. Pharm. Assoc.*, **44**, 367 (1955)). One of the demethylated compounds, 5,5-dimethyloxazolidine-2,4-dione, is included for comparison.

gether with activity data, in Table V. There is no correlation between the calculated atomic charges and observed activity, indicating that hydrogen-bonding ability, in terms of net atomic charges, is unrelated to the type or extent of activity. Indeed the charges on these atoms remain fairly constant, and it seems possible that their specific hydrogen-bonding ability is involved in both convulsant and anticonvulsant activity.

On this basis it is suggested that the CNS activity of the drugs studied may be due to a strong and specific hydrogen-bonding complex with a cellular substrate, where the type and extent of action depend on the position and size of substituent groups. Recent ir[9] and X-ray crystallography[10] studies demonstrated that a hydrogen-bonded complex is formed between a model substrate, 9-ethyladenine, and a number of barbiturates, including those studied here. It has been suggested subsequently[11] that the physiological activity of the barbiturates may be due to their disruption of the coenzyme, flavin-adenine dinucleotide. However the results of the calculations reported here, together with preliminary ir studies, indicate that the convulsant β-methyl-β-ethylglutarimide also associates with 9-ethyladenine. This cannot readily be explained by the coenzyme disruption hypothesis.

Acknowledgments.—I wish to express my gratitude to Professor A. S. Buchanan and Dr. R. D. Harcourt for many helpful discussions on this work. Financial support from a CPGA is gratefully acknowledged.

(9) V. Kyogoku, R. C. Lord, and A. Rich, *Nature*, **218**, 69 (1968).
(10) S. Kim and A. Rich, *Proc. Natl. Acad. Sci. U. S.*, **60**, 402 (1968).
(11) Y. Kyogoku and B. S. Yu, *Bull. Chem. Soc. Jap.*, **41**, 1742 (1968).

Molecular Orbital Calculations on a New Series of Substituted-Phenyl Choline Ethers

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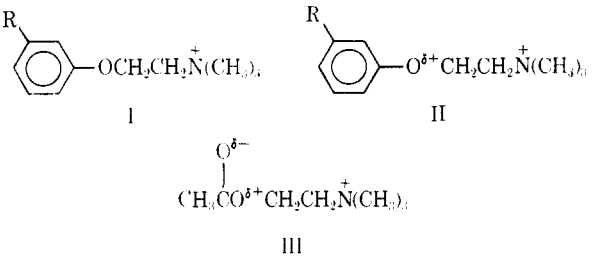
In addition to the onium head, it has been suggested that the electron density at some other points in the molecule of phenyl and substituted-phenyl choline ethers contribute to the intensity of nicotine-like activity. Simple Hückel molecular orbital calculations revealed that charge densities in the remainder of the molecule could not be correlated with pharmacologic activity. However, superdelocalizability at ring positions 2 and 6 and the energy of the highest occupied molecule orbital showed good parallelism with biologic activity. It was suggested that the aromatic ring may interact with the receptor by forming a charge-transfer complex.

The ganglionic stimulant action (nicotine-like action) of phenyl choline ethers (I) varies greatly with the substituent,[2] but the underlying mechanism of this activity remains obscure. In addition to the onium head, it has been postulated that the electron density at some other points in the molecule contributed to the intensity of nicotine-like activity.



(1) (a) Data presented are in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Mississippi. (b) Department of Pharmacology, University of Kiel, Germany. (c) Supported in part by U. S. Public Health Service Grant No. HE 08678.
(2) (a) P. Ney, *Brit. J. Pharmacol.*, **7**, 117 (1952); (b) M. E. Coleman, A. S. Hunte, and W. C. Holland, *J. Pharmacol. Exptl. Therap.*, **148**, 66 (1965).