since the normalized hyperfine splitting due to the metal nucleus is among the largest observed to date in the bis and tris complexes containing bidentate, unsaturated sulfur-donor ligands.[6] As soon as definitive crystal structural work now in progress[8] is completed, we shall attempt to derive a molecular orbital scheme which will be able to formulate consistently these interesting new complexes.

(8) R. Eisenberg and J. A. Ibers, private communication.
(9) National Science Foundation Predoctoral Fellow, 1963–1964.

DEPARTMENT OF CHEMISTRY
COLUMBIA UNIVERSITY
NEW YORK, NEW YORK 10027
JAMES H. WATERS
RAYMOND WILLIAMS[9]
HARRY B. GRAY

INSTITUT FÜR ANORGANISCHE CHEMIE
DER UNIVERSITÄT MÜNCHEN
MÜNCHEN, GERMANY
G. N. SCHRAUZER
H. W. FINCK

RECEIVED JULY 21, 1964

## A Quantitative Scale of Acceptor Strengths from Fluorine Nuclear Magnetic Resonance Shielding[1]

*Sir:*

The shielding of the fluorine atom in a *p*-fluorophenyl derivative, *p*-$FC_6H_4X$, has been shown to be a highly sensitive measure of the power of the group X to contribute or withdraw electronic charge from the benzene ring in its ground electronic state.[2] If the group X is formed by interaction between a common donor function and a series of Lewis acids, the relative polarizing power of the X group, as measured by the shielding, should reflect the strength of this interaction. With a donor function of minimum steric requirements, this physical measurement can potentially provide an "intrinsic" scale of acceptor strengths with useful chemical applications.

We report here the result of preliminary studies which appear to establish definitely the potential of this method. The donor molecule used is *p*-fluorobenzonitrile (FBN). Brown[3] has demonstrated previously the minimal steric requirements of the spike-shaped nitrile function.

Figure 1 records the results of a series of experiments carried out with an approximately constant concentration (~0.4 *M*) of FBN and varying concentrations of *p*-fluorophenylboron dichloride. These experiments constitute a "double-label" investigation of the complexing. The shielding parameters for the single observed fluorine signal (obtained at 40 Mc.) from both acid and base are plotted in Fig. 1 *vs.* the stoichiometric acid–base ratio (*a*/*b*). For a rapid reversible equilibrium, the fluorine signal is the weighted average of the shielding parameters for complexed and uncomplexed acid or base.[4] On complexing, the FBN signal appears at decreased field strength, and the acid fluorine signal at increased field, as anticipated for the flow of charge from base to acid.[5] The concentration dependence of both signals is satisfactorily described by assuming the formation of a 1–1 complex having a formation constant of 6.0 ± 0.6 $M^{-1}$, as illustrated in Fig. 1 by the agreement between experimental points and the theoretical curves.[6] The change in shielding parameters $\Delta_{complex}$ between completely complexed and uncomplexed FBN is given in Table I. The corresponding (estimated[6]) value for the *p*-fluorophenylboron dichloride is $\Delta_{complex} = +12 \pm 1$ p.p.m.

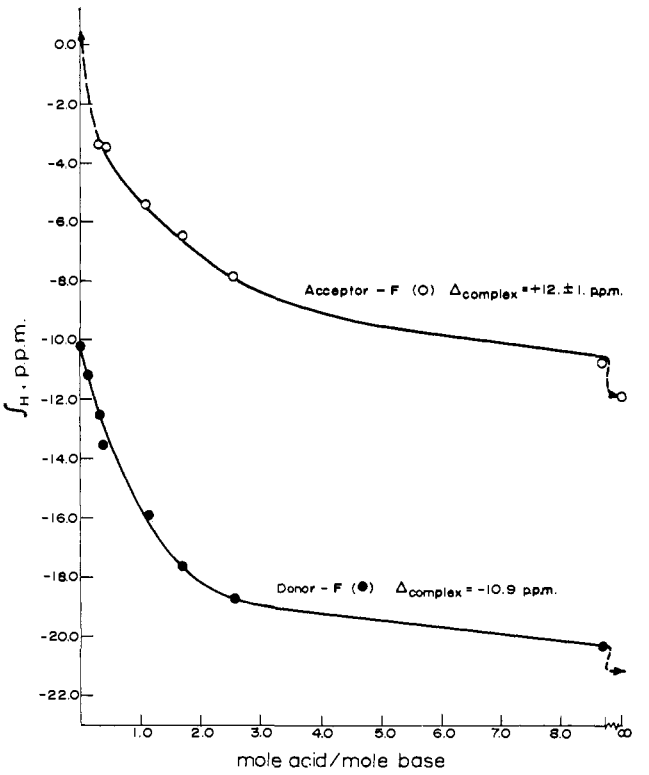



Fig. 1.—Double-label investigation of donor-acceptor complexing between *p*-fluorophenylboron dichloride and FBN in methylene chloride at 25°; theoretical curves based on $K_{form}$ = 6.0 ± 0.6 $M^{-1}$ and indicated limiting shifts.

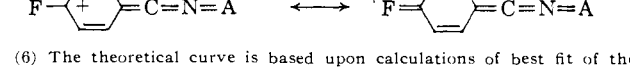
TABLE I

F N.M.R. SHIELDING PARAMETERS OF *p*-FLUOROBENZONITRILE DONOR–ACCEPTOR COMPLEXES. A QUANTITATIVE MEASURE OF ACCEPTOR STRENGTHS

| Acceptor | $\Delta_{complex}$,[a] p.p.m. | $\Delta H_d$,[b] kcal./mole | $K_f$, $M^{-1}$ |
|---|---|---|---|
| None | 0.00[c] | 0.0 | ... |
| $B(CH_3)_3$ | ... | 15.3 ± 0.2 | Very small |
| $BF_3$ | −9.25[d] | 25.0 ± 1.0 | 76 ± 20 |
| *p*-$FC_6H_4BCl_2$ | −10.90[d] | ... | 6 ± 0.6 |
| $B_2Cl_4$ | −11.50[e] | ... | ≥5000 |
| $BCl_3$ | −12.30[e] | 30.8 ± 0.2 | ≥5000 |
| $BBr_3$ | −13.10[e] | 32.0 ± 0.2 | ≥5000 |

[a] Experimental error ±0.10 p.p.m. [b] Reference 10. [c] $\int_H^{p\text{-}CN}$ = −10.30; *cf.* ref. 2 for symbolism. [d] Computed value, *cf.* ref. 6. [e] Observed value.

(1) This work was supported in part by the Office of Naval Research.
(2) *Cf.* R. W. Taft, *et al.*, *J. Am. Chem. Soc.*, **85**, 709, 3146 (1963), and references cited therein.
(3) H. C. Brown and R. B. Johannesen, *ibid.*, **72**, 2934 (1950); note Fig. 3 and 4 given therein.
(4) J. S. Pople, W. A. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 218.
(5) In the valence bond description of the donor–acceptor complex (*cf.* R. S. Mulliken and W. B. Person, *Ann. Rev. Phys. Chem.*, **13**, 107 (1962)), the following additional (F n.m.r. shielding sensitive; *cf.* ref. 2) forms are expected to contribute to the ground electronic state.


(6) The theoretical curve is based upon calculations of best fit of the data by the Penn State IBM 7074 computer using the 1–1 formation constant and the limiting F n.m.r. shift as adjustable (but concentration-independent) parameters. We are indebted to Dr. Stanton Ehrenson, Brookhaven National Laboratory, for this program. Any small medium effects are unimportant for present purposes.

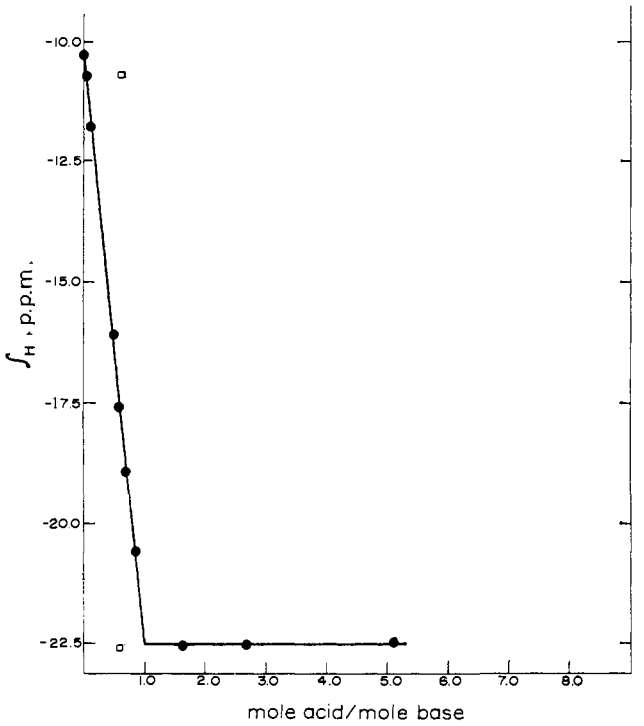



Fig. 2.—Demonstration of 1–1 donor–acceptor complex between boron trichloride and FBN in methylene chloride solution: ●, at 40 Mc. and 25°; □, at 56 Mc. and ~−20°.

More definitive evidence for the formation of the 1–1 complex has been obtained with FBN using as acid $BCl_3$. Figure 2 plots (in the same manner as Fig. 1) the results obtained (under the same conditions) for this system. The experimental points in Fig. 2 satisfactorily follow the theoretical curve for a 1–1 complex with infinite formation constant. The data are only fitted by such a formation constant with values exceeding $5 \times 10^3$ $M^{-1}$. A conclusive additional result is the resolution of the hybrid fluorine signal for the solution of $a/b = 0.59$ into the two component signals of appropriate relative intensities for complexed and uncomplexed FBN (*cf.* Fig. 2) which is observed when the spectrum is taken at about −20° and 56 Mc.[7] These observations also indicate that the 1–1 complex is not appreciably dissociated to ions under our conditions.[8]

The acid $BBr_3$ with FBN gives a plot at 25° which is identical in form with that of Fig. 2. With the stronger base, fluorocyanodurene[9] ($a/b \cong 0.5$), the resolved signals for uncomplexed and complexed base are observed at 25° (and 40 Mc.) with this acid ($\Delta_{complex}$ = −13.0 p.p.m.). The acid $BF_3$ with FBN at 25° gives a curve which is intermediate in form between that of Fig. 1 and 2. The data are well fitted by a 1–1 formation constant of 76 ± 20 $M^{-1}$.[6] The acid $B_2Cl_4$ with FBN in $a/b$ = 1.0 to 3.3 gives a constant limiting shift for what appears to be a 1–1 complex. At $a/b$ of less than unity, material precipitated from the methylene chloride and no signals could be observed. The acid $B(CH_3)_3$ with FBN gives very small shifts to lower field even at an $a/b$ ratio of 20 and −20°.

All solutions have been prepared in a vacuum line at $10^{-6}$ mm. Accurately weighed samples of FBN were introduced to the line from ampoules and transferred into the n.m.r. sample tube. All other components were measured as vapors in calibrated constant volume manometers, and transfers were made through appropriate mercury float valves. Condensation into the n.m.r. sample tube was made with liquid nitrogen baths, and the tube was sealed off under vacuum. Weighing of *p*-fluorophenylboron dichloride was achieved by distillation into tubes fitted with magnetic breaker seals.

Table I summarizes values of $\Delta_{complex}$ observed for FBN in methylene chloride solution at 25° for a series of acceptors. Listed for comparison are the heats of dissociation, $\Delta H_D$, for the corresponding pyridine complexes obtained by Brown, *et al.*,[10] in nitrobenzene solution. The shifts and heats are clearly parallel. The formation constants for the FBN complexes obtained in this work are also listed in Table I. We believe the results given in Table I clearly confirm the potential of the method. Work is in progress involving an extensive series of acceptors with FBN and other *p*-fluorophenyl-labeled bases.

(7) Obtained with a Varian A-56–60 spectrometer, Pittsburgh airport. We are indebted for the assistance of Mr. Jerry Holcomb.

(8) We are indebted to Professor R. S. Drago for pointing out this possibility.

(9) Kindly supplied by Professor G. Illuminati, Rome, Italy.

(10) H. C. Brown and R. R. Holmes, *J. Am. Chem. Soc.*, **78**, 2173 (1956); H. C. Brown and D. Gintis, *ibid.*, **78**, 5378 (1956).

DEPARTMENT OF CHEMISTRY R. W. TAFT
THE PENNSYLVANIA STATE UNIVERSITY J. W. CARTEN
UNIVERSITY PARK, PENNSYLVANIA 16802

RECEIVED JULY 13, 1964

## The Synthesis of an Octapeptide Corresponding to a Sequence around the "Reactive Serine" of Chymotrypsin

*Sir:*

Recent investigations have shown that the "active site" of many proteolytic enzymes includes a "reactive serine" residue. In particular the sequence Gly-Asp-Ser-Gly is found around this serine in chymotrypsin, trypsin, and elastase.[1] Syntheses of this aspartyl tetrapeptide and the analogous glutamyl compound have been reported previously.[2,3] We report here the synthesis of these tetrapeptide sequences with end groups so blocked that further extension of the peptide chain may be readily accomplished. We then describe the synthesis of the octapeptide sequence Gly-Asp-Ser-Gly-Gly-Pro-Leu-Val, which has been shown[4] to comprise residues 193 through 200 of bovine chymotrypsinogen A.

The crystalline octapeptide I (with terminal amino and carboxyl groups blocked) was synthesized[5] according to the scheme shown in Chart I.[6] All peptide bonds were formed using Woodward's reagent (N-ethyl-5-phenylisoxazolium 3′-sulfonate)[7] except for the syn-

(1) J. A. Cohen, R. A. Oosterbaan, H. S. Jansz, and F. Berends, *J. Cellular Comp. Physiol.*, **54** (Suppl. 1), 231 (1959); F. Sanger, *Proc. Chem. Soc.*, 76 (1963).

(2) H. Kienhuis, A. van de Linde, J. P. J. van der Holst, and A. Verweij, *Rec. trav. chim.*, **80**, 1278 (1961).

(3) A. van der Linde, H. Kienhuis, A. Verweij, and J. P. J. van der Holst, *ibid.*, **80**, 1305 (1961).

(4) B. S. Hartley, *Nature*, **201**, 1284 (1964).

(5) Satisfactory analyses and spectral data were obtained for all crystalline compounds described here. Melting points were uncorrected. $[\alpha]_D$ refers to about 0.5% solution in methanol at 23–25°.

(6) The nomenclature adopted is that recommended at the Fifth European Symposium on Peptides, Oxford, 1962; see "Peptides, Proceedings of the Fifth European Symposium, Oxford, Sept., 1962," G. T. Young, Ed., Pergamon Press, Oxford, 1963, p. 261. "For-" denotes "formyl-"; (a) after a Roman numeral refers to the glutamyl analog.

(7) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Am. Chem. Soc.*, **83**, 1010 (1961).