Table I. K_i Values and Thermodynamic Constants for the Binding of $C_nH_{2n+1}N^+(CH_3)_3$ on AChE

n	$K_i^{25°}$; 10^4 M	ΔF,[a] kcal./mole	ΔH, kcal./mole	ΔS, e.u.	Max. cholinergic response,[b] %
1	23.3 ± 0.07	−3.59	−6.60 ± 0.30	−10.1 ± 1.0	100
2	16.0 ± 0.05	−3.81			100
3	13.4 ± 0.05	−3.92	−6.32 ± 0.30	−8.1 ± 1.0	100
4	8.4 ± 0.04	−4.20	−5.22 ± 0.22	−3.4 ± 0.7	100
5	17.4 ± 0.02	−3.76	−5.40 ± 0.20	−5.5 ± 0.7	100
6	13.4 ± 0.05	−3.92			100
7	10.2 ± 0.05	−4.08	−4.49 ± 0.10	−1.4 ± 0.4	60–80[c]
8	6.6 ± 0.15	−4.34	−4.40 ± 0.05	−0.2 ± 0.2	20–40[c]
9	4.8 ± 0.11	−4.53	−4.40 ± 0.05	+0.44 ± 0.17	5–10[c]
10	2.26 ± 0.05	−4.97	−4.26 ± 0.10	+2.4 ± 0.4	0[d]
11	1.16 ± 0.05	−5.37			0[d]
12	0.52 ± 0.07	−5.85	−2.75 ± 0.10	+10.4 ± 0.5	0[d]

[a] Reproducibility is ±0.01. [b] Data from ref. 1 and E. J. Ariëns, "Molecular Pharmacology," Vol. I, Academic Press Inc., New York, N. Y., 1964, pp. 164, 295. [c] Partial stimulants and partial antagonists. [d] Antagonists.

carbon atoms in the side chain of the inhibitors) is shown in Figure 2.

The results shown in Figure 2 are in partial disagreement with the earlier report of Bergmann and Segal[3] in that a significant break in the free-energy relationships with n occurs at C_5. However, the slopes from C_1 to C_4 and C_5 to C_8 are almost identical. More significant is the break at C_9, where a third linear relationship of markedly different slope and extending to C_{12} occurs. Each CH_2 group in the C_9 to C_{12} series has a significantly greater affinity for the enzyme than the CH_2 groups of the lower homologs. This difference is not attributable to a shift from competitive to noncompetitive inhibition (or *vice versa*) (Figure 1). It appeared probable that the higher homologs C_9 to C_{12} interact with the enzyme active surface by a different mechanism (but nevertheless competitive) than the shorter chain members. That this is the case becomes evident when the enthalpies and entropies of binding are examined (Table I). Whereas the homologs from C_1 to C_7 (including C_2 and C_6 by inference) have *negative* entropies of binding (the C_8 member producing little change in ΔS), the C_9 to C_{12} (C_{11} included by inference) members have a *positive* entropy of complex formation. The lower enthalpies of binding of the longer chain members is amply compensated by the positive values for their entropies of adsorption on AChE. This chain length dependent transition from negative to positive entropies of complex formation is not attributable to micelle formation with the long-chain members since the concentrations for inhibition are about 100 times lower than the critical micelle concentration of the dodecyl ion.[5] This transition from an ordering ($-\Delta S$) to a disordering effect ($+\Delta S$) upon complex formation with AChE finds a remarkable parallel in the well-documented transition from stimulant to prevalent antagonistic activity with a chain of similar length in the same series of quaternary ions at the level of certain physiological cholinergic receptors.[1,2] This phenomenon is illustrated in Table I (last column). It seems reasonable on that basis to ascribe the stimulant activity of the C_1 to C_7 members and the antagonistic properties of the C_9 to C_{12} homologs to the induction of ordering and disordering effects, respectively, at the receptor protein level. The above findings

provide a rational physicochemical basis for the concept of a dualism in drug-induced perturbations of physiological receptors[6] and point to a biophysical link between the AChE active surface and the binding sites of certain cholinergic receptors. It appears to be the first time that drug-induced stimulation or blockade can be rationalized in basic physicochemical terms. The significance of these findings in relation to receptor theory will be discussed elsewhere.

B. Belleau, H. Tani,[7] **F. Lie**[8]
Department of Chemistry, University of Ottawa
Ottawa, Ontario, Canada
Received November 20, 1964

On Arylboron Free Radicals

Sir:

In a recent article Leffler, Doland, and Tanigaki[1] reported the e.s.r. spectra of the reaction product of dimesitylboron fluoride with sodium–potassium alloy and its complex with pyridine. They found that the first product gives the same e.s.r. spectrum as trimesitylboron (TMB) after prolonged reaction with Na–Hg. They state that TMB treated with Na–Hg in THF first gives a broad four-line spectrum with a splitting of 8 gauss, and that after prolonged reduction a new spectrum appears with more hyperfine structure and a boron hyperfine splitting of 10 gauss. Their conclusions are that dimesitylboron fluoride over the Na–K alloy gives radical 1, that addition of pyridine to this radical gives radical 2, and that the TMB negative ion 3 (which gives the four-line spectrum) decomposes to 1 after prolonged reduction.

$Mes_2B\cdot$	$Mes_2B \rightarrow Pyr$	$Mes_3B\cdot$
1	**2**	**3**
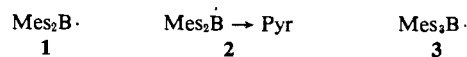
Previous studies of TMB[2,3] and recent experiments performed in our laboratory do not agree with their conclusions.

(1) J. E. Leffler, E. Doland, and T. Tanigaki, *J. Am. Chem. Soc.*, 87, 928 (1965).
(2) H. C. Brown and V. H. Dodson, *ibid.*, 79, 2302 (1957).
(3) T. L. Chu and T. J. Weismann, *ibid.*, 78, 23 (1956).

(5) J. A. Cella, D. N. Eggenberger, D. R. Noel, L. A. Harriman, and H. J. Harwood, *J. Am. Chem. Soc.*, 74, 2061 (1952).
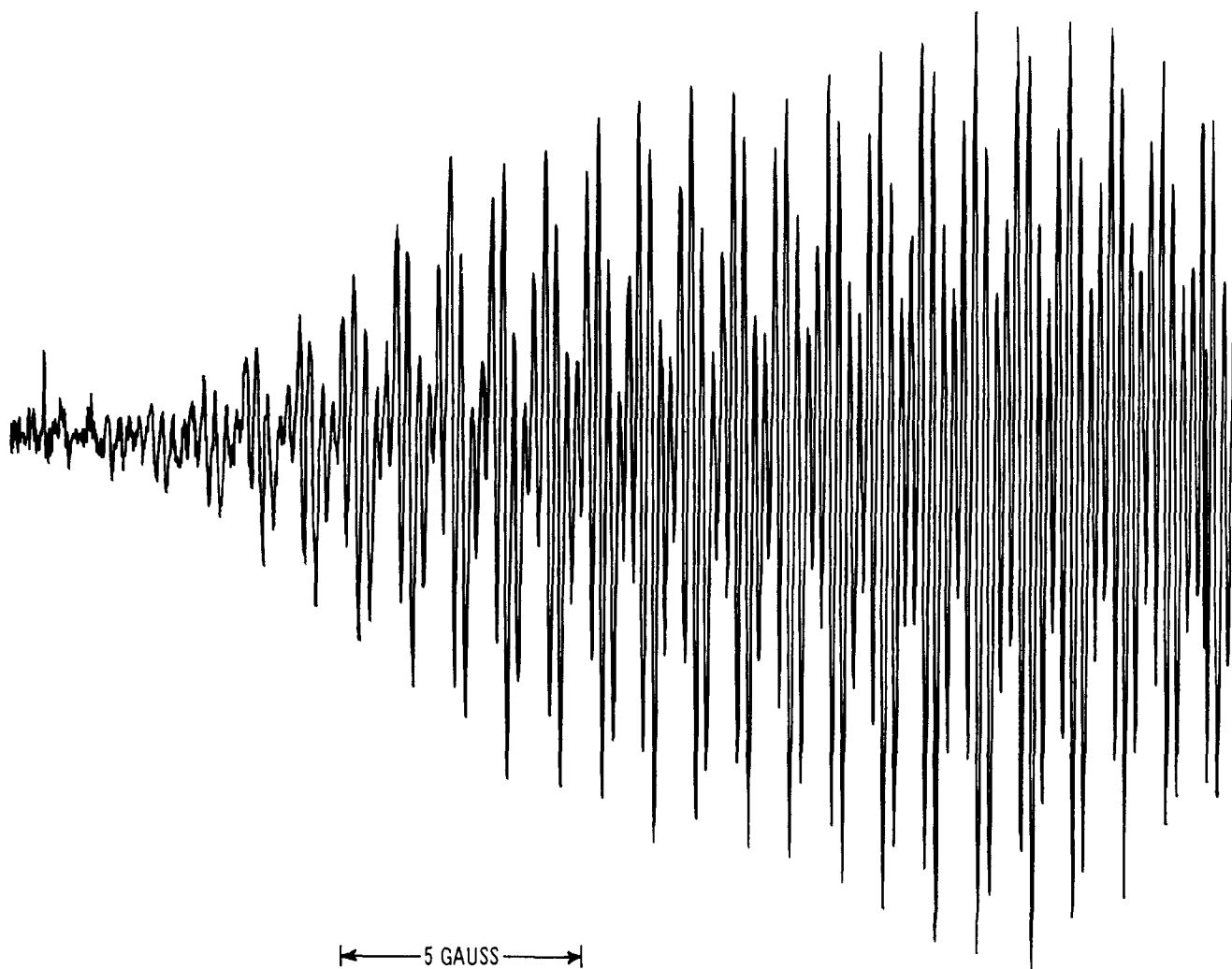
Figure 1. $d\chi''/dH$ *vs.* H for TMB⁻ in liquid ammonia at room temperature. Only half of the spectrum is shown.

Qualitative and quantitative work of Brown and Chu shows that the starting material is recovered after quenching with water of the radical which is formed during prolonged treatment of TMB with Na–Hg. Optical spectra of TMB reduced with Na, recorded in this laboratory, show no sign of decomposition of TMB⁻ as the reduction progresses.

Our experiments show that TMB reduced over Na–Hg in THF under mild conditions gives immediately the spectrum which Leffler, *et al.*, have attributed to radical **1**. We measured a rate of exchange between TMB⁻ and TMB of the order of 4×10^9 mole⁻¹ sec.⁻¹. Because of this very rapid exchange, we presume that in the four-peak spectrum with a splitting of 8.0 gauss which Leffler, *et al.*, attribute to **3** the proton hyperfine splittings are broadened out by exchange with unreduced TMB. Ultraviolet spectra show that several hours is required to reduce the TMB quantitatively. The high spin exchange rate between neutral material and radical is in itself an indication that the radical is the undecomposed TMB⁻. The discrepancy between the reported boron hyperfine coupling constants of TMB⁻ merely shows that it is hard to assign a value if the spectrum is badly resolved, especially in this case where the B¹⁰ isotope distorts the center of the four-line spectrum slightly.

When we tried to obtain the e.s.r. spectrum which was assigned to radical **2** by adding pyridine to a solution of TMB⁻Na⁺ in THF, we observed no change in the original spectrum. We note further that a solution of the TMB radical in liquid NH_3, where we would expect complex formation by **1**, shows no sign of complex formation and is stable for months. The spectrum in liquid ammonia is shown in Figure 1.

Our conclusion is that it is the dimesitylboron fluoride or its radical which decomposes and forms the trimesitylboron negative ion. Formation of radical **2** is highly improbable, and Leffler, *et al.*, produce no evidence for its existence. The recorded e.s.r. spectrum might be due to reaction of the pyridine with one of the decomposition products of **1**.

A complete description of our observations of the behavior of the trimesitylboron anion radical is in preparation.

S. I. Weissman, Hans van Willigen
*Department of Chemistry, Washington University
St. Louis, Missouri 63130*