that the difference in activation enthalpy noted in Table IX may not be attributed to this factor. Our experiments favor explanation 3 since we find that under turnover conditions at pH 7.8, ionic strength 0.1, the enthalpy of activation for *p*-nitrophenyl acetate is some 5.5 kcal lower in Tris than in phosphate and barbital buffers. It is likely that this buffer effect, which has been noted before,[5b] influences values of and trends within activation parameters of other chymotrypsin reactions.

The first four normal fatty acid esters of the series react with elastase according to enthalpy control. However, the longest (C-6) has its reactivity reduced by an unfavorable entropy increment. This may be related to the special effect on the reactivity of substrates[21] and inhibitors[22] of longer chain lengths which has been interpreted as being related to limited conformational change in the region on direct ligand contact.[23]

Substrates of different structures may have entirely different patterns of activation parameters. For example, the two most specific substrates of elastase examined, *p*-nitrophenyl *N*-benzyloxycarbonylglycinate and *p*-nitrophenyl *N*-*tert*-butyloxycarbonyl-L-alaninate, have nearly identical enthalpies of activation. The entropies of activation differ slightly, distinguishing their reactivity, and are much less negative than those of the fatty acid esters. Thus we find entropy control, wherein differences in reactivity, *i.e.*, specificity, result from differences in entropy of activation. It may be significant that these *N*-acyl amino acids are capable of three-point attachment to the enzyme surface in the acyl enzyme whereas the normal fatty acids are capable of only two-point attachment.

The hypothesis that thermodynamic parameters are characteristic of a type of ligand structure is supported by the results of Belleau and DiTullio who studied the effect of varying chain length of *n*-alkyl tetramethylammonium activators on the methanesulfonylation of the acetylcholinesterase active site.[24] *n*-Alkyl substituents gave rise to bell-shaped curves (not unlike our system[3]) when acceleration was plotted against molar volume of the *n*-alkyl chain. Significantly, the enthalpy of binding, but not the free energy, showed some correlation with molar volume and with degree of acceleration. The hypothesis was submitted that binding enthalpy may reflect conformational changes such as would be initiated by ligand release of water from the binding cleft of acetylcholinesterase.[24] The observation that ligand binding to chymotrypsin displaces water may be of interest.[25] Regardless of the molecular mechanism, our results and those of Belleau and DiTullio suggest that enthalpy may be the fundamental thermodynamic parameter characterizing interaction between *n*-alkyl side chains and proteins regardless of whether the ligand is an activator or a substrate. We wish to suggest an analogy between enthalpy of binding and of activation.

It should be emphasized that it is difficult to interpret activation parameters in terms of a detailed mechanism. There has been a tendency to associate enthalpy effects with conformational or strain processes in the enzyme–substrate complex.[6,26] However, a recent discussion of solvation in enzyme-catalyzed reactions predicts interestingly that rate accelerations should result from favorable enthalpy of activation.[27] Recent studies of a model system whose rate enhancement was explained by "stereo-population control," or loss of configurational freedom in the substrate, revealed the rate acceleration was due to more favorable enthalpy of activation.[28] However, configurational restraint of the substrate was orginally offered as an explanation of entropy control of rates of deacylation of acyl chymotrypsins.[4a] Rate enhancement and specificity is a matter of differences in free energy of activation and it may be premature at this time to expect a unitary theory to be capable of accounting for all classes of substrates in terms of pure enthalpy or pure entropy effects.

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Communications to the Editor

Stereochemistry of the Thermal Isomerization of 5-Methylenebicyclo[4.2.0]octa-2,7-dienes Leading to Tricyclo[4.3.0.0^{4,6}]nona-2,8-dienes[1]

Sir:

There remain some ambiguities on the reaction mechanism of the thermally induced isomerization of the fused cyclobutenes which concern ring opening.[2] For instance, a few contradictory arguments have been reported[3,4] against the proposal of antara–antara Cope

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Table I. Chemical Shifts (τ, 60 MHz in $CDCl_3$) of Protons Concerned in I and III

	Ia	Ib	Ic		IIIa	IIIb	IIIc
H_6	5.70	5.60	4.91	H_2	2.82	2.76	1.80
H_{4a}	6.59	6.03	6.60	H_8	6.67	6.33	6.68

Table II. Spectral Properties of IIa, V, and VI

Compd	Uv max (EtOH), nm (log ϵ)	Ir max (KBr (a) or neat (b)), cm^{-1} Cyclopropane	CN	Nmr coupling constant, Hz[a] a–b	a–c	b–c	b–d	c–d
IIa	212 (3.67)	a 3086, 1005	2246	5.5	2.2	2.0	2.0	2.0
V	212 (3.57)	a 3070, 1005	2250 2238	5.5	2.0	2.0	2.2	2.0
VI	214 (3.67)	b 3070, 1020	2246	5.5	2.2	2.0	2.2	2.0

[a] a, b, c, and d represent protons with marks in structure A.

rearrangement for thermal isomerization of bicyclo[3.2.0]hepta-3,6-dien-2-ones.[5,6] With this type of rearrangement, it would be of interest to examine the influence of an exocyclic double bond substituted with electron-attracting groups in the place of the 2-keto group of the bicyclo[3.2.0]hepta-3,6-dien-2-one or bicyclo[4.2.0]octa-4,7-dien-2-one system. For this reason, we investigated firstly the thermal reaction of 5-dicyanomethylenebicyclo[4.2.0]octa-2,7-diene (Ia) and the cyanomethoxycarbonyl derivatives Ib and Ic, in which cases an intriguing rearrangement affording tricyclo[4.3.0.$0^{4,8}$]nona-2,8-dienes (IIa, IIb, and IIc) has been found.[7] In addition, we elucidated the stereochemistry of this rearrangement, and an outline of the study is reported here.

Starting materials Ia, Ib, and Ic, all oils, were synthesized in almost quantitative yields by irradiation, using a high-pressure Hg lamp with a Pyrex filter, of an ethereal solution of dicyano- (IIIa), mp 94°, and cyanomethoxycarbonylmethylenecycloocta-2,4,6-trienes (IIIb and IIIc), mp 103 and 78°,[8] which were obtained from cycloocta-2,4,6-trienone.[9] Under these irradiation conditions no cis–trans isomerization of the exocyclic double bond of IIIb and IIIc or of the products Ib and Ic was detected. Definitive evidence for the structure of Ia was obtained by catalytic hydrogenation affording 2-dicyanomethylenebicyclo[4.2.0]octane (IV), an oil, which was also obtained by the condensation of bicyclo[4.2.0]oct-2-one[10] with malononitrile. The constitution of Ib and Ic was deduced by comparison of their spectral properties with those of Ia. As an example, spectral data of Ia are presented here: uv max (cyclohexane) 242 nm (log ϵ 4.08); ir max (neat) 3040, 2915, and 2227 cm^{-1}; see footnote 11. However, chemical shifts of protons located next to the cyano and methoxycarbonyl groups are different as shown in Table I. Accordingly, discrimination of Ib and Ic as well as IIIb and IIIc was easily accomplished using these data.

Refluxing of a xylene solution of Ia for 1 hr afforded IIa, mp 73°, and IIIa in 73 and 14% yields, respectively.[7] The structural assignment of IIa was based on its spectral evidence (Table II), which is very similar to that of 6,6-dicyanobicyclo[3.1.0]hex-2-ene (V), mp 85°,[12] and 5,5-dicyanotricyclo[4.3.0.$0^{4,6}$]non-2-ene (VI), an oil.[13] Mass spectra of IIa, V, and VI (A) exhibit common fragments (B and C) which originate from the loss of HCN (27) and NC–C–CN (64), supporting the correctness of their structures.[14]

When Ib or Ic was heated under the same conditions as Ia, tricyclo compounds IIb (mp 93°), IIc (mp 71°), and a mixture of IIIb and IIIc were obtained in the yields shown in Table III. The structures of IIb and IIc were elucidated by comparison of their spectral data with those of IIa. For example, the nmr spectra

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(8) Elemental analyses were satisfactory for all new compounds except for Ia, Ib, and Ic which are unstable compounds.

(9) When cycloocta-2,4,6-trienone was treated with malononitrile or methyl cyanoacetate in the presence of ammonium acetate, IIIa or a mixture of IIIb and IIIc (ratio 4:3) was obtained in 76 and 86% yields, respectively. Fractional recrystallization of the mixture resulted in separation of IIIb and IIIc; *cf.* A. C. Cope, S. F. Scharen, and E. R. Trumbull, *J. Amer. Chem. Soc.*, **76**, 1096 (1954).

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(11) Nmr (100 MHz, $CDCl_3$, τ) 3.80 (H_7 and H_8), 4.09 (H_2), 4.26 (H_3), 5.75 (H_6), 6.25 (H_1), 6.59 (H_{4a}), 6.80 (H_{4b}); J values (Hz) $J_{1,2}$ = 4.5, $J_{1,6}$ = 3.7, $J_{2,3}$ = 9.5, $J_{2,4a}$ = 2.0, $J_{2,4b}$ = 2.5, $J_{3,4a}$ = 5.0, $J_{3,4b}$ = 2.5, $J_{4a,4b}$ = 19.0.

(12) Prepared by treating 3,5-dibromocyclopentene with malononitrile; *cf.* F. Korte, D. Scharf, and K. H. Buchel, *Justus Liebigs Ann. Chem.*, **664**, 97 (1963).

(13) Heating of 2-dicyanomethylenebicyclo[4.2.0]oct-7-ene afforded VI in a good yield. This result including a kinetic study will soon be reported elsewhere.

(14) As an example, the mass spectrum of IIa is presented here: *m/e* (70 eV) 168 (M^+, 71%), 142 (M − CN, 30), 141 (M − HCN, 100), 114 (M − 2HCN, 55), 104 (M − $C(CN)_2$, 5), and 103 (26).

Table III. Results of the Thermal Isomerization of Ib and Ic

From	Yields, %,[a] of IIb	IIc	IIIb + IIIc	IIb:IIc	
Ib	66	12	15	85	15
Ic	11	52	7	17	83

[a] Yields were determined by vpc (20% DC-11 on Chromosorb W at 140°) and uv spectroscopy.

Table IV. Chemical Shifts (τ, 60 MHz in $CDCl_3$) of Protons in IIa, IIb, and IIc

	H_2	H_3	$H_{8,9}$	H_1	H_4	H_{7a}	H_{7b}
IIa	3.80	4.17	4.17	6.10	7.10	6.80	7.43
IIb	3.85	4.20	4.20	6.10	7.10	7.37	7.37
IIc	3.80	4.27	4.03	5.73	7.13	6.80	7.40

of IIa, IIb, and IIc are shown in Table IV.[15] Under these thermal conditions, no interconversion between the products IIb and IIc and IIIb and IIIc was observed. This fact along with the findings shown in Table III clarify that the thermal isomerization of the 5-methylenebicyclo[4.2.0]octa-2,7-diene system I leading to the tricyclo[4.3.0.0^{4,6}]nona-2,8-diene system II takes place with *moderate stereospecificity*.

These results would be accommodated by considering the rearrangement of I to II to be mainly a concerted process, but not a stepwise radical process as suggested by the Syntex group.[16] However, the reaction path *via* a short-lived diradical intermediate VII which is formed from I by a one-step process could not be ruled out. Such an intermediate (VII) would be expected to cyclize with the observed stereochemistry because the orbital at the C_2 position is closer to one lobe of the side-chain p orbital.[17] On the other hand, in the concerted mechanism, two orbital symmetry allowed paths are possible. The first is a one-step concerted reaction, *i.e.*, a [$_\pi 2_a + {}_\sigma 2_s$] process as shown in VIII. The second is a two-step reaction composed of each concerted process, *i.e.*, conrotatory ring opening followed by internal Diels–Alder reaction of an intermediate such as *cis,trans,cis*-triene (IX) having an exocyclic double bond.[18] Although the Diels–Alder reaction is noted as a [$_\pi 4_a + {}_\pi 2_a$] process, the bond formation between the C_1 and C_5 positions seems quite feasible because the distance between them is less than 2.3 Å. This two-step concerted mechanism is similar to an alternative one proposed by Baldwin and Kaplan[3] for the thermal antara–antara Cope rearrangement of bicyclo[3.2.0]hepta-2,6-dienes and bicyclo[4.2.0]octa-2,7-dienes. Thus, a real reaction mechanism for the rearrangement of I to II is still ambiguous at present and further discussion from the viewpoint of a kinetic study will be reported in the near future.[13]

(15) Some of the coupling constants in compounds IIa and IIb could not be determined due to overlap of some signals (*cf.* Table II). However, those in IIc could be measured as follows: $J_{1,2} = 2.2$, $J_{1,3} = 2.0$, $J_{1,4} = 2.0$, $J_{1,7a} = J_{1,7b} = 2.1$, $J_{1,8} = 2.0$, $J_{1,9} = 1.3$, $J_{2,3} = 5.5$, $J_{3,4} = 2.0$, and $J_{8,9} \simeq 6$ Hz.

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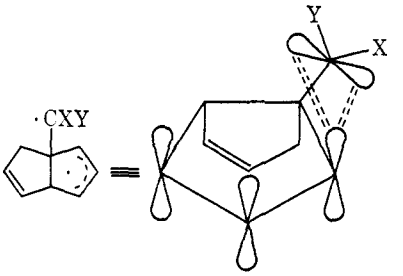
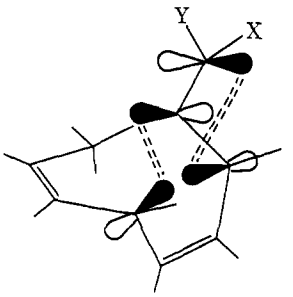
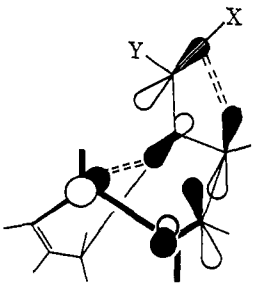


VII



VIII



IX

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Structure and Absolute Configuration of (+)-Coronaridine Hydrobromide. A Comment on the Absolute Configuration of the Iboga Alkaloids

Sir:

The Iboga alkaloids have attracted the interest of numerous groups over the years. The elegant investigations of the Ciba group[1,2] culminated in a structure proposal for this family and this was subsequently confirmed by the X-ray analysis of ibogaine hydrobromide.[3] This latter determination provided only relative configuration and thereby the absolute configuration remained on a tentative basis. During more recent investigations in one of our laboratories[4-13] it was possible to interrelate various nine-membered derivatives of the cleavamine series (I) with the rigid pentacyclic members, dihydrocatharanthine (III) and coronaridine (VII), according to the sequences I → II → III and I →

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