Influence of Pressure on the Equilibrium of Hydration of Aliphatic Aldehydes[1]

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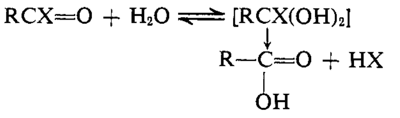
Abstract: Elevated hydrostatic pressure enhances the equilibrium constant for hydration of aliphatic aldehydes, to an extent which varies with aldehyde structure. Observed volumes of reaction, calculated from the dependence of the equilibrium of hydration on pressure, vary from −1.5 ml/mol for glyceraldehyde to −13.1 ml/mol for isobutyraldehyde. Effects of substituents on the volume of hydration of aldehydes are comparable with those previously observed for the volume of ionization of carboxylic acids and appear to be due to effects on the structure of solvating water. In the case of acetaldehyde, the observed volume of hydration (−7.8 ml/mol) is less negative than that for equilibrium addition of 2-mercaptoethanol, and is comparable in magnitude with volumes of *activation* reported for acid- and base-catalyzed hydrolysis of acetic acid esters and for acid-catalyzed hydrolysis of acetamide.

The theory of absolute reaction rates has prompted numerous investigations of the effects of pressure on enzymatic and nonenzymatic reaction velocities.[2-6] These studies have provided some support for the idea that structural changes, whereby reactants are converted to transition states, might be associated with characteristic volumes of activation. Relatively little work, however, appears to have been done to determine the effects of pressure on equilibria of reactions leading to known products which might bear some structural resemblance to possible high-energy intermediates, or to determine whether "reaction volumes" so determined[7] do in fact fall within a reasonably narrow range for reactions of a given type.

We describe here the pressure dependence of the covalent hydration of aldehydes (reaction 1), which serves as an analog of the hypothetical partial reaction in ester and amide hydrolysis whereby these carboxylic acid derivatives may be converted to "tetrahedral" intermediates (reaction 2). If the transition state for hydrolysis shares this tetrahedral character, pressure might be expected to exert a similar influence on the *equilibrium* of reaction 1 and on the *rate* of reaction 2.

$$RCH{=}O + H_2O \rightleftharpoons RCH(OH)_2 \qquad (1)$$



$$RCX{=}O + H_2O \rightleftharpoons [RCX(OH)_2] \rightarrow R{-}\underset{\displaystyle OH}{\underset{|}{C}}{=}O + HX \qquad (2)$$

Our results suggest that the volume of aldehyde hydration may indeed be comparable in magnitude with the volume of activation for hydrolysis of esters and amides. In addition, the pressure dependence of aldehyde hydration is found to be remarkably sensitive to changes in the structure of the substituent R.

Experimental Section

Materials. Acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, pivaldehyde, pentanal, biacetyl, and 2-mercaptoethanol were obtained commercially, redistilled, and stored under nitrogen. Formaldehyde hydrate was obtained by rapid distillation from an aqueous solution of formaldehyde, from which methanol had previously been removed by slow distillation as described by Walker.[11] An aqueous solution of *dl*-glyceraldehyde (obtained as the solid from Matheson and Co., Inc.) was purified by charcoal chromatography as described by Swenson and Barker.[12] All compounds gave extinction coefficients in satisfactory agreement with values reported in the literature (Table I).

Of the various carbonyl compounds tested, acetaldehyde, formaldehyde, and glyceraldehyde are unusual in being much more extensively hydrated than the others at equilibrium in dilute aqueous solution (see below). For this reason, the ultraviolet absorbance of aqueous solutions of these aldehydes is relatively low. Ultraviolet absorbing impurities, if present in these aldehydes, would be a major source of error in the determination of their hydration equilibria. It was desirable to obtain some assurance that the ultraviolet absorption of these compounds was indeed due mainly to compounds showing the reactions expected of aldehydes. In the presence of ammonia, formaldehyde and acetaldehyde are known to yield hexamethylenetetramine[11] and hexahydrotriazine,[13] respectively. When mixed with an equal volume of concentrated ammonia, samples of formaldehyde (13 *M*) and acetaldehyde (0.01 *M*) were found to undergo an immediate and virtually complete loss of extinction at the wavelengths of maximum absorption indicted in Table I. The same test could not be applied to glyceraldehyde, which forms an aldimine in the presence of ammonia, resulting in an increase in ultraviolet absorption.[13] Instead, this aldehyde was converted to the cyanohydrin[13] by mixing equal volumes of glyceraldehyde (5×10^{-2} *M*) and aqueous KCN (1 *M*). Immediate disappearance of virtually all extinction at the wavelength of maximum absorbance of glyceraldehyde showed that no unreactive component absorbing at this wavelength was present.

Methods. The concentration of aldehyde remaining unhydrated was determined by comparing the extinction at λ_{max} of the same concentration of total aldehyde in aqueous soution and in hexane

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[1] This work was supported by a research grant (GM-18325) and a career development award (AM-08560, to R. W.) from the National Institutes of Health, U. S. Public Health Service.

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[3] E. Whalley, *Advan. Phys. Org. Chem.*, 2, 93 (1964).

[4] W. J. LeNoble, *Progr. Phys. Org. Chem.*, 5, 207 (1967).

[5] C. A. Eckert, *Annu. Rev. Phys. Chem.*, 23, 239 (1972).

[6] As well as references cited in 2 through 5.

[7] Volumes of activation, calculated from the observed effect of pressure on rate constants, include differences between reactants and their respective transition states not only in volume, but also in compressibility.[8-10] Such volumes of activation might be compared with "apparent volumes of reaction" (here designated $\Delta V'$) obtained from the effect of pressure on equilibrium constants of model systems, uncorrected for compressibility effects.

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[9] S. W. Benson and J. A. Berson, *ibid.*, 84, 152 (1962).

[10] S. W. Benson and J. A. Berson, *ibid.*, 86, 259 (1964).

[11] J. F. Walker, "Formaldehyde," 3rd ed, Reinhold, New York, N. Y., 1964.

[12] C. A. Swenson and R. Barker, *Biochemistry*, 10, 3151 (1971).

[13] Y. Ogata and A. Kawasaki in "The Chemistry of the Carbonyl Group," Vol. 2, S. Pati, Ed. Interscience, New York, N. Y., 1970, pp 1–69.

Table I. Equilibrium Constants, Ultraviolet Data, Bomb Solution Concentration, and Determined Volumes of Reaction[a] for Hydration of Aliphatic Aldehydes and Addition of 2-Mercaptoethanol to Acetaldehyde under High Pressure

	No. of experiments	Bomb soln concn, *M*	Hexane soln		Water soln			$\Delta V' \pm$ range, ml
			ϵ_{max}	λ_{max}	ϵ_{max}	λ_{max}	K_H	
Formaldehyde	5	*b*	*b*	*b*	0.063[c]	281	2420[d]	−4.00 ± 0.3[e]
Acetaldehyde	4	1.85×10^{-2}	18.0	293	8.10	274	1.2[f]	−7.84 ± 0.3
Propionaldehyde	4	1.06×10^{-2}	21.0	292	9.81	278	0.714[g]	−12.25 ± 0.3
dl-Glyceraldehyde	11	1.81×10^{-2}	18.4	272[i]	5.00	273	21.70[h]	−1.54 ± 0.4
Butyraldehyde	11	9.90×10^{-3}	18.5	293	12.25	281	0.426[g]	−12.45 ± 0.8
Isobutyraldehyde	4	1.05×10^{-2}	18.0	293	12.0	280	0.500[g]	−13.12 ± 0.4
Biacetyl	8	2.65×10^{-2}	15.2	420	19.8	404	3.33[g]	−9.92 ± 0.6
							2.00[j]	−10.92 ± 0.6
Pentanal	7	9.50×10^{-3}	23.5	293	16.3	283	0.44[k]	−11.96 ± 0.2
Pivaldehyde	8	9.40×10^{-3}	15.2	294	14.5	284	0.244	−11.77 ± 0.4
Acetaldehyde +	5	4.5×10^{-2} ald						−14.00 ± 0.6
2-mercaptoethanol		1.0×10^{-1} thiol		*l*	0.634[c]	275	33.3[k] ($K_{addition}$)	

[a] Calculated from the pressure dependence of the equilibrium constant as described in the text. [b] Preparation of formaldehyde solution made these measurements impossible. [c] Absorbance of bomb solution, not a molar extinction. [d] Estimated from all known values of this constant: L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5217 (1963); P. Valenta, *Collect. Czech. Chem. Commun.*, **25**, 853 (1966); N. Landqvist, *Acta Chem. Scand.*, 9, 867, 1127 (1955); R. Biebler and G. Trumpler, *Helv. Chim. Acta*, **30**, 1860 (1947); A. Iliceto, *Gazz. Chim. Ital.*, **84**, 536 (1954). [e] Calculated over 1700 atm pressure range, due to curvature above this pressure. [f] J. L. Kurz, *J. Amer. Chem. Soc.*, **89**, 3524 (1967). [g] Reference 14. [h] Calculated from data in ref 12. [i] Measured in ethanol solution. [j] P. Greenzaid, Z. Luz, and D. Samuel, *J. Amer. Chem. Soc.*, **89**, 749 (1967). [k] Calculated from tabulated uv data. [l] Not measured.

(conditions in Table I).[14] The equilibrium constant for hydration was calculated by eq 3 from the fraction of aldehyde remaining as free carbonyl compound

$$K_H = [\text{hydrate}]/[\text{free aldehyde}] = (T - A)/A \qquad (3)$$

where T = concentration of total aldehyde in solution and A = concentration of free aldehyde calculated from absorbance measurements.

The equilibrium constant for addition of 2-mercaptoethanol to acetaldehyde was determined by studying the effect of various concentrations of thiol (0.05–0.5 *M*) on the absorbance of free aldehyde (0.05 *M*) in aqueous solutions. The equilibrium constant, corrected for hydration, was calculated by

$$K_{addition} = [\text{adduct}]/[\text{free aldehyde}][\text{free thiol}] = T - A - (AK_H)/(A)[M - T + A + (AK_H)] \qquad (4)$$

where M = concentration of total thiol in solution. Equilibria of hydration and thiol addition were found to be established in less than the time (approximately 1 min) required for measurement, and maintained a constant value over a period of at least 12 hr.

High-Pressure Studies. The high-pressure optical bomb used in these studies was designed by Dr. W. B. Daniels of the University of Delaware and is described elsewhere.[15] The aldehyde sample was isolated from the high-pressure fluid (hexane) by means of a quartz cuvet (3.7-cm light path) fitted with a flexible Teflon sleeve. This sleeve served to isolate the sample from the high-pressure fluid while at the same time being flexible enough to permit transmission of the pressure to the sample. Two manual pressure generators of 10,000 and 30,000 psi capacity (High Pressure Equipment Co., Erie, Pa.) equipped with Bourdon tube gauges were used to supply and control the pressure of hexane applied to the bomb.

The cuvet was loaded by submerging it in an aldehyde solution of known absorbance. It was then dried and rinsed with hexane before being placed in the hexane-filled chamber of the bomb. The sealed bomb was placed in a cradle positioned to obtain maximum transmittance in the light path of a Zeiss PMQ II spectrophotometer. Effects of pressure were determined by recording the absorbance (corrected for bomb transmittance) at increments of 1000 psi, beginning at atmospheric pressure. At each interval the system was allowed to equilibrate for 2 min, much longer than the time required to attain chemical equilibrium. A series of measurements was made at both increasing and decreasing pressures, with similar results. In each case, close agreement between initial and final values provided assurance of the reversibility of the system. Experiments were performed at 25° and conducted over a sufficient time period that thermal effects due to compression were found to be negligible.

In order to calculate values for equilibrium constants at elevated pressures, correction was made for the increase in concentration produced by compression of water as determined by Grindley and Lind.[16] Beer's law was assumed to apply in each case, and the absorbance of the free carbonyl compound was assumed to be unaffected by pressure, as previously demonstrated in the case of 4-octanone by Kliman.[17]

Results

Plots of log K as a function of pressure were nearly linear in the pressure range employed. Figure 1 shows the logarithm of the relative equilibrium constant (compared with that at 1 atm) for various aldehydes as a function of pressure. Equilibrium constants at several elevated pressures are shown in Table II. Volumes of reaction for hydration and for thiol addition, calculated from the slope of the best straight line describing the effect of pressure on the equilibrium constant as expressed by eq 5, are shown in Table I.

$$\Delta V' = -2.3RT\text{d}(\log K)/\text{d}P \qquad (5)$$

Table II. Equilibrium Constants for Hydration at 1 Atm and at Elevated Pressures

	1 atm	680 atm	1360 atm	2040 atm
Formaldehyde	2420	2685	2960	3180
Acetaldehyde	1.20	1.505	1.88	2.31
Propionaldehyde	0.714	1.037	1.453	1.993
dl-Glyceraldehyde	21.7	22.75	23.65	24.5
Butyraldehyde	0.426	0.626	0.883	1.183
Isobutyraldehyde	0.500	0.739	1.07	1.47
Biacetyl	3.33	4.425	5.79	7.63
Pentanal	0.443	0.623	0.884	1.20
Pivaldehyde	0.244	0.355	0.476	0.644
2-Mercaptoethanol addition to acetaldehyde	33.2	48.75	72.75	104.1

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(15) A. Zipp, Ph.D. Thesis, Princeton University, Princeton, N. J., 1972.

(16) T. Grindley and J. E. Lind, Jr., *J. Chem. Phys.*, **54**, 3983 (1971).

(17) H. L. Kliman, Ph.D. Thesis, Princeton University, Princeton, N. J., 1969.

Biacetyl, a diketone, undergoes hydration of only one carbonyl group.[18] The effect of pressure on the 280-nm peak of biacetyl was slight. In contrast, absorbance at 404 nm was greatly diminished by high pressure. Volumes of this reaction were calculated on the basis of two different equilibrium constants in the literature. As shown in Table I, the value of the calculated volume of reaction is relatively insensitive to the assumed equilibrium constant for hydration, and is similar to those for the hydration of the higher aldehydes.

In the case of acetaldehyde, thiol addition was also studied. The equilibrium constant for 2-mercaptoethanol addition to acetaldehyde, at atmospheric pressure, was comparable with equilibria determined by Lienhard and Jencks[19] for the formation of other thiohemiacetals of acetaldehyde. The volume of this reaction was considerably more negative than that for the hydration of acetaldehyde (Table I).

Discussion

Of the various aldehydes described, only formaldehyde was studied under conditions deviating greatly from ideality (as a 13 M solution, as compared with approximately 10^{-2} M solutions in the other cases). Results obtained for formaldehyde may not be strictly comparable with those obtained in the case of the other aldehydes; however, formaldehyde shares with glyceraldehyde (studied at much lower concentrations) a small negative volume of reaction and a large equilibrium constant for hydration, suggesting that their behavior is indeed similar.

A small negative change of volume occurs with formaldehyde and glyceraldehyde. With higher aldehydes the value approaches an apparent limit in the neighborhood of −13 ml/mol. This limit falls short of the molar volume change (−18 ml) for simple removal of water from solution, but is comparable with values expected for hydration on the basis of Traube's[20] semiempirical rule; the exact value predicted by Traube's rule depends on the "group volume" chosen for the carbonyl oxygen of anhydrous aldehydes, and falls in the range between −12.7 and −15.4 ml/mol. Gruen and McTigue[21] have previously noted that entropies of hydration become more negative with increasing chain length in a similar series of aldehydes. Kauzmann, *et al.*,[22] have observed that volume changes for ionization of monocarboxylic acids analogous to the present aldehydes also show a considerable range of values (from −7.8 ml/mol for formic acid to −18 ml/mol for trimethylacetic acid).

Substituents thus appear to exert an influence on the volume of aldehydes which differs, in an absolute sense, from their influence on the volume of aldehyde hydrates in aqueous solution. It is of interest that substituent effects on reaction volumes are as pronounced in the case of ionization of carboxylic acids. Kauzmann[22] has drawn attention to the failure of the Drude–Nernst electrostatic model to account for the effects of substituents on the volumes of ionization of carboxylic acids, and has suggested that substituent effects may be exerted on "the structure of water in the vicinity of the ion." In the present case substituent effects on volume are found to be substantial even for a reaction where no formal electrostatic charge is generated. Since these substituents would not be expected to influence the reaction volumes markedly through direct steric or inductive interactions, it appears reasonable to suppose that their influence is exerted through the solvent.

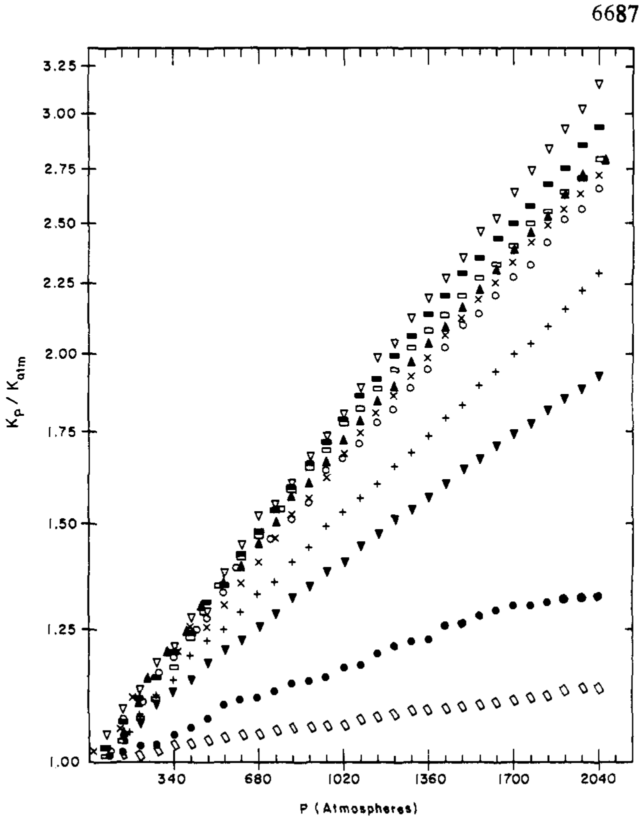

Figure 1. Semilogarithmic plot of the pressure dependence of the normalized equilibrium constants for hydration of the following aliphatic aldehydes: (●) formaldehyde, (▼) acetaldehyde, (▲) propionaldehyde, (◇) *dl*-glyceraldehyde, (□) butyraldehyde, (■) isobutyraldehyde, (+) biacetyl, (×) pentanal, (○) pivaldehyde, and (▽) addition of 2-mercaptoethanol to acetaldehyde.

Substituent effects seem likely to be significant in other reactions, and should be given due consideration when attempts are made to interpret volumes of activation in terms of transition-state structure. It might be anticipated, for example, that volumes of activation for a homologous series of substrates, reacting through a mechanism with a transition state structurally resembling an aldehyde hydrate, would exhibit a range of volumes of activation somewhat comparable with the range of volumes of reaction for aldehyde hydration reported here. Sufficient data are not yet available to test this prediction; however, Gonikberg, *et al.*,[23] have observed a strong substituent dependence of the Menschutkin reaction, believed to proceed through an intermediate involving pentavalent carbon. The observed volume of hydration of acetaldehyde does appear to be comparable in magnitude with volumes of activation which have been obtained for hydrolysis of acetic acid esters in acid and base, and for the acid-catalyzed hydrolysis of acetamide (Table III). Other

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(19) G. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3982 (1966).

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(23) G. M. Gonikberg and A. I. Kitaigorodskii, *Dokl. Akad. Nauk SSSR*, **122**, 231 (1958).

Table III. Volumes of Activation for the Acid- and Base-Catalyzed Hydrolysis of Carboxylic Acid Esters and Amides in Water

Compd	Catalyst	Temp, °C	$\Delta V^{\ddagger}$, ml	Ref
Methyl acetate	NaOH	25	−9.9	*a*
	HCl	30.5	−8.3	*b*
	HCl	14	−10.1	*c*
	HCl	35	−9.1	*d*
Ethyl acetate	NaOH	2.4	−4.5	*e*
	NaOH	25	−8.8	*a*
	NaOH	20	−5.6	*f*
	NaOH	30	−6.4	*f*
	HCl	14	−8.4	*c*
	HCl	35	−9.3	*g*
	HCl	0	−7.9	*g*
Isopropyl acetate	NaOH	20	−5.6	*f*
Butyl acetate	NaOH	20	−5.6	*f*
Isobutyl acetate	NaOH	20	−6.3	*f*
tert-Butyl acetate	HCl	60	0.0	*g*
Amyl acetate	NaOH	20	−5.8	*f*
Acetamide	NaOH	25	−14.2	*a*
	$HClO_4$	55	−9.4	*h*
Propionamide	NaOH	25	−16.9	*a*

[a] K. J. Laidler and D. Chen, *Trans. Faraday Soc.*, **50**, 1026 (1958). [b] A. Bogojawlensky and G. Tammann, *Z. Phys. Chem.*, **23**, 13 (1897). [c] V. Rothmund, *ibid.*, **20**, 168 (1896). [d] B. T. Baliga, R. J. Withey, D. Poulton, and E. Whalley, *Trans. Faraday Soc.*, **61**, 517 (1965). [e] E. Cohen and H. F. G. Kaiser, *Z. Phys. Chem.*, **89**, 338 (1915). [f] B. Anderson, F. Grønlund, and J. Olsen, *Acta Chem. Scand.*, **23**, 2458 (1969). [g] A. R. Osborn and E. Whalley, *Can. J. Chem.*, **39**, 1094 (1961). [h] A. R. Osborn, T. C.-W. Mak, and E. Whalley, *ibid.*, **39**, 1101 (1961).

evidence suggests that in these cases the transition state is reached during generation of a tetrahedral intermediate.[24] The base-catalyzed hydrolysis of acetamide, on the other hand, shows an unusually large negative volume of activation. In this exceptional case the breakdown of a tetrahedral intermediate, rather than its formation, appears to be rate limiting.[24] The present findings thus appear to provide some support for earlier mechanistic interpretations[3,4] of volumes of activation observed for nonenzymatic hydrolysis of carboxylic acid esters. Substituent effects are, however, quite marked, and need to be examined more extensively if volumes of activation are to serve as a more exact basis for speculation concerning reaction mechanisms. Since these effects appear to be exerted through solvent, it appears that particular caution should be exercised in comparing volumes of activation for enzymatic reactions (proceeding in the chemically unique environment of the active site) with volumes of activation for nonenzymatic model reactions in aqueous solution.

Some diving mammals encounter a considerable range of environmental hydrostatic pressures; in an extreme case, a whale was found trapped in the Pacific Ocean at a depth of 1135 m.[25] Pressure effects on aldehyde hydration might in principle constitute a serious problem in metabolic control, since changes in the state of hydration of simple aldehydes are known to affect their activities in several enzymatic reactions.[26] The present results suggest that these effects are not biologically significant. Even in the case of the aldehydes most sensitive to pressure, the effect of submersion to such depths would be to change the equilibrium constant for hydration by 5% or less.

Acknowledgment. We are grateful to Drs. Adam Zipp and Walter Kauzmann for familiarizing us with the high-pressure apparatus used in this work.

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Quantitative Assessment of the Antiaromaticity of Cyclobutadiene by Electrochemical Studies on Quinone Derivatives

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Abstract: Precursors of cyclobutadienonaphthoquinone derivatives have been prepared by novel procedures, utilizing photochemical additions. These may be oxidized electrochemically to the quinones, generating cyclobutadiene rings or models which help to correct for strain and inductive effects. The electrochemical potentials, obtained by extensive cyclic voltammetric studies, may be analyzed to indicate the conjugation energy of the cyclobutadiene system. The data indicate that cyclobutadiene is destabilized by at least 12–16 kcal/mol, and is thus clearly antiaromatic. Substituent effects on the thermodynamic and kinetic stability of cyclobutadiene have also been explored.

Cyclobutadiene has fascinated chemists ever since the early evidence that, contrary to simple expectations, it did not share the stability of benzene.[2] Many studies have been devoted to detecting this molecule, and preparing various stabilized derivatives, in the past

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(1) (a) Taken principally from the Ph.D. Thesis of Dennis R. Murayama, Columbia University, 1973. (b) Taken in part from the Ph.D. Thesis of Robert Grubbs, Columbia University, 1969.

(2) M. P. Cava and M. L. Mitchell, "Cyclobutadiene and Related Compounds," Academic Press, New York, N. Y., 1967.