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Marianne Byrn and Melvin Calvin

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Contribution from Laboratory of Chemical Biodynamics, Lawrence Radiation Laboratory, and Department of Chemistry, University of California, Berkeley, California.

Abstract

Using infra-red spectroscopy, the equilibrium exchange times have been determined for a series of ketones, aromatic aldehydes, and β-ketoesters reacting with oxygen 18 enriched water. These exchange times have been evaluated in terms of steric and electronic considerations, and applied to a discussion of the exchange times of chlorophylls *a* and *b* and chlorophyll derivatives.

Introduction

This investigation of the exchange reactions of aldehydes and ketones with O^{18} enriched water has been undertaken in order to be able to examine the participation of chlorophyll carbonyl groups as chemical intermediates in the oxidation of water during photosynthesis. Photosynthetic mechanisms have been proposed by Calvin[1] and Franck[2] in which the separation of oxidant and reductant, required for oxygen evolution and carbon dioxide fixation, is a photocatalytical chlorophyll reaction. Essential to these mechanisms is the ability of a chlorophyll carbonyl group to undergo hydration. The present work evaluates the exchange ability of chlorophyll in comparison with simple ketones, aldehydes, and β-ketoesters.

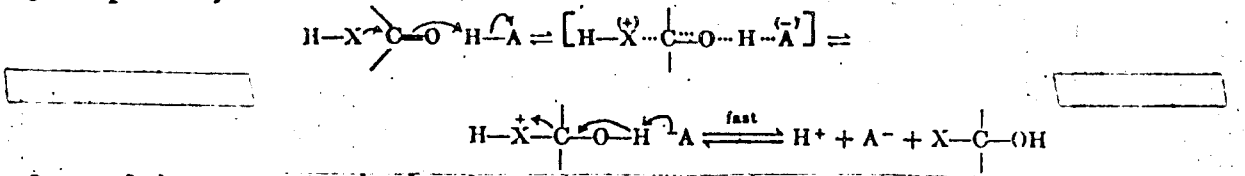
The literature on the O^{18} exchange reactions of carbonyl functions

indicates that aldehydes exchange very rapidly in comparison to ketones. Acetaldehyde exchanges completely at room temperature in neutral solution within 24 hr.,[3] while acetone exchange is incomplete after 24 hr. at 100°.[4] A comprehensive survey of the literature by Samuel and Silver[5] gives exchange rates in various solvents, acidic and basic, for acetone, acetaldehyde, acetoacetate, para-substituted benzophenones, methyl cyclohexanones, and substituted benzaldehydes.

Compounds were chosen for this study because of their similarities to chlorophylls a and b (see Fig. 1). Ring V of chlorophyll a is a β-ketoester of cyclopentanone which is fused to an aromatic nucleus, and chlorophyll b has a pyrrole aldehyde subunit as a part of a larger aromatic system. Thus, cyclopentanones, other cyclic ketones, simple β-ketoesters, and aromatic and heterocyclic aldehydes have been studied.

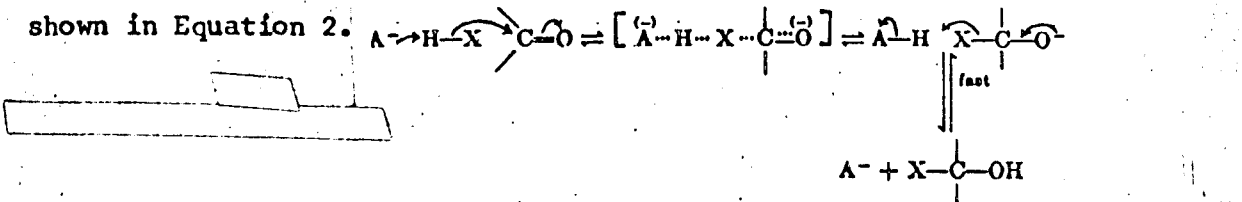
An infrared technique is used to analyze the rate of O^{18} incorporation in the carbonyl group. Halmann and Pinchas[6] showed in 1958 that the $C{=}O^{18}$ band of benzophenone appears at 1635 cm^{-1}, whereas the $C{=}O^{16}$ band is at 1664 cm^{-1}. This 29 cm^{-1} shift is similar to those obtained more recently by numerous observers studying both esters and ketones.[7-9] In addition, the magnitude of the shift is in fair agreement with the theoretical value of 40 cm^{-1} calculated using the harmonic oscillator approximation.[6] With this large shift one can easily follow the loss of the $C{=}O^{16}$ band as the $C{=}O^{18}$ band increases. The exchange time is measured as a complete exchange time rather than a half-time--that is, when the $C{=}O^{16}$ band no longer decreases and the $C{=}O^{18}$ band no longer increases the exchange reaction is complete. The primary advantage of using infrared rather than mass spectroscopy is that several carbonyl groups on one compound can often be distinguished, as is the case with chlorophyll.

Investigations which elucidate the mechanism of addition reactions to carbonyl groups have been summarized recently by Jencks.[10] General acid catalysis involves the concerted addition of HX (H_2O^{18}) and transfer of a proton, as shown in Equation 1.



(1)

General base catalysis involves the concerted removal of a proton from the attacking reagent, to facilitate attack at the carbonyl group, as shown in Equation 2.



(2)

In the back reactions, the roles of the acid and base catalysts are reversed, thus completing the O^{18} exchange.[10]

Experimental

Tetrahydrofuran (THF), which is freshly distilled from lithium aluminumhydride, was found to be the only suitable solvent for the hydrochloric acid catalyzed exchange reactions. It is miscible with water, transparent in the infrared from 1500-1800 cm^{-1}, and dissolves chlorophyll, chlorophyll derivatives, ketones, aldehydes and β-ketoesters. Piperidine was used as the solvent and catalyst for the basic reactions. Pyridine was the only other basic solvent examined which did not possess interfering absorption in the infrared, but it was not even strong enough a base to catalyze the exchange reaction for acetone. In all cases, 10 µl or .01 g. of the substrate, and 10 µl of 60.7% D_2O^{18} (analysis by Weizmann Institute) were used. A high deuterium content water was used because normalized water absorbs in the infrared at 1650 cm^{-1}. A control sample using D_2O^{16} was run for each compound,

to ensure that spectral changes were not due to chemical change or deuterium exchange. The molar excess of O^{18} in the water/over exchangeable O^{16} was of the order of 25- to 50-fold for the ketones and 100-fold for the aldehydes. For the ketones, 50 µl of THF or piperidine were used, whereas the aldehydes were less soluble and required 150 µl of solvent.

Infrared cells (0.025 mm. path length) with IR-tran windows were used as the reaction vessels, since these windows are resistant to aqueous solutions, both acidic and basic. This enabled the exchange to be followed using a Beckman IR-7 spectrometer as the reaction proceeded at room temperature. The first few minutes of reaction time are spent in order to fill the cell and obtain the first spectrum, thus making it impossible to obtain a "zero time" reading. Because as much as 5 min. may have elapsed, in several instances the reaction was complete by the time the first spectrum was obtained. In such cases, the designation in the following tables is for an immediate reaction (Imm.). For the remainder of the cases the time is stated for the earliest spectrum which shows no/change in the carbonyl bands, this being the time required for the substrate and O^{18} enriched water to have come to equilibrium according to the above mentioned mechanisms. The type of spectra obtained is illustrated in Figure 2, depicting a mixture of benzaldehyde in .001 N HCl in THF. The exchange time of 20 min. is in the optimum range for accuracy using this technique. As the exchange times become longer, they are more difficult to follow because the kinetics are exponential, and as the end point is approached the spectroscopic changes become very small. If the exchange time is greater than an hour, spectra taken every 10-15 min. show little change after the first few.

High temperature exchange reactions were accomplished in sealed tubes in an oil bath. At the completion of the reaction, the solutions were evaporated and the materials purified using thin layer chromatography.

Using this infrared technique, it is impossible to determine the exact extent of incorporation; the molar extinction coefficient for the heavy isotope band has been shown in previous research not to be the same as for the O^{16} carbonyl band, and the extinction coefficients are not yet predictable.[7-9] A rough comparison of the peak sizes indicates the exchange approaches 100% of the theoretically possible O^{18} incorporation, but in some cases the equilibrium appears to be at about 60-80% exchange. This could be a solvent effect on the extinction coefficient. However, the extent of incorporation of O^{18} in several of the compounds was determined using low voltage on the CEC Mass Spectrometer 21-130. Ten µl of cyclopentanone, cyclohexanone, and benzaldehyde were respectively mixed in 100 µl of acidic THF and 10 µl of D_2O^{18}, and allowed to stand until completion of the exchange. Fifty µl were used for an IR spectrum, and 50 µl were taken for a mass spectrum. The tetrahydrofuran had to be evaporated in order not to drown out the carbonyl compound mass spectrum. From the ratio of the peak heights, the extent of O^{18} incorporation was determined:

$$\% \ O^{18} = \frac{(M+2)\ 100}{M + (M+2)}$$

The limit of detection of $C{=}O^{18}$ by infrared was evaluated by preparing benzaldehyde samples using successively smaller amounts of O^{18} and determining the extent of incorporation by mass spectroscopy. It was found that a 2% O^{18} incorporation is barely detectable above the noise level, assuming the spectrum is intense and the location of the isotope absorption is known. For less ideal conditions, 5-10% incor-

poration can easily be detected.

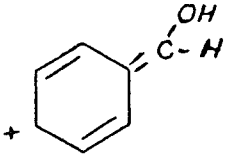
The assignments for the bands of the β-ketoesters were taken from the work by Rhoades et al.[11] The simple ketones and aldehydes showed single bands in the carbonyl region and presented no difficulty. Cyclopentanone is an exception to this fact in some aqueous solvent systems, in which case two peaks are found. Two peaks are also found for several other compounds, as noted on the tables. The infrared spectrum of chlorophyll has been recently studied by Anderson[12] and Katz,[13] and their assignments are in agreement. The carbonyl region is clear in polar solvents and allows for relatively easy analysis of an isotope shift of 30 cm^{-1}.

The ketones, aldehydes and β-ketoesters were obtained from commercial sources and used without further purification. The chlorophylls were prepared by the method of Calvin and Anderson.[14] The Pyro compounds were prepared by the method of Pennington et al.,[15] although a single homogeneous product was not obtained as their procedure stated. Separation from starting materials using thin layer chromatography yielded the pure products possessing the correct spectral properties.

Results and Discussion

An unfortunate limitation in determining exchange time with this infrared technique is the very small range (5 to 60 min) which can be determined with appreciable accuracy, thus making it necessary to change acid concentrations in order to bring the exchange time into a measurable region. The exchange time is known to be linear with the log of the acid concentration, as demonstrated with indanone and anthraldehyde from 0.001 to 0.1 N HCl. (see Fig. 3). This was used to determine relative exchange rates when necessary.

Aldehydes. The results of the acid catalyzed reactions of a series of aldehydes are summarized in Table I. For the series of aromatic aldehydes which exchange in 0.001 N HCl, the results are consistent with the mechanism discussed earlier. The effect of the protonation of the oxygen is to increase the electrophilicity of the carbonyl carbon and make it more reactive toward addition reactions. Opposing this increased electrophilicity is the effect of the extensive aromatic system, which acts as an electron donor to delocalize the positive charge on the carbonyl carbon, and hence, reduce the reactivity of the group in addition reactions, as shown in the following resonance form:

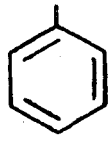
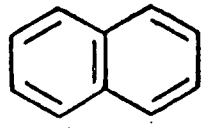
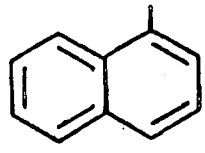
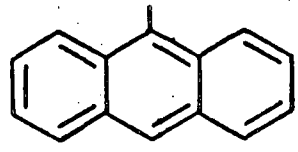
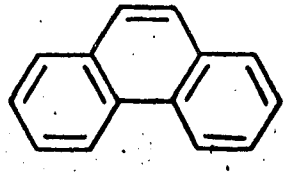
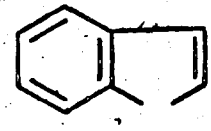


This ability of an aromatic system to delocalize charge can be measured as the empirical resonance energy,[16] which is directly related to the HMO delocalization energy and corresponds to the resonance hybrid.[17]

For the exchange reactions of these aromatic aldehydes, a good correlation exists between the empirical resonance energy, the time of the exchange reaction, and the frequency of the carbonyl absorption, both for $C=O^{16}$ and $C=O^{18}$ (see Fig. 4). The relationship between the frequency of absorption and the rate of reaction is a reflection of the well known effect of conjugation on carbonyl stretching frequencies.

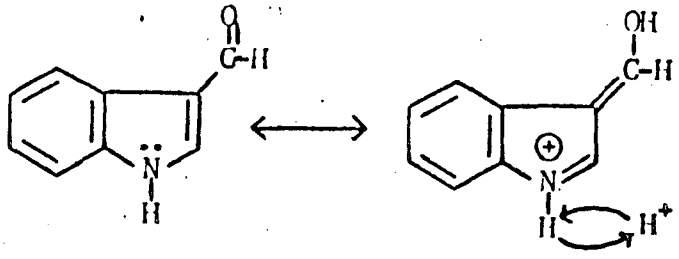
The three remaining heterocyclic aldehydes, indolealdehyde, chlorophyll b and pheophytin b, have identical exchange times. For indolealdehyde this exchange time, which is three times slower than benzaldehyde, is not caused by the aromatic ring since it is not directly conjugated with the carbonyl group. The slow rate can be attributed to a very stable resonance form involving the nitrogen atom, which would

Table I. Exchange Reactions of Aldehydes

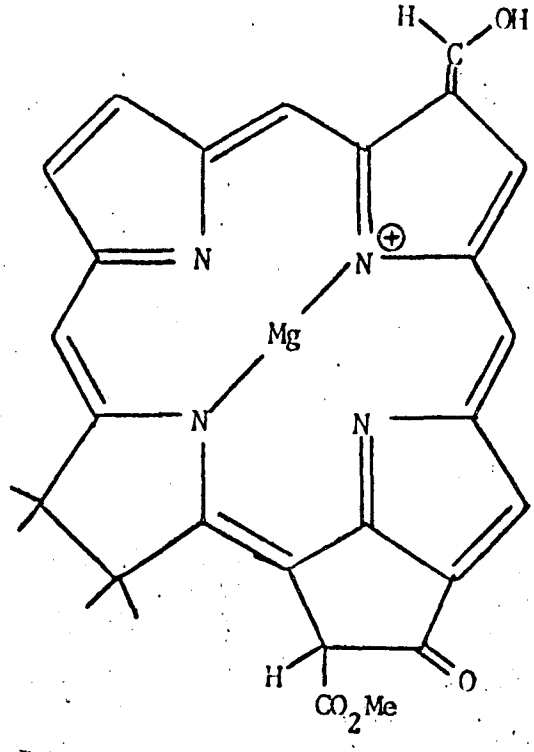
Compound	Conc. HCl	Time (Min)	ν in cm^{-1} $C=O^{16}$	ν in cm^{-1} $C=O^{18}$	Empirical resonance energy
Acetaldehyde[a] CH_3CHO	.001 N	Imm.	1720	1692	0
Benzaldehyde[b] 	"	20	1703	1675	36.0
2-Napthaldehyde 	"	25	1697	1668	61.0
1-Napthaldehyde 	"	35	1692	1664	61.0
9-Anthraldehyde 	"	45	1676	1650	83.5
9-Phenanthraldehyde 	"	55	1691	1661	91.3
3-Indolealdehyde 	.005 N	20	1667	1641	--
Chlorophyll b[c]	"	20	1665	1637	--
Pheophytin b[d]	"	20	1663	1636	--

a decomposes rapidly
b 47% O^{18} determined by mass spectroscopy
c purification of $C=O^{18}$ compound on Mannitol TLC using 2% methanol in isooctane
d purification of $C=O^{18}$ compound on Mannitol TLC using 13% acetone in isooctane. Frequently, a considerable amount of the labeling was lost during purification.

inhibit carbonyl addition reactions.



The same type of resonance structure can be drawn for both chlorophyll b and pheophytin b.



However, such contributors are much less stable than the one for indolealdehyde because of the electrostatic repulsion of the chelated magnesium and the positively charged nitrogen. With indolealdehyde, the hydrogen can be easily removed from the positively charged nitrogen, while this is not true of the magnesium. It follows then, that the hydrogens which replace the magnesium in pheophytin b must also be unable to freely leave the heterocyclic nucleus since the exchange times for the two compounds are identical. Thus /the slow exchange time for chlorophyll b and pheophytin b is due to the extensive chlorin aromatic system, whereas indole aldehyde exchange is inhibited by the presence of the nitrogen atom.

Base catalyzed aldehyde exchange reactions were attempted using two different solvents, pyridine and piperidine. Pyridine was not sufficiently basic to catalyze the reactions at a rate which can be detected using the infrared technique. Piperidine was found to be so strongly basic that it formed an addition product, removing the carbonyl absorption band. Inorganic hydroxides were not used because they are known to allomerize chlorophyll.

Ketones. The results of a series of base catalyzed ketone exchange reactions and several ß-ketoester exchange reactions are summarized in Table II. There are no direct correlations between the exchange times, the stretching frequencies, or any other readily measurable quantity. Cook[18] has found a relationship between the XX'C=O bond angle, the ionization potential and the carbonyl stretching frequency; but these relationships cannot be extended to encompass the exchange times. However, these results can be qualitatively analyzed according to the mechanism presented above, on the basis of both electronic and steric considerations.

Acetone has the fastest exchange time having neither steric interference nor electron donating groups to reduce the electrophilicity of the carbonyl carbon. Ninhydrin (1,2,3-triketohydrindene) is also extremely rapid, as could be expected with the electron withdrawing effects of the opposed keto groups and the lack of any steric interference.

The series cyclohexanone, cyclobutanone, cyclopentanone can be evaluated by considering the amount of ring strain which is lost when the sp^2 carbonyl bond is hydrated to form an sp^3 tetrahedral carbon in the intermediate,

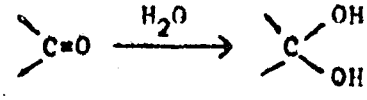
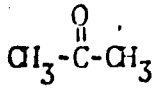
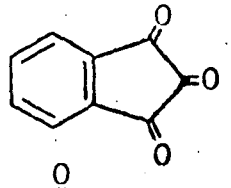
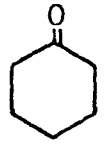
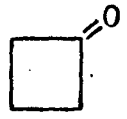
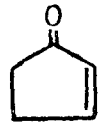
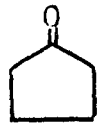
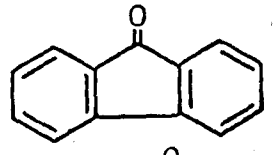
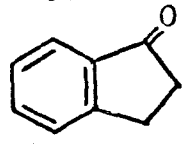
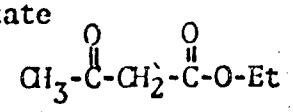
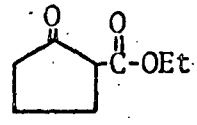


Table II. Exchange Reactions of Ketones - Base Catalyzed - Piperidine

Compound	Time	ν in cm^{-1} $C{=}O^{16}$	$C{=}O^{18}$
Acetone 	Imm.	1708	1678
Ninhydrin 	Imm.	1714[a] 1739	1692
Cyclohexanone 	10 min	1707	1678
Cyclobutanone 	10 min	1780	1747
Cyclopentenone 	15 min	1739	1708
Cyclopentanone 	1 hr	1735	1702
Fluorenone 	1 hr	1716	1685
Indanone 	3.5 hr	1713	1683
Ethylacetoacetate 	10 min	1711	1684
Carboethoxycyclopentanone[b] 	--	1735	

a Two carbonyl frequencies are observed for ninhydrin, as they often are for anhydrides.

b The ester carbonyl and keto carbonyl stretching frequencies are both in the same region and overlap; therefore, it is impossible to determine a rate for the reaction.

The angles are 117°, 94°, and 108° respectively, for the carbonyl bond, whereas the bond formed for the hydrate is 110°. Thus, cyclopentanone is the slowest because it loses the least amount of ring strain. The relationship between acetone, cyclohexanone and cyclopentanone can be seen in other carbonyl addition reactions such as semicarbazone formation.[10] Additional views are those of Price and Hammett[19] who note the increased reactivity of cyclohexanone compared to acetone as almost entirely due to a lower heat of activation. Brown, Fletcher, and Johannessen[20] have pointed out that a cyclohexane ring in which all of the carbon atoms are tetrahedral may exist in the particularly stable chair form, in which all of the valences are staggered, but that when one of the carbon atoms is trigonal, as in cyclohexanone, this stable configuration is impossible. Since the rate-controling step involves the transformation of a trigonal carbon atom to a tetrahedral configuration, the reaction occurs particularly easily with cyclohexanone. In the case of cyclopentanone, the valences are more easily staggered in the ketone than in the reactive intermediate, and a decrease in reactivity is observed.

In the remainder of the compounds, cyclopentenone, fluorenone, and indanone, the ring strain is approximately the same since cyclopentanone rings are the fundamental units involved. The exchange times can be considered on the basis of the number of hydrogens which are eclipsed in the intermediate and the effect of aromatic rings in reducing the electrophilicity of the carbonyl carbon. Cyclopentenone is faster than cyclopentanone although a decrease in reactivity could be expected from the additional unsaturated bond of cyclopentenone. However, the unsaturated

compound has one less hydrogen to sterically interfere in the intermediate hydrate.

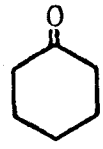
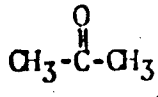
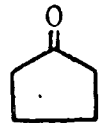
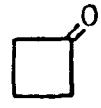
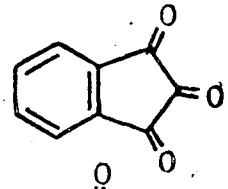
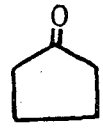
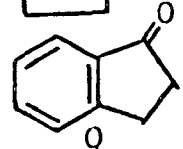
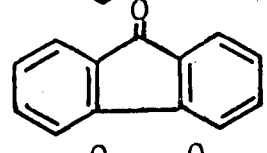
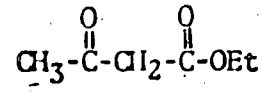
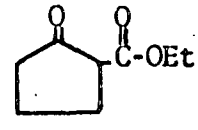
Another example of the predominance of steric interference over electronic inhibition is the difference in exchange times between indanone and fluorenone. Fluorenone, with two aromatic rings adjacent to the cyclopentanone ring, is 3.5 times faster than indanone, which has one adjacent aromatic ring, but two hydrogens which interfere.

The results of the acid catalyzed exchange reactions of ketones and several β-ketoesters are summarized in Table III. It is immediately obvious that the sequence of compounds from the fastest to the slowest acid catalyzed reaction is quite different from the base catalyzed reactions. This reversal of order on going from acid to base catalysis was also noted by Menon[21] when studying p-substituted benzophenones.

The inversion of cyclobutanone and cyclopentanone can be explained on the basis of the basicities of the ketones. The pK_{BH^+} for cyclohexanone, acetone, cyclopentanone and cyclobutanone are -6.8, -7.2, -7.5, and -9.5 respectively.[22] The rate of exchange correlates with the increasing basicity of the ketones; the least basic, cyclobutanone, is least stable in the hydrated form and thus has the slowest exchange rate.

Campbell and Edward[22] showed that the basicity of cyclic ketones paralleled changes in stretching frequency; this correlation can be made with exchange rates for the first four compounds, although for the remainder of the compounds there is no relationship between stretching frequency, exchange rates, and basicity.

Table III. Exchange Reactions of Ketones - Acid Catalyzed

Compound	Conc. HCl	Time	ν in cm^{-1} $C=O^{16}$	$C=O^{18}$	Relative Rates
Cyclohexanone[c] 	.001 N	Imm.	1705	1682	< .3
Acetone 	.001 N	Imm.	1710	1680	< .3
Cyclopentanone[c] 	.005 N	10 min	1745[a] 1728	1706	1
Cyclobutanone[e] 	.01 N	Imm.	1782	1749	1.2
Ninhydrin 	.01 N	1.5 hr	1730[a] 1757	1704	11
Cyclopentenone 	.1 N	10 min	1664[a] 1703	1647 1682	12
Indanone 	.1 N	15 min	1713	1686	19
Fluorenone[d] 	.01 N	2.5 hr	1719	1686	>76
Ethylacetoacetate 	.005 N	20 min	1719	1688	
Carboethoxy-Cyclopentanone[b] 	.1 N	Imm.	1750	--	

a shows two ketone peaks in some solvents

b The keto peak of carboethoxycyclopentanone is a shoulder of the larger ester carbonyl peak, making it difficult to follow the exchange. The reaction time was determined from the disappearance of the O^{16} shoulder.

c 46% O^{18}, determined by mass spectroscopy

d 65°C; at room temperature in acid concentration of 1 N some exchange takes place immediately, but the spectrum is very broad and difficult to interpret.

e decomposes rapidly

Ninhydrin is quite slow, and could be compared in basicity to a diketone. For diketones, basicity decreases as n decreases $\left[\begin{matrix}O\\ \|\\ -C-(CH_2)_n-C-\end{matrix}\right]$ and when n=0 basicity is less than typical ketones--that is, the form: $\begin{matrix}OH & OH\\ | & |\\ -C & -C-\\ \| & \|\\ O & O\end{matrix}$ is very unlikely.[19] Since ninhydrin has three consecutive keto groups (2-hydrate), it follows that the reaction rate should be slower than the simple ketones. The fact that ninhydrin is faster then indanone reflects the electron withdrawing effect of the additional keto group to increase the reactivity of the/carbonyl group. opposed

For the remainder of the acid catalyzed ketone exchange reactions, the balance between electronic and steric effects are the reverse of those for the base catalyzed reactions. Cyclopentenone is considerably slower than cyclopentanone and reflects the importance of the additional unsaturated bond and the relative unimportance of the steric effects of the additional hydrogen. [Dahn[23] found the rate of cholestanone (cyclohexanone) to be 10^3 times faster than cholestenone (2-cyclohexenone), which again demonstrates the effect of one alpha-beta unsaturated bond.] Another instance of the predominant effect of electron donating functions is the very slow fluorenone exchange time relative to indanone. The aromatic ring hinders the reaction more than the additional hydrogens on the indanone moiety.

The predominate effect of electron donating aromatic rings over sterically interfering hydrogen atoms in the acid catalyzed reactions is mechanistically sound, since the stability of the conjugate acid will be dependent on the electronic effects while the formation of the hydrate in the base catalyzed reactions depends not only on the carbonyl carbon electrophilicity but on the ability of the nucleophile to overcome steric interference in order to attack the carbonyl.

β-Ketoesters. Cohn and Urey[4] showed that the exchange reaction of acetone does not follow the path of enolization, but is faster than enolization. The enol form is not subject to electrophilic attack and would decrease the rate of exchange. This is demonstrated with both ethylacetoacetate and carboethoxycyclopentanone, which are considerably slower than acetone and cyclopentanone.

Biological Model Compounds. Table IV summarizes the exchange reactions that were attempted with chlorophyll and chlorophyll derivatives.

Table IV. Exchange Reactions of Biological Model Compounds

Compound	Acid	Base
Chlorophyll *a*	pheophytinization in HCl. No incorporation in 10% HOAC, 66 hr.	decomposition
Pyrochlorophyll *a*	pheophytinization	no incorporation in piperidine 1 day; 65°
Pheophorbide *a*	no incorporation .1 N HCl in THF; 1 day at 65°	decomposition
Pyropheophorbide *a*	incorporation in .01 N HCl in THF; 1 day at 65°	decomposition

The exchange reactions that were attempted with chlorophyll *a* and chlorophyll derivatives generally were unsuccessful. The pigments are unstable in basic solution and the magnesium is removed in acid solution. However, those compounds for which there were stable exchange conditions were quite resistant to hydration and exchange. The reactions were carried out under much more vigorous conditions than the model compounds, using temperatures of 65°. For the acid exchange reactions it appears that the

large aromatic ring of the porphyrin nucleus has considerably decreased the reactivity of the C_9 carbonyl beyond that of any of the model compounds.

From the results of the ketone exchange reactions in basic solution, it was expected that the simple ketone derivative of chlorophyll a, pyrochlorophyll, would show some exchange reaction under these strong conditions. Steric hindrance of the two C_{10} hydrogens is no greater than for indanone, although the electronic effects are considerably greater. Nevertheless, there is no obvious reason for such complete lack of reactivity of the carbonyl group. It is, however, clear that the isocyclic carbonyl oxygen atom would be stable to exchange during the course of any normal isolation procedure from the biological material.

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Fig. 1. Nomenclature and Substituent Designations.

	Compound	Mg present[a]	R	R'	R"
Ia	Chlorophyll *a*	+	CH_3	CO_2Me	Phytol
IIa	Pyrochlorophyll *a*	+	CH_3	H	Phytol
IIIa	Methyl pheophorbide *a*	-	CH_3	CO_2Me	Me
IVa	Methyl pyropheophorbide *a*	-	CH_3	H	Me
Ib	Chlorophyll *b*	+	CHO	CO_2Me	Phytol
Vb	Pheophytin *b*	-	CHO	CO_2Me	Phytol

[a] +, magnesium present; -, magnesium absent.

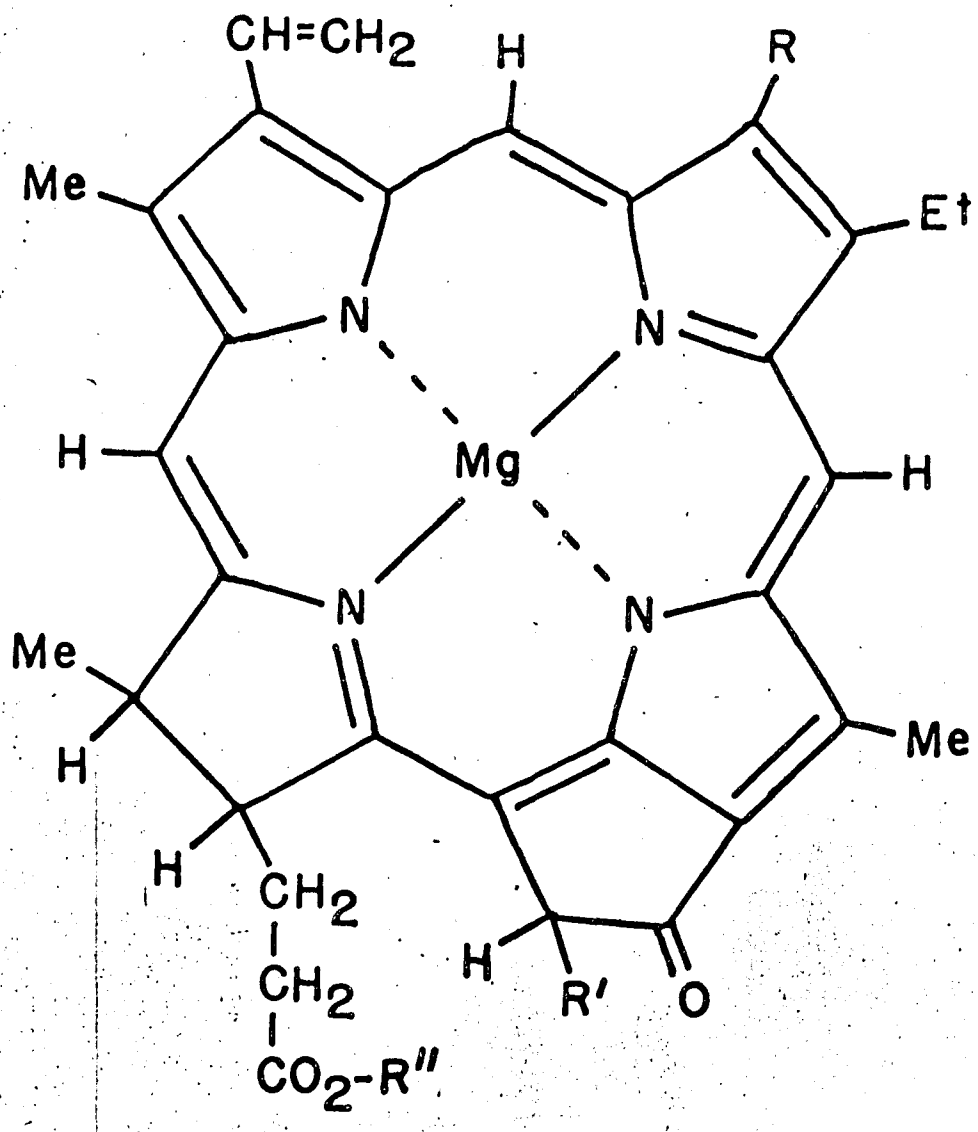

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Fig. 1

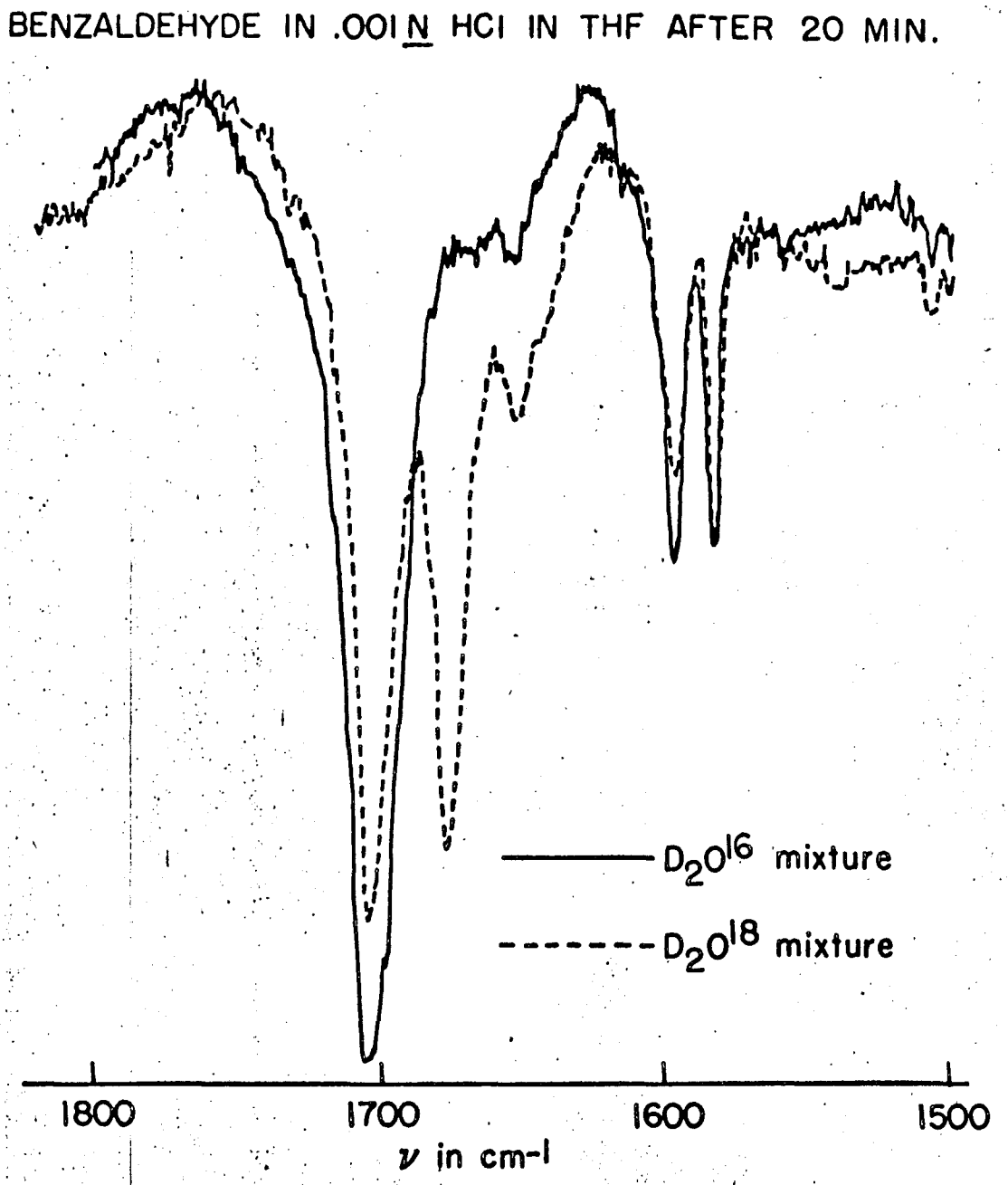

Fig. 2

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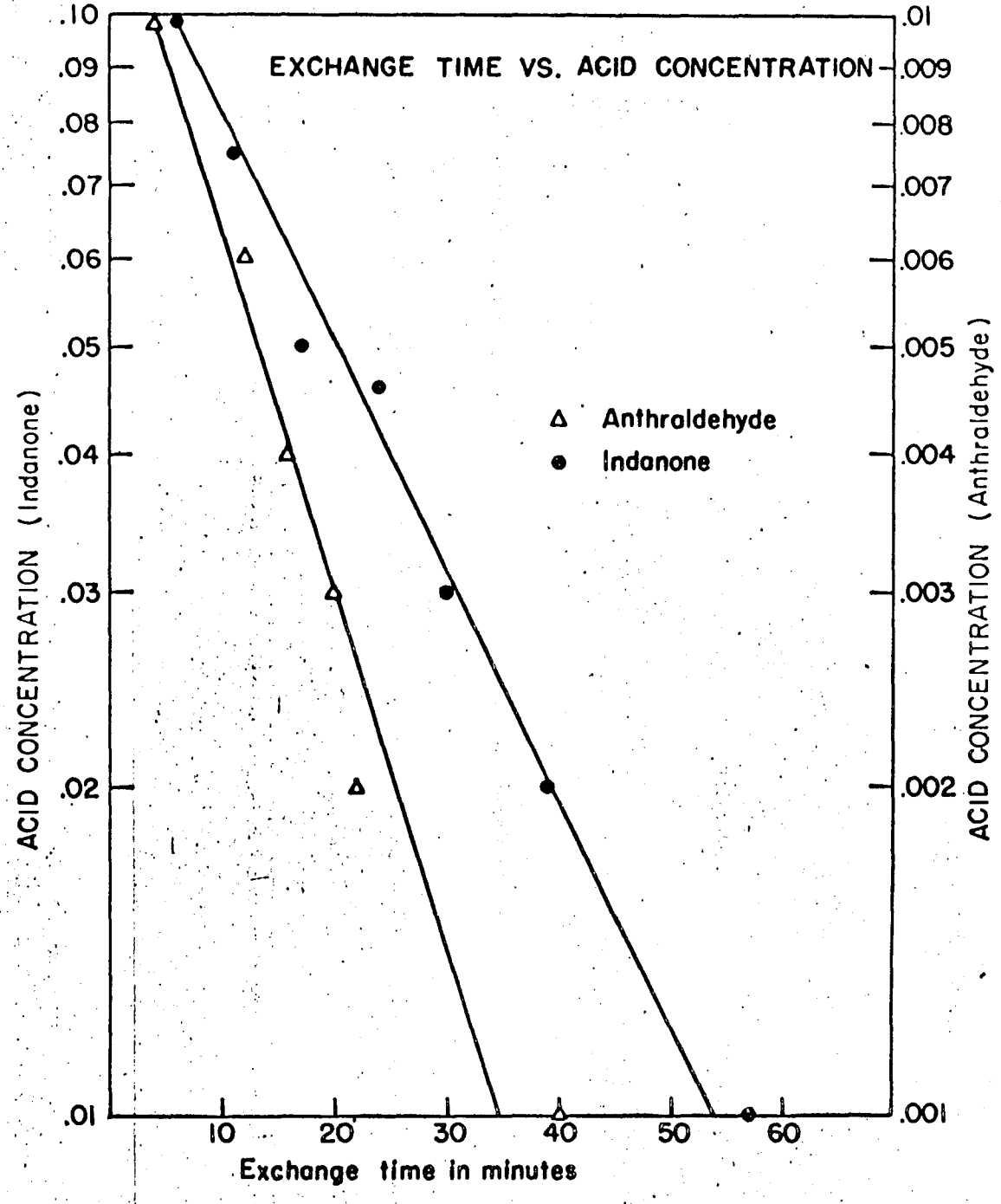

Fig. 3

MUB-8619

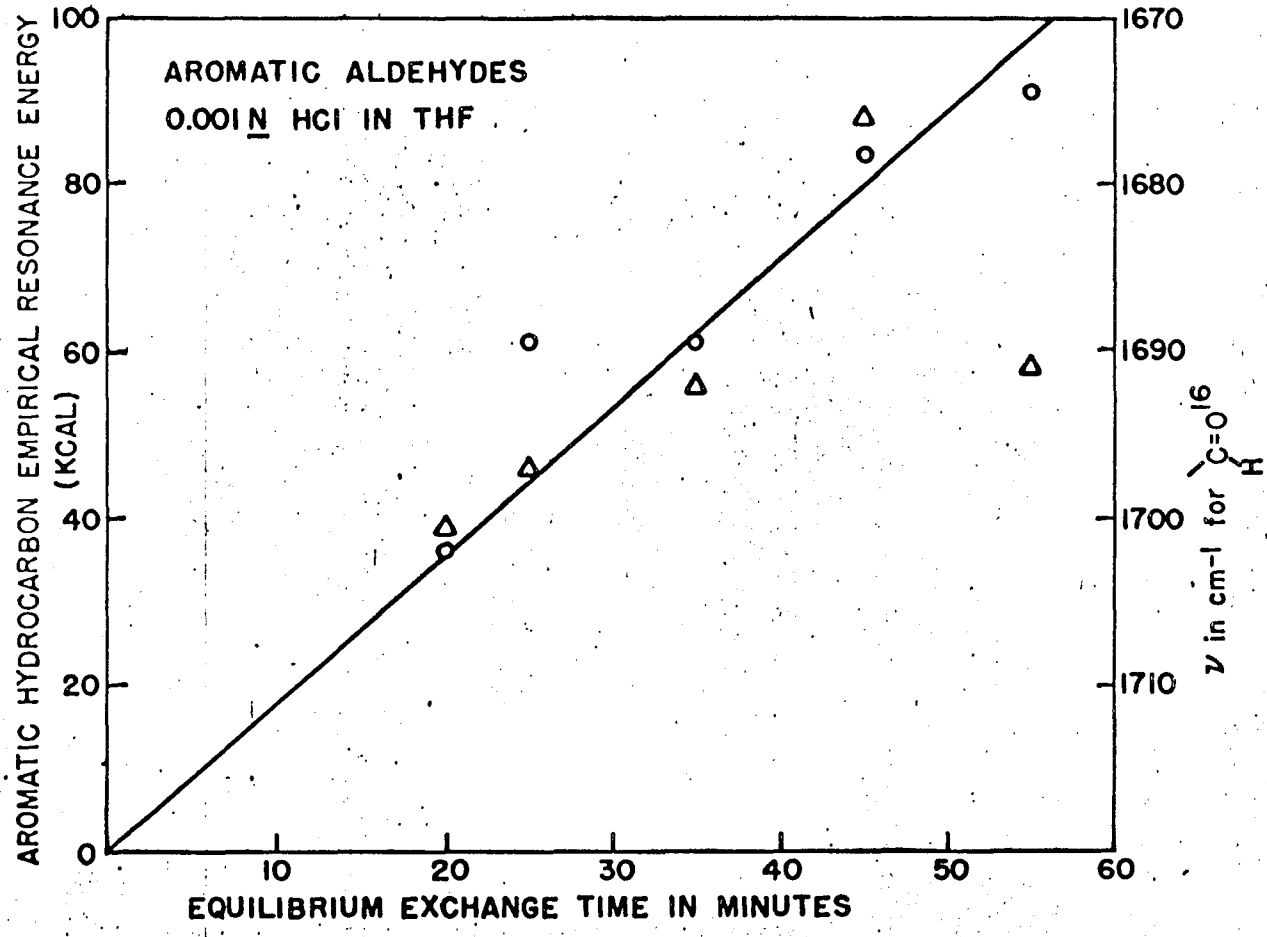

Fig. 4

MUB-8617