Table IV. Thermal Parameters of Nonhydrogen Atoms ($\times 10^3$), with Estimated Standard Deviations in Parentheses, for Compound 1

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	289 (9)	798 (13)	747 (13)	−51 (10)	−55 (11)	70 (13)
O(2)	445 (13)	785 (16)	1072 (20)	147 (13)	−61 (16)	−134 (16)
N	300 (11)	563 (15)	491 (13)	−10 (11)	−33 (11)	−43 (11)
C(1)	526 (19)	538 (19)	828 (24)	19 (16)	−25 (19)	−154 (18)
C(2)	336 (14)	782 (22)	459 (16)	42 (15)	−45 (14)	−53 (17)
C(3)	361 (14)	517 (16)	466 (16)	−32 (13)	10 (14)	−29 (15)
C(4)	366 (14)	587 (17)	375 (14)	−55 (13)	−1 (13)	−11 (14)
C(5)	359 (14)	593 (17)	337 (13)	−50 (13)	1 (12)	23 (12)
C(6)	388 (15)	616 (20)	588 (18)	−113 (14)	−76 (16)	79 (17)
C(7)	447 (17)	572 (18)	386 (15)	71 (16)	37 (14)	−33 (13)
C(8)	450 (16)	570 (17)	393 (15)	16 (15)	18 (13)	−8 (14)
C(9)	397 (15)	416 (15)	477 (16)	−84 (13)	20 (18)	28 (13)
C(10)	556 (18)	534 (18)	395 (15)	31 (16)	48 (15)	−93 (14)
C(11)	536 (18)	457 (16)	369 (14)	−36 (15)	−25 (14)	−7 (12)
C(12)	410 (15)	480 (16)	451 (15)	−63 (14)	−33 (14)	−71 (14)
C(13)	529 (19)	440 (17)	563 (18)	−56 (16)	−25 (16)	30 (14)
C(19)	694 (24)	521 (19)	606 (19)	−30 (18)	−125 (21)	68 (16)
C(15)	601 (22)	515 (20)	769 (24)	65 (18)	−118 (20)	−36 (18)
C(16)	474 (18)	646 (21)	776 (24)	45 (17)	14 (19)	−113 (19)
C(17)	508 (18)	541 (18)	546 (19)	2 (16)	40 (16)	−8 (15)

formed with tris[2,2-bis(trideuteriomethyl)-1,1,1-trideuterio-6,6,7,7,8,8,8-heptafluorooctane-3,5-dionato]praseodymium(III) [Pr(fod)$_3$-d_{27}], from Aldrich (Uvasol grade), which was purified by sublimation at 0.1 mmHg. All measurements were performed for the range of substrate concentrations between 0.08 and 0.25 M, while ligand concentration was constant (0.008 M). All manipulations with this reagent, solvents, and compound **2** were carried out in a glovebox which was continuously flushed with dry nitrogen. All other experimental details have been recently described.[11]

Calculations were performed on a CDC 6200 computer using the programs for linear regression, simulation of spectra, and calculation of the bound shifts which were set up in our laboratories. In the bound-shifts program the minimization of the agreement factor was accomplished in two successive steps: a broad search with a Monte Carlo technique,[12] followed by a minimization with the SIMPLEX algorithm.[13]

Crystal Data for Compound 1: $C_{17}H_{17}NO_2$, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 6.071 (3) Å, b = 24.227 (12) Å, c = 9.558 (4) Å, V = 1405.8 Å^3, Z = 4, mol wt 265.998, d_{exptl} = 1.256 g cm^{-3}, φ = 0.7107 Å. Three-dimensional intensity data were collected on an automatic Philips PW-1100 diffractometer (ω mode, $4.58 < 2\theta < 64°$). The set of observed data (1840 reflections) was completed by introducing all the unobserved reflections (957 reflections) within $\sin\theta/\varphi = 0.75$, with a statistically evaluated amplitude.[14] The structure was solved by direct methods using the MULTAN program.[15] Thirty-one sets of phases were produced by MULTAN, and the E map calculated from the set with the highest "combined figure of merit" allowed all 20 nonhydrogen atoms to be identified. The positional and anisotropic thermal parameters of the nonhydrogen atoms were refined by full-matrix least-squares calculations. The positions of the hydrogen atoms on the biphenyl rings were calculated. The positions of the hydrogen atoms apart from those of the oxazine ring and the methyl group were found from a three-dimensional difference Fourier synthesis. All hydrogen atoms were then refined with isotropic temperature factors by using the XRAY-72 program.[16] The final reliability index was R = 0.057 (R_w = 0.059). The $w = 1/\sigma^2(F_o)$ weighted function was used, with $\sigma(F_o)$ as the structure factor standard deviation. Final positional and thermal parameters are given in Tables III and IV.[17]

Acknowledgment. The authors are grateful to Professor H. Staab and his staff, Abtailung Organische Chemie, Max Planck Institut für medizinische Forschung, Heidelberg, West Germany, for providing 360-MHz spectra of compound **2**.

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(17) A list of structure factors for compound 1 can be obtained on request from the authors at the University of Zagreb. A program developed for the NMR bound-shift calculations can be obtained on request from A. Lisini (present address: Istituto di Chimica, Università degli Studi di Trieste, 34127 Trieste, Italy).

Investigation of *o*-Acetoxyaryl Radicals

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o-Acetoxyphenyl radicals (**4a**) and 3-methyl-2-acetoxyphenyl radicals (**4b**) have been generated by decarboxylation of the corresponding benzoyloxy radicals. CIDNP studies and product analysis reveal no evidence for neighboring group participation by the acetoxy group or for acetoxy migration. The CIDNP investigations demonstrate that *o*-acetoxybenzoyloxy radicals decarboxylate slower than benzoyloxy radicals.

The 1,2 migration of an acetoxy group in a carbonium ion is a well-documented process which involves the acetoxy-bridged species **1a**.[1] The corresponding rearrangement has been observed in β-acetoxy radicals, **2b**.[2] Oxy-

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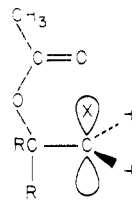
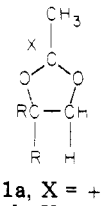
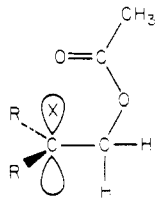


2a, X = +
b, X = ·



1a, X = +
b, X = ·

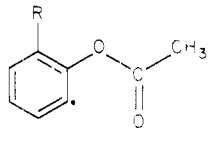


3a, X = +
b, X = ·

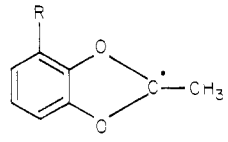
gen-18 labeling studies have shown that the carbonyl oxygen in **2b** forms the new carbon–oxygen bond in **3b**.[3] ESR studies have shown, however, that dioxolanyl radicals, **1b**, cannot be intermediates in this rearrangement.[4,5] Under conditions where both **2b** and **3b** can be detected by ESR, cyclization of **2b** to **1b** cannot be observed. However, when dioxolanyl radicals are generated, ESR studies show that they cleave to β-acetoxy radicals too slowly for them to be intermediates in the rearrangement of **2b** to **3b**.

Although the geometry of the intermediate or transition state for the radical rearrangement shown above is unknown, it is clear that this species must lie on an energy surface which is separated from **1b** by a kinetic and/or thermodynamic barrier.

It is the purpose of this work to examine the chemistry of β-acetoxy radicals in which a thermodynamic driving force for acetoxy participation has been provided. Since aryl radicals are less stable than alkyl radicals, we have examined the reactions of *o*-acetoxyphenyl radicals, **4**, in order to determine if there is evidence for the intermediacy of bridged structures such as **5**.



4a, R = H
b, R = Me



5a, R = H
b, R = Me

Among the methods that have been used to evaluate the effect of neighboring group participation in radicals are studies of the rate of radical formation[6] and chemically induced dynamic nuclear polarization (CIDNP)[7] investigations of radical structure. CIDNP investigations of bridging in radicals can utilize two general methods. One approach takes advantage of the fact that in many cases the bridged radical will have a different symmetry than the corresponding nonbridged radical, leading to different polarizations for the products. We have used this method to show that the ground state of the β-bromoethyl radical is nonbridged.[8] Another method takes advantage of the fact that bridging often places unpaired spin on atoms which are remote from the radical center in the nonbridged radical. NMR signals from these remote nuclei are often polarized in products resulting from a bridged radical. Iwamura et al.[9] have used this technique to demonstrate

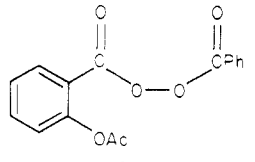
Table I. ^{1}H and ^{13}C Polarizations Observed in Thermolysis of Peroxides 6, 7, and 8 at 150 °C

		^{1}H NMR		^{13}C NMR	
	peroxide product	cyclohexanone	HCA	cyclohexanone	HCA
6	benzene	E	*a*	E	
	chlorobenzene		E		E
	ester 11	A	A	A	A
	o-acetoxybiphenyl	nb[b]	nb	nb	A
	$PhC(Cl)_2C(O)C(Cl)_3$		nb		E
	CO_2	nb	nb	nb	E
7	phenyl acetate	E		E	
	o-chlorophenyl acetate		E		E
	ester 13	A	A	A	A
8	*o*-acetoxytoluene	E		nc[c]	
	m-chloro-*o*-acetoxytoluene	nb	E		nc

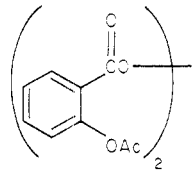
[a] Inappropriate solvent. [b] Not observed. [c] Experiment not conducted.

participation by a methylthio group in the formation of the *o*-(methylthio)benzoyloxy radical.

In the present study, we investigate the *o*-acetoxyphenyl radicals generated by the thermolysis of peroxides **6**, **7**, and **8**. If cyclized structures such as **5** have appreciable life-



6



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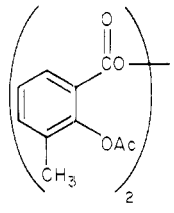

8

times, we expect to see either products resulting from these intermediates or nuclear polarizations for the carbons and hydrogens of the acetoxy group in products resulting from the o-acetoxy radicals.

Results

Decomposition of Peroxide 6. A CIDNP investigation of the thermolysis of **6** gave only nuclear polarizations that would be expected to result from radical pair (**9** + **10**) (eq 1). For example, the ^{1}H NMR spectrum obtained during the 150 °C thermolysis of **6** in cyclohexanone solvent showed only emission for benzene and enhanced absorption for the protons on the unsubstituted aromatic ring of phenyl *o*-acetoxybenzoate, **11**. CIDNP studies of **6** were carried out by using both ^{1}H and ^{13}C NMR in cyclohexanone and hexachloroacetone (HCA) solvents. The resulting polarizations, which are summarized in Table I, are all consistant with the intermediacy of radical pair (**9** + **10**). The signs of all observed polarizations are those predicted by Kaptein's rules.[10]

These data show that the initial radical pair resulting from thermolysis of **6** preferentially loses carbon dioxide

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(6) Martin, J. C. In "Free Radicals"; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1973; Vol. 2, p 509.
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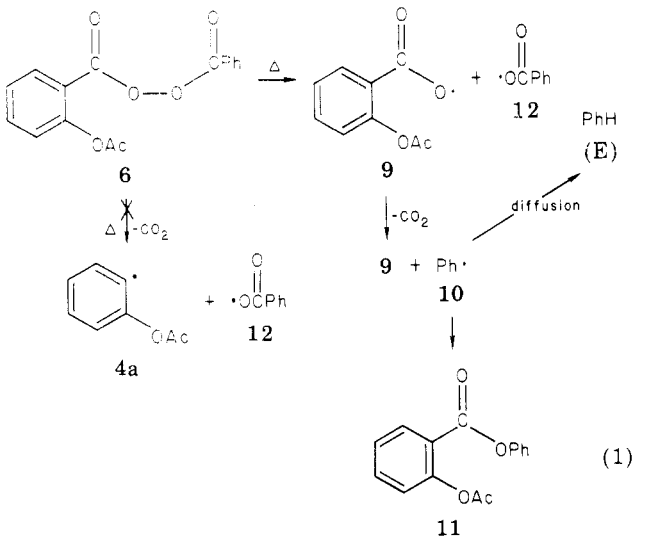
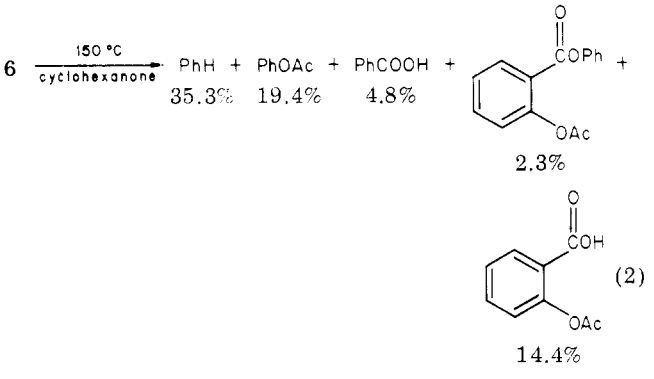


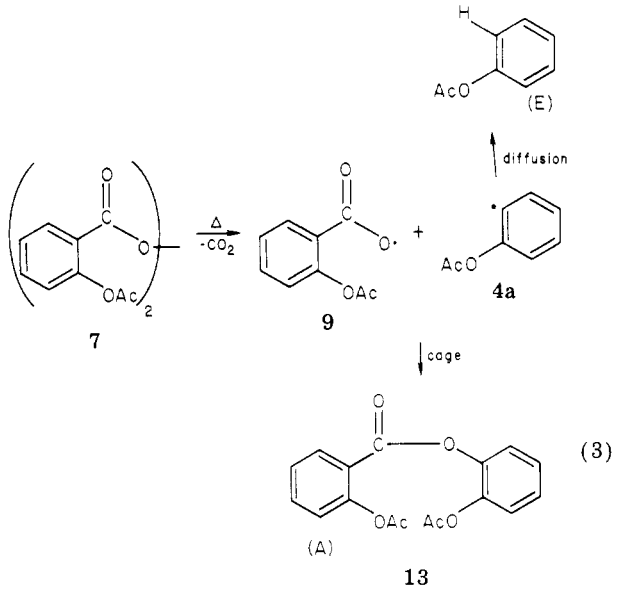
from the benzoyloxy radical, **12**, rather than from **9**. This preference is also indicated by the product analysis shown in eq 2, which shows a ratio of acetylsalicylic acid to benzoic acid of 3:1.



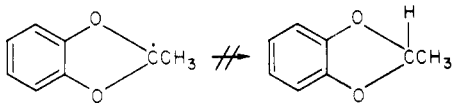
The fact that pair (**9** + **10**) is formed in preference to pair (**12** + **4**) indicates that either radical **9** is stabilized by the *o*-acetoxy group or that radical **4** is destabilized by the *o*-acetoxy group. That the *o*-acetoxy group is acting to stabilize the carboxyl radical is indicated by a study of the rate of decomposition of peroxide **7** as compared to benzoyl peroxide. These experiments, which were carried out in refluxing benzene, show that **7** decomposes twice as fast as benzoyl peroxide.

If this modest rate difference is assumed to result from a small amount of stabilizing interaction between the *o*-acetoxy group and the developing carboxyl radical, we may postulate that radical **9** is stabilized toward decarboxylation to a greater extent than is radical **12**. Anchimeric assistance by ortho groups in the thermolysis of perbenzoates has been reported.[11]

Thermolysis of Peroxide 7. Inasmuch as decomposition **6** does not lead to CIDNP signals from products of radical **4a**, we turned to an investigation of peroxide **7** in order to generate **4a** as a member of a radical pair. As is shown in Table I, these studies lead to CIDNP signals arising from radical pair (**4a** + **9**). For example, thermolysis of **7** in cyclohexanone leads to phenyl acetate, showing strong emission in the ^{1}H NMR. An enhanced absorption in the aromatic region was attributed to ester **13**. The important fact about the CIDNP results summarized in Table I is that in no case is polarization observed for the carbons or protons of the acetoxy group in products.



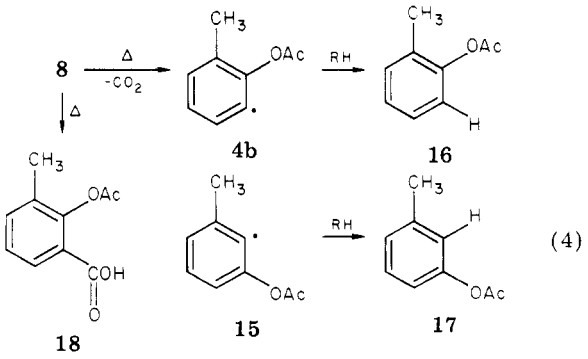
The possibility that **4a** cyclizes to radical **5a** which subsequently abstracts hydrogen to give acetal **14** was considered. However, no polarization attributable to **14** in either the ^{1}H or ^{13}C NMR could be detected. That **14** was not a product in the thermolysis of **7** was confirmed by subjecting the reaction mixture to aqueous acid hydrolysis.



This procedure did not result in detectable amounts of catechol, the product expected from the hydrolysis of **14**.

These results indicate that structures such as **5** with delocalization of the unpaired spin on to the acetoxy group are not involved in the chemistry of **4**. If an acetoxy bridged intermediate is involved, it does not live long enough to permit spin selection and consequent nuclear polarization to occur. Hence the lifetime of **5**, if it exists at all, must be less than 10^{-10} s.[12]

Search for an Acetoxy Migration in the 3-Methyl-2-acetoxyphenyl Radical (4b). The above experiments demonstrate the absence of a detectable bridged intermediate in the chemistry of **4**. In order to determine if an acetoxy group will actually undergo a 1,2 migration in an *o*-acetoxyphenyl radical, we have generated the 3-methyl-2-acetoxyphenyl radical, **4b**, by the thermolysis of peroxide **8** (eq 4). If acetoxy migration occurs in **4b**, the 6-



methyl-2-acetoxyphenyl radical, **15**, will be formed, and

(11) Koenig, T. In "Free Radicals"; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1973; Vol. 1, p 137.

(12) Kaptein, R. In "Chemically Induced Magnetic Polarization"; Lepley, A. R.; Closs, G. L., Eds.; Wiley-Interscience: New York, 1973; p 141.

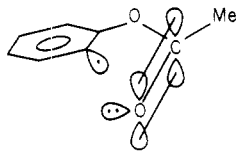


Figure 1.

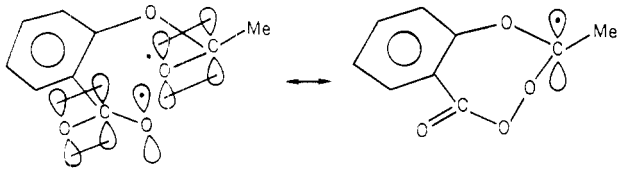


Figure 2.

both o-acetoxytoluene, **16**, and m-acetoxytoluene, **17**, will result. However, thermolysis of **7** at 150 °C in cyclohexanone gave **16** (6.1%), a 70.4% yield of 2-acetoxy-3-methylbenzoic acid, **18**, and no detectable **17**. In order to increase the amount of decarboxylation in the thermolysis of **8**, the peroxide was decomposed at 300 °C in mineral oil. This experiment gave **16** (9.3%), but **17** was not detected. Hence, we conclude that acetoxy migration in o-acetoxyphenyl radicals does not occur.

Discussion

Two interesting points that have emerged from this study are the reluctance of the o-acetoxybenzoyloxy radical to decarboxylate and the failure of the o-acetoxyphenyl radical to cyclize to a bridged structure. We believe that both of these facts may be explained by examining the steric requirements for acetoxy bridging in these systems.

Although the cyclization of **4** → **5** would appear to be thermodynamically favorable, the inability of the sp^2 orbitals of the aryl radical to become coplanar with the π orbitals of the carbonyl group imposes a large kinetic barrier to cyclization. Radical **4** has the configuration shown in Figure 1 in which the unpaired electron is coplanar with the n orbital on oxygen. If bridging were to occur from the geometry in Figure 1, the unpaired electron would initially reside in a σ^* orbital of the newly formed C–O bond. The importance of coplanarity between the carbonyl π orbital and the orbital containing the unpaired electron has been discussed in connection with the cleavage reaction.[13]

In the case of the o-acetoxybenzoyloxy radical, Figure 2, the greater flexability of the structure renders coplanarity between the radical and the π orbital possible, and it may be this affect which stabilizes this radical toward decarboxylation. It should be emphasized that the rate enhancement due to this latter effect is exceedingly small due to a rather unfavorable entropy. However, the CIDNP signals observed during the decomposition of **6** dramatically illustrate that the rate of decarboxylation of radical **9** relative to that of **12** in the cage is small. Studies such as this, in which pairs of substituted benzoyloxy radicals are generated, may be an additional way to evaluate stabilization of the carboxy radical by a neighboring group.

Experimental Section

Procedure for Obtaining CIDNP Spectra. All ^1H NMR spectra were obtained on a Varian EM-390 NMR spectrometer. Into 0.4 mL of solvent was placed 50 mg of either **6** (0.17 mmol), **7** (0.14 mmol), or **8** (0.13 mmol). The probe of the spectrometer was heated to 150 °C and allowed to equilibrate. The 5-mm tube containing the peroxide was then introduced, and the spectra were recorded.

Carbon-13 CIDNP were obtained by injecting 100 mg of either **6** (0.33 mmol) or **7** (0.28 mmol) dissolved in 1.0 mL of the appropriate solvent into an 8-mm tube in a preheated probe at 150 °C on a Varian CFT-20 spectrometer. Lock was held on the 8-mm tube by 0.5 mL of solvent and a Me_2SO-d_6 capillary. The spectra recorded consisted of one 20 μs pulse which gave satisfactory signal to noise. Fourteen consecutive free induction decays (FID's) were stored on a Sykes Flexible Disc Recorder. The FID's were Fourier transformed at the conclusion of the reaction and the spectra plotted. Each experiment was approximately 2 min in length. The identity of the signals was established by comparison of chemical shifts with those of the authentic compounds.

A product analysis of the reaction mixture obtained from the thermolysis of **6** (0.17 mmol) in cyclohexanone under the conditions of the CIDNP experiment was carried out on a Waters Associates high-pressure liquid chromatograph equipped with a μBONDAPAK C-18 column, using 60/40 CH_3CN–H_2O eluent at a flow rate of 2 mL min^{-1} (except benzoic acid–acetylsalicylic acid separation). Benzoic acid–acetylsalicylic acid separation was accomplished by a 20/80 CH_3CN–H_2O eluent at a flow rate of 1.0 mL min^{-1}. This analysis revealed benzene (0.060 mmol, 35.3%), phenyl acetate (0.033 mmol, 19.4%), phenyl o-acetoxybenzoate (0.004 mmol, 2.4%), benzoic acid (0.008 mmol, 4.7%), and acetylsalicylic acid (0.024 mmol, 14.1%).

Benzoyl o-Acetylsalicyloyl Peroxide (6). Perbenzoic acid[14] (100 mL; 31.4 mmol in chloroform) was placed in an ice–salt cooled 200-mL three-necked flask. o-Acetylsalicyloyl chloride[15] (6.16 g, 3194 mmol) was then added all at once. A solution of 50 mL of methylene chloride and pyridine (2.5 g; 31.4 mmol) was added dropwise over a period of 30 min. The solution was then allowed to mix for 1 h. The reaction mixture was washed with four 50-mL portions of cold 5% sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and the solvent removed on a rotary evaporator at room temperature. The resulting oil was placed in a freezer where it solidified. The peroxide was purified by dissolving crystals in acetone and precipitating at −78 °C. The peroxide was then quickly washed with very cold acetone until it was white: 1.5 g (16%); mp 64–65 °C; NMR ($CDCl_3$) δ 7.2–8.0 (m, 9 H, ArH), 2.3 (s, 3 H, CH_3).

Bis(o-acetylsalicyloyl) Peroxide (7). The symmetric peroxide was prepared according to the procedure of Swern,[16] with the exception that 90% H_2O_2 was employed. The pure peroxide was obtained by precipitating it from $CHCl_3$ with petroleum ether: 7.3 g (51%); mp 89–90 °C; NMR ($CDCl_3$) δ 7.2–8.0 (m, 8 H, ArH), 2.3 (s, 6 H, CH_3). Hydrolysis of the reaction mixture obtained after thermolysis in cyclohexanone under the conditions of the CIDNP experiment was carried out as follows. Aqueous hydrochloric acid (1.0 M) was added, and the mixture was heated for 15 min. Neutralization, followed by ether extraction, followed by high pressure LC analysis failed to reveal any catechol under conditions where a percent yield could be detected.

3-Methyl o-Acetylsalicyloyl Peroxide (8). Preparation was by the Swern method[16] as for **7**: 5 g (41%); mp 120 °C dec; NMR ($CDCl_3$) δ 7.2–7.8 (m, 6 H, ArH), 2.3 (s, 6 H, CH_3), 2.2 (s, 6 H, CH_3). A liquid chromatographic analysis of the reaction mixture obtained from the thermolysis of **8** (0.13 mmol) in cyclohexanone revealed 2-acetoxy-3-methylbenzoic acid (**17**, 70.4%) and o-acetoxytoluene (**15**, 6.1%). A high-temperature decomposition of **8** was carried out by heating parafin to 300 °C in a three-necked flask equipped with an addition funnel, condenser, collection flask, and drying tube. The peroxide (100 mg, 0.28 mmol) in 5 mL of $CHCl_3$ was slowly added. After addition, an extra 2 mL of $CHCl_3$ was added dropwise. The distillate which consisted of volatile products and chloroform was rotary evaporated, and 1 mL of toluene was added. The o-acetoxytoluene (**16**, 9.3%) was determined by gas chromatography on a Varian Aerograph 2700 gas chromatograph equipped with a 5 ft 3% SE 30 on Variport 30,

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100–125 mesh column, operating at 125 °C. No *m*-acetoxytoluene (17) was detected in this analysis.

Kinetics of Peroxide Decompositions. A kinetic study of the rate of decomposition of 7 and that of benzoyl peroxide was carried out, using a modified procedure of Bartlett and Nozaki.[17] Benzoyl peroxide and 5 were weighed out and dissolved in benzene (0.028 M). These solutions were than placed in two 100-mL three-necked flasks equipped with condensers and placed in a constant temperature bath at 79.8 °C. Aliquots (2 mL) were removed at 60-min intervals and placed in a solution containing potassium iodide, water, and isopropyl alcohol. After 10 min, the liberated iodine was treated with 0.1 M thiosulfate.

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Registry No. 6, 71549-44-5; 7, 71549-45-6; 8, 71582-23-5; 11, 134-55-4; 13, 71549-46-7; 16, 533-18-6; 17, 122-46-3; 18, 4386-39-4; benzene, 71-43-2; phenyl acetate, 122-79-2; *m*-chloro-*o*-acetoxytoluene, 6341-98-6; benzoic acid, 65-85-0; acetylsalicylic acid, 50-78-2; perbenzoic acid, 93-59-4; *o*-acetylsalicyloyl chloride, 5538-51-2; chlorobenzene, 108-90-7; *o*-acetoxybiphenyl, 3271-80-5; phenylpentachloropropanone, 71549-47-8; CO_2, 124-38-9; *o*-chlorophenyl acetate, 4525-75-1.

Biotin Model Studies. Coordination of Magnesium(II) Ion to 1-(Methoxycarbonyl)-2-imidazolidinones in Acetonitrile

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Several 1-(methoxycarbonyl)-2-imidazolidinones and their analogues have been synthesized as models for 1-carboxybiotin. In their ^{13}C NMR spectra both carbonyl carbon signals shifted downfield as much as 2–5 ppm in the presence of magnesium(II) ion in acetonitrile. This has been interpreted in terms of the magnesium(II) coordination to the acylurea moiety. Formation of the magnesium(II) complex with (methoxycarbonyl)-2-imidazolidinones in solution was also revealed by IR spectroscopic studies, in which significant low-frequency shifts of carbonyl stretching vibration bands were observed.

Biotin-dependent enzymes mediate a number of carboxylation, transcarboxylation, and decarboxylation reactions in biological systems.[1,2] The first step involved in these reactions is the carboxylation of biotin, usually at the expense of bicarbonate and ATP, and this reaction very likely takes place at the 1-N position of biotin.[3] A very basic question about this process is how the enzymes activate the ureido nitrogen, because it is well-known from model experiments that the nucleophilicity of the ureido nitrogen is extremely low.[4,5] In enzymic systems the reactivity of biotin seems to be enhanced by a proton transfer from a certain functional group(s) of the enzyme to the ureido carbonyl, thereby shifting the keto–enol tautomerism to afford the more nucleophilic imide nitrogen. Indeed, X-ray crystallographic studies on biotin and related compounds have proved that this carbonyl forms a hydrogen bond in crystals.[6-8] This suggests that the ureido carbonyl has a high affinity toward electrophilic reagents such as proton and metal ions even in solution.[9,10] In model studies, alterations in the reactivity of the carboxyl or methoxycarbonyl group attached to 1-N have been observed in the presence of certain divalent metal ions; these are ascribed to the metal chelation to the ureido carbonyl and carboxyl groups.[11,12] But, to the best of our knowledge, metal complex formation has never been proved in an explicit way even in model systems.[9]

We have prepared several 1-(methoxycarbonyl)-2-imidazolidinones bearing a long alkyl chain at the 4-position of the imidazolidinone ring as a model for 1-carboxybiotin in hopes of carrying out a reaction in a micellar phase, where a large rate acceleration is often achieved.[13] Although a possible involvement of the thioether moiety during the biotin catalysis via hydrogen bonding or chelation to a metal(II) ion has been suggested,[14,15] we omitted

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