identical configurations at C_5 and C_8 and accounts for the fact that four of the eight possible diastereomers are observed as major products.[20] We also note a stereochemical preference in the addition of oxygen to free-radical centers at C_5 and C_9; viz., products with vicinal chiral centers having opposite configuration are favored. Thus, **5b** (having opposite configuration at both pairs of vicinal centers, C_4/C_5 and C_8/C_9) is the major isomer formed while **5c**, which has identical configuration at these centers, is the minor product.

Although the formation of peroxide compounds by a mechanism like the one outlined in Scheme II has been proposed in the autoxidation of natural and synthetic polymers,[21,22] no serial cyclization products have been previously characterized.[23] From the present study, we suggest that serial cyclization is an important mechanistic pathway in polyolefin autoxidation, and we anticipate that peroxides containing many consecutive rings could form. While serial cyclization was demonstrated here for 1,5-diene systems, homoconjugated dienes like those present in unsaturated fatty acids and esters would also be capable of serial cyclization.[5] Such cyclization products may thus be important derivatives of lipid natural products, and we are currently investigating this possibility.

Acknowledgment. Crystallographic calculations, performed at the Triangle Universities Computation Center, Research Triangle Park, NC, were supported by a grant of computer time from Duke University. The research was supported by grants from the National Science Foundation and the Army Research Office.

Supplementary Material Available: Tables of atomic positional and thermal parameters, interatomic distances and angles, and lists of observed and calculated structure amplitudes for **5a** and **5b** (31 pages). Ordering information is given on any current masthead page.

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(19) Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484.

(20) We have isolated a less polar minor product that may be the α,α' trans compound. Nevertheless, α,α' cis stereochemistry appears to be dramatically preferred.

(21) Bevilacqua, E. M.; "Thermal Stability of Polymers"; Conley, R. T., Ed.; Marcel Dekker: New York, NY, 1970, p 189.

(22) Mayo, F. R. *Ind. Eng. Chem.* **1960**, *52*, 614.

(23) The evidence presented here does not necessarily contradict that of Gemmer and Golub who indicate that the major products of thermal oxidation of polybutadiene are epoxides and alcohols: Gemmer, R. V.; Golub, M. A. *Polym. Preprints Am. Chem. Soc., Div. Polym. Chem.* **1976**, *17(2)*, 676. Their work was generally carried out at temperatures between 90 and 180 °C where the peroxide products we find at 30 °C would not be expected to survive.

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Absolute Rate Constants for Additions of Phenylchlorocarbene to Alkenes

Sir:

The reactivity of carbenes toward alkenes has been extensively characterized by competition (relative rate) experiments,[1] but very little is known about the absolute kinetics of these reactions. Tyerman reported an activation energy of $\sim$6 kcal/mol for the addition of CF_2 to $CF_2{=}CF_2$ in the gas phase,[2] whereas Nefedov et al. derived $E_a = 11.2$ kcal/mol for CF_2 addition to cyclopentadiene (580–720 °C, gas phase).[3] The competition between intramolecular 1,2-hydride shift and intermolecular addition of F_2CHCF to alkenes (gas phase, 167–350 °C) has been kinetically analyzed. Measured relative Arrhenius parameters and the application of several approximations to the intramolecular reaction afforded $E_a = 11.7$ and 11.9 kcal/mol, respectively, for F_2CHCF additions to propene and *cis*-butene.[4] These activation parameters and requisite rate constants for (singlet) CF_2 and F_2CHCF additions either derive from complicated kinetic analyses or require various approximations in their derivation. The situation is somewhat better for addition reactions of triplet diphenylcarbene and fluorenylidene.

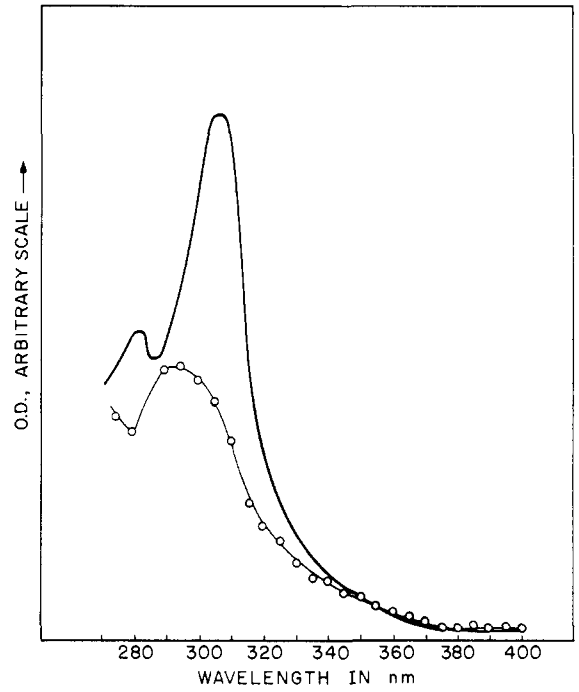

Figure 1. Absorption spectra of phenylchlorocarbene. The solid line is the spectrum recorded at 77 K in 3-methylpentane. The dotted line is the point-by-point (transient) spectrum obtained at 23 °C in isooctane at 5-nm intervals with $\sim$15-nm bandpass.

Analysis of the decay of the Ph_2C triplet ESR signal in solid diphenylethylene ($\sim$90–105 K) gave $E_a = 7.8 \pm 0.3$ kcal/mol for the addition reaction.[5,6] Flash photolysis of diphenyldiazomethane (benzene, 25 °C) in the presence of varying concentrations of butadiene gave $k_2 = 6.5 \times 10^5\ M^{-1}\ s^{-1}$ for the triplet Ph_2C/butadiene cyclopropanation.[6,7] Spectroscopic monitoring of the olefinic quenching of triplet fluorenylidene, generated by flash photolysis of 9-diazofluorene, gave rate constants for the cyclopropanation of various alkenes; e.g., $CH_2{=}CHCN$, 7.1×10^5; *trans*-$NCCH{=}CHCN$, 4.7×10^7 ($M^{-1}\ s^{-1}$).[8] In addition, rate constants for reactions of *singlet* fluorenylidene with alkenes could be obtained, albeit indirectly, by monitoring the yield of triplet fluorene in the presence and absence of quencher and combining these data with the observed rate constant for singlet → triplet crossing. Singlet fluorenylidene is thus reported to be highly reactive and indiscriminate in additions to seven electron-rich or electron-poor alkenes (e.g., $k_2 \sim 3 \times 10^8\ M^{-1}\ s^{-1}$ for $Me_2C{=}CHMe$ or $CH_2{=}CHCN$).[8]

We are pleased to report here the first directly measured absolute rate constants for olefin additions of a selective, singlet

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(1) (a) Moss, R. A. *Carbenes* **1973**, *1*, 153. (b) Moss, R. A.; Jones, M., Jr. *Reactive Intermediates* **1978**, *1*, 69. (c) Moss, R. A. *Acc. Chem. Res.*, **1980**, *13*, 58.

(2) Tyerman, W. J. *Trans. Faraday Soc.* **1969**, *65*, 1188.

(3) Kishina, I. D.; Politanski, S. F.; Shevchuk, V. U.; Gutor, I. M.; Ivashenko, A. A.; Nefedov, O. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1974**, *23*, 946.

(4) Haszeldine, R. N.; Parkinson, C.; Robinson, P. J.; Williams, W. J. *J. Chem. Soc., Perkin Trans. 2* **1979**, 954.

(5) Doetschman, D. C.; Hutchison, C. A., Jr. *J. Chem. Phys.* **1972**, *56*, 3964.

(6) Closs, G. L. *Carbenes* **1975**, *2*, 159.

(7) Closs, G. L.; Rabinow, B. E. *J. Am. Chem. Soc.* **1976**, *98*, 8190.

(8) Zupanic, J. J.; Schuster, G. B. *J. Am. Chem. Soc.* **1980**, *102*, 5958. We thank Professor Schuster for a preprint of this work.

0002-7863/80/1502-7576$01.00/0

Table I. Rate Constants for Addition of Phenylchlorocarbene to Alkenes

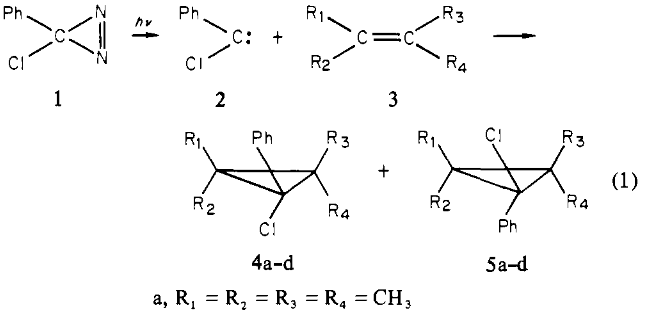
alkene	k_{addn}, $M^{-1}\,s^{-1}$ ^{a,b}	$k_{\text{rel}}^{\text{abs}\ c}$	$k_{\text{rel}}^{\text{comp}\ d}$
tetramethylethylene (3a)	1.3×10^{8} ^{e}	1.0	1.0
trimethylethylene (3b)	7.7×10^{7}	0.59	0.62^{f}
trans-2-pentene (3c)	3.4×10^{6}	0.026	0.028
1-hexene (3d)	1.3×10^{6} ^{e}	0.010	0.011

^{a} These data were determined in isooctane solution at 23 °C. ^{b} Absolute rate constants were determined by laser flash photolysis; errors are ±20% except where indicated. ^{c} Relative rate constants derived from k_{addn}; errors are ~±20%. ^{d} Relative rate constants determined by competition experiments in neat alkenes at 25 °C; errors are <±2%. ^{e} Error is ±10%. ^{f} From ref 12.

carbene in solution at ambient temperature. Laser flash excitation of phenylchlorodiazirine (**1**)[9] in aerated isooctane at room temperature produced a transient absorption whose decay followed second-order kinetics in the time domain 100–10 000 ns after the laser pulse.[10] Measurement of the absorption as a function of wavelength revealed good correspondence ($\lambda_{\max} \sim 295$ nm) with the absorption spectrum obtained upon irradiation of **1** in 3-methylpentane at 77 K ($\lambda_{\max} \sim 308$ nm); see Figure 1. We assign both absorptions to phenylchlorocarbene, **2**.

The intensity of the transient absorption was essentially insensitive to the presence of oxygen, and its decay followed second-order kinetics in oxygen-purged, aerated, or nitrogen-purged isooctane solutions. These results contrast strikingly with the high reactivity toward oxygen of ground-state triplet Ph_2C.[7] Although irradiation of **1** in 3-methylpentane at 77 K produced an intense absorption assignable to **2**, no detectable ESR signal was observed for the sample.[11] The weight of these experiments points to the assignment of singlet **2** as the carrier of the laser-produced transient absorption, a conclusion further supported by the identity of the kinetic parameters derived from absolute and relative rate studies.

We have also generated **2** by conventional photolysis of **1** in olefinic solution, where the carbene proved to be moderately selective and *stereospecific* on addition to simple alkenes.[1a,c,12] Combination of the flash and conventional photolytic experiments provides independently verified, directly measured absolute rate constants for the cycloadditions of singlet phenylchlorocarbene to alkenes (eq 1).



a, $R_1 = R_2 = R_3 = R_4 = CH_3$
b, $R_1 = R_2 = R_3 = CH_3$, $R_4 = H$
c, $R_1 = CH_3$, $R_4 = C_2H_5$, $R_2 = R_3 = H$
d, $R_1 = n\text{-}C_4H_9$, $R_2 = R_3 = R_4 = H$

Laser excitation[10] of **1** in alkene **3a** (25 °C, isooctane solution) afforded the expected product **4a** (=**5a**).[12,13] The transient absorption of **2** (followed at 320 nm) was "quenched" upon addition of alkenes **3a–d**, with transient decay becoming (pseudo) first order in the presence of sufficiently high [alkene]. For each alkene, a good straight line was obtained correlating the pseudo-first-order rate constant for transient decay (τ^{-1}) with [alkene]; see Figure 2. The slope is the quenching rate constant (k_q) for the alkene. From the experimental value of k_q, we computed the absolute bimolecular rate constant, k_{addn} (Table I).

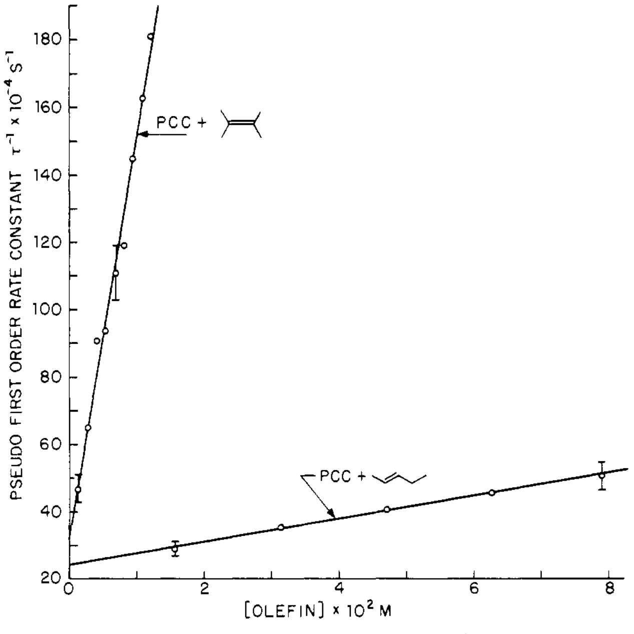


Figure 2. Pseudo-first-order rate constants (τ^{-1}, s^{-1}) vs. [alkenes] for cycloaddition reactions of phenylchlorocarbene (PCC) to alkenes **3a** and **3c**.

The reliability of k_{addn} was independently verified. From the measured absolute rate constants, *relative* rate constants ($k_{\text{rel}}^{\text{abs}}$) are immediately available (Table I). For comparison, analogous relative rate constants were *experimentally* determined in the conventional manner.[1a] Thus, photolysis ($\lambda > 300$ nm) of **1** in alkenes **3a–d** afforded the appropriate cyclopropanes which were purified by recrystallization (**4a**)[12] or distillation (**4b**/**5b**–**4d**/**5d**). New compounds were characterized by NMR spectroscopy and elemental analysis. Generation of **2** in selected binary alkene mixtures, coupled with quantitative high-performance LC analysis (calibrated UV detector) of the product cyclopropanes,[14] and standard competition reaction analysis[1a] gave $k^{3c}/k^{3a} = 0.0276 \pm 0.0005$ (three experiments) and $k^{3d}/k^{3c} = 0.40 \pm 0.01$ (two experiments). These data afford the $k_{\text{rel}}^{\text{comp}}$ values displayed in Table I. The agreement between $k_{\text{rel}}^{\text{abs}}$ and $k_{\text{rel}}^{\text{comp}}$ is extraordinarily good.

In contrast to indiscriminate singlet fluorenylidene,[8] the k_{addn} values of Table I show that phenylchlorocarbene is responsive to the substrate's substitution pattern. Absolute rate constants are significantly lower than the diffusion-controlled limit, and they decrease regularly with decreasing substrate alkylation. An overall rate decrease of about 100-fold is observed upon comparison of tetra- and monosubstituted alkenes. Our ability to directly determine k_{addn} for phenylchlorocarbene with a variety of alkenes opens the way for measurements of activation parameters. This, in turn, should permit us to decide whether carbenic selectivity is determined solely by entropic effects,[15] or whether there are also substantial enthalpic contributions. The necessary experiments are planned.

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(9) Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396.

(10) The laser flash photolysis apparatus employed a Lambda Physik EMG 101 excimer laser as the excitation source (KrF lasing medium, 12-ns pulse, 249 nm, 250 mJ). The transient absorbance was handled with a Tektronix WP2250 system, equipped with a 7912 AD transient digitizer and computer for data processing.

(11) The absorption and ESR spectra of Ph_2C, generated by photolysis of diphenyldiazomethane, were readily observed under comparable experimental conditions.

(12) Moss, R. A.; Whittle, J. R.; Freidenreich, P. *J. Org. Chem.* **1969**, *34*, 2220.

(13) This cyclopropane was identified by high-performance LC and UV comparisons with authentic material.[12]

(14) High-performance LC separations: Waters Radial-Pak column A (reverse phase), solvent CH_3CN (0.7 mL/min), separated adducts **4c**/**5c** (7.02 min) from adducts **4d** and **5d** (7.67 and 8.15 min); Radial-Pak column B (normal phase), solvent 2,2,4-trimethylpentane (1.0 mL/min), separated adducts **4c**/**5c** (16.0 min) from adduct **4a** (18.16 min).

(15) Giese, B.; Meister, J. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 595.

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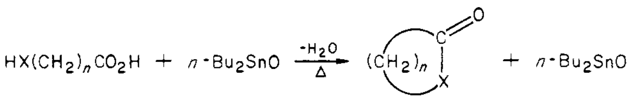
Reagents for Organic Synthesis: Use of Organostannyl Oxides as Catalytic Neutral Esterification Agents in the Preparation of Macrolides[1]

Sir:

Recent landmark achievements in the synthesis of natural products of the macrolide type[2-4] have necessitated the development of mild and efficient methods for ring closure to macrocyclic lactones, lactams, and related systems.[2-4] In several instances, macrolide formation has been the penultimate critical synthetic hurdle in a multistep sequence consisting of a meticulous assembly of functional groups on carbon chains containing multiple centers of chirality. Several techniques have recently been developed that are specifically addressed to this difficult synthetic problem, and these almost universally rely on high dilution and or some form of functional activation through prior derivatization.[4]

We herein report on a synthetically useful new approach toward the preparation of lactones and lactams including several macrocyclic types directly from ω-hydroxy and ω-amino carboxylic acids, respectively, by using catalytic amounts of various organotin oxides under neutral conditions and without resorting to high dilution techniques.[5] Thus, treatment of 15-hydroxypentadecanoic or 16-hydroxyhexadecanoic acid (10 mmol) with n-Bu_2SnO (1 mmol) in refluxing mesitylene (250 mL) for ~20 h by using a Dean-Stark apparatus gave the corresponding lactones in ~60% isolated yield. Diolides were also formed as minor products except for the case of the nine-membered lactone for which no monomer could be isolated. The procedure is also applicable to the formation to lactams in excellent to moderate yields (Table I).[6]

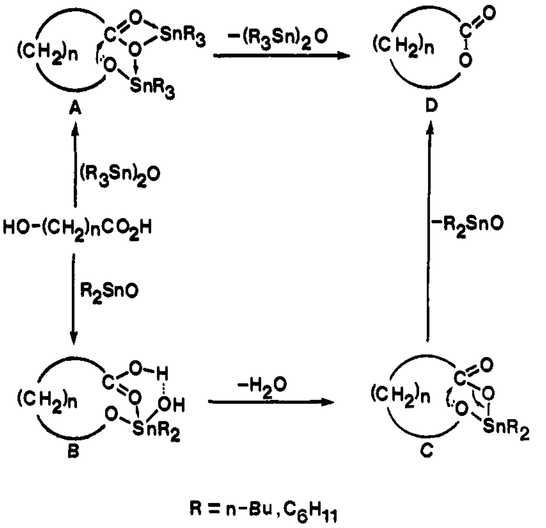
Table I



X	n	solvent[a]	reaction time, (h)	monolide,[b] %	diolide,[b] %
O	7	M	19	0	20
O	14	M	23	63	8
O	15	M	17	60	15
HN	3	X	12	>95	
HN	4	X	12	>95	
HN	5	X	20	>95	
HN	10	M	24	22	
HN	11	M	24	25	

[a] M = mesitylene, X = xylene. [b] Products were identified by comparing IR, MS, VPC, and melting point with commercially available authentic samples. The remaining products constituted polymeric residues which were uncharacterized.

Scheme I



The mechanism by which these reactions proceed is particularly intriguing, since we could find no literature precedence for ester or amide formation with carboxylic acids and alcohols or amines, respectively, using tin oxides. Indeed, the reverse reaction (ester cleavage) by various organotin oxides has been reported.[7a] We have found this type of reaction to be reversible such that the direction of equilibrium (ester formation or cleavage) is heavily dependent upon the nature of the substrate and, more importantly, on the concentration and type of the organotin oxide used. For example, treatment of methyl benzoate with an equivalent amount of $[n\text{-}Bu_3Sn]_2O$ in refluxing xylene gave a mixture of tri-n-butylstannyl benzoate and tri-n-butylstannyl methoxide. On the other hand, similar treatment of benzyl benzoate resulted in approximately 50% cleavage. When benzoic acid and benzyl alcohol were treated with an equivalent amount of $[n\text{-}Bu_3Sn]_2O$, an equal distribution of benzyl benzoate and the stannylated acid and alcohol were achieved, as with the previous reaction. It is important to note that both the acid and the alcohol are each readily stannylated and that an anhydride is not formed under these reaction conditions.[8] However, if benzoic acid and benzyl alcohol are treated with a 10% molar equivalent of $[n\text{-}Bu_3Sn]_2O$ or n-Bu_2SnO, a 90% yield of benzyl benzoate is readily obtained. Similarly benzoic acid and aniline yield benzanilide quantitatively. With lactones such as propiolactone[7b] or hexadecanolide, equimolar amounts of $[n\text{-}Bu_3Sn]_2O$ in refluxing mesitylene readily cause opening of the ring to yield the bis-stannylated hydroxy acid, but

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[1] Presented in part at the 180th National Meeting of the American Chemical Society, Los Vegas, NV, August 1980; "Abstracts of Papers"; American Chemical Society: Washington DC, 1980; ORGN 299.

[2] (a) W. Keller-Schierlein, *Fortschr. Chem. Org. Naturst.*, **30**, 313 (1973); (b) T. Mukaiyama, M. Usui, and K. Saigo, *Chem. Lett.*, 49 (1976).

[3] (a) S. Masamune, G. S. Bates, and J. W. Corcoran, *Angew. Chem., Int. Ed. Engl.*, **16**, 585 (1977); (b) K. C. Nicolaou, *Tetrahedron*, **33**, 683 (1977); (c) T. G. Back, *ibid.*, 3041 (1977).

[4] See for example: (a) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974), and references therein; (b) G. Gerlach, K. Oertle, and A. Thalmann, *Helv. Chim. Acta*, **59**, 755 (1976); (c) S. Masamune, S. Kamata, and W. Schilling, *J. Am. Chem. Soc.*, **97**, 3515 (1975). See also: (d) T. Takahashi, S. Hashiguchi, K. Kasuga, and J. Tsuji, *ibid.*, **100**, 7424 (1978); (e) K. Naraska, K. Maruyama, and T. Mukaiyama, *Chem. Lett.*, 885 (1978); (f) B. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **102**, 4743 (1980), and references cited therein.

[5] The preparation of macrolide type compounds using the coordinative ability of organotin derivatives by a procedure different from ours was published during the course of this study. A. Shanzer and N. Mayer-Shochet, *J. Chem. Soc., Chem. Commun.*, 176 (1980); A. Shanzer and E. Barman, *ibid.*, 259 (1980).

[6] For other recent methods of lactam formation see, for example,: (a) A. Bladē-Font, *Tetrahedron Lett.*, 2443 (1980); (b) R. Pellegata, M. Pinza, and G. Pifferi, *Synthesis*, 614 (1978); (c) L. Birkoffer and J. Schramm, *Justus Liebigs Ann. Chem.*, 2195 (1975).

[7] (a) A. G. Davies, T. N. Mitchell, and W. R. Symes, *J. Chem. Soc. C*, 1311 (1966); (b) K. Itoh, Y. Kato, and Y. Ishii, *J. Org. Chem.*, **34**, 459 (1969); (c) A. G. Davies, D. C. Kleinschmidt, P. R. Palan, and S. C. Vasishtha, *J. Chem. Soc. C*, 3972 (1971).

[8] Refluxing a solution of benzoic or capric acid in mesitylene with or without n-Bu_2SnO by using a Dean-Stark apparatus for several days did not give rise to the formation of any spectroscopically (IR) detectable anhydride.

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