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Ketene Reactions with the Aminoxyl Radical TEMPO: Preparative, Kinetic, and Theoretical Studies

Annette D. Allen, Bernice Cheng, Michael H. Fenwick, Babak Givehchi, Huda Henry-Riyad,
Valerij A. Nikolaev, Elena Aleksadrovna Shikhova, Daryoush Tahmassebi,
Thomas T. Tidwell,* and Silas Wang

Department of Chemistry, University of Toronto, Toronto, Ontario, M5S 3H6 Canada, and Department of Chemistry, St. Petersburg State University, St. Petersburg, 198904, Russia

ttidwell@chem.utoronto.ca

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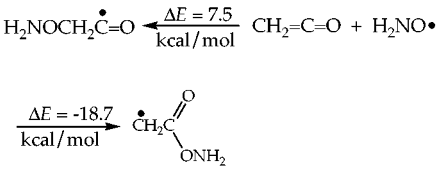
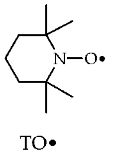
Tetramethylpiperidinyloxy (TEMPO, TO•) reacts with ketenes $RR^1C{=}C{=}O$ generated by either Wolff rearrangement or by dehydrochlorination of acyl chlorides to give products resulting from addition of one TEMPO radical to the carbonyl carbon and a second to the resulting radical. Reactions of phenylvinylketenes **4b** and **4f**, phenylalkynylketene **4c**, and the dienylketene AcOCMe═CHCH═CHCMe═C═O (**11**) occur with allylic or propargylic rearrangement. Even quite reactive ketenes were generated as rather long-lived species by photochemical Wolff rearrangement in isooctane solution, characterized by IR and UV, and used for kinetic studies. The rate constants of TEMPO addition to eight different ketenes have been measured and give a qualitative correlation of $\log k_2(\text{TEMPO}) = 1.10 \log k(H_2O) - 3.79$ with the rate constants for hydration of the same ketenes. Calculations at the B3LYP/6-311G**//B3LYP/6-311G** level are used to elucidate the ring opening of substituted cyclobutenones leading to vinylketenes and of 2,4-cyclohexadienone (**17**) forming 1,3,5-hexatrien-1-one (**18**).

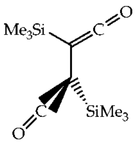
Free radical additions of H•, CH_3•, HO•, F•, Cl•, and SiH_3• to ketene are predicted by molecular orbital calculations to be highly exothermic.[1a] Calculations for the stabilized aminoxyl radical H_2NO• at the B3LYP/6-31G*//B3LYP/6-31G* level indicate that attack at CH_2 is endothermic by 7.5 kcal/mol, while addition to the carbonyl carbon is exothermic by 18.7 kcal/mol (eq 1).[1b] This prediction was tested experimentally using tetramethylpiperidinyloxy (TEMPO, TO•) with diphenylketene (**1**), bisketene **2**, and allenylketene **3**,[1b] and each of these reacted at the carbonyl carbon with one molecule of TEMPO to give a radical which in the case of **1** gave the peroxide $(OCPh_2CO_2T)_2$ on exposure to O_2 (eq 2), and cyclized with expulsion of tetramethylpiperidinyl radical in the case of **2** and **3**.[1b] Further calculations of reactions of Cl[1c] and OH[1d] radicals with ketenes have appeared, and there have been experimental studies of reactions of $(CF_3)_2NO$•,[1e] NO•,[1f] NO_2•,[1f] and NO_3•[1g] with ketenes.



(1)[1b]



TO•



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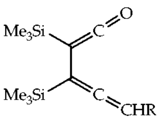


3

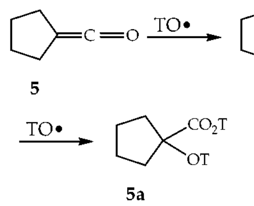
$$\underset{\mathbf{1}}{Ph_2C{=}C{=}O} \xrightarrow{TO\bullet} Ph_2\dot{C}CO_2T \xrightarrow{O_2} Ph_2C(CO_2T)OO\bullet$$

$$\xrightarrow{Ph_2\dot{C}CO_2T} Ph_2C(CO_2T)OOC(CO_2T)Ph_2 \qquad (2)$$

In a preliminary communication[1h] we reported the reaction with TEMPO of ketenes RCH═C═O (**4a**−**c**) and **5** generated from Wolff rearrangements (eq 3, 4), and of **4e** (R = *t*-Bu) and **4h** (R = PhO) formed by dehydrochlorination of acyl chlorides.[1h] In each case facile reaction occurred, and on the basis of the theoretical[1a,b] as well as kinetic and product studies[1h] the reactions were interpreted as proceeding as in the example of eq 4 through initial attack of one TEMPO at the carbonyl carbon forming an α-acyl radical intermediate. The fate of the intermediate radical was either simple reaction with another TEMPO at C_β (eq 3) or addition of TEMPO with allylic or propargylic rearrangement in the case of **4b**,**c**.

$$\underset{\mathbf{6a\text{-}d}}{RCOCHN_2} \xrightarrow{h\nu} \underset{\mathbf{4a\text{-}d}}{RCH{=}C{=}O} \longrightarrow \underset{\mathbf{7a,d}}{RCH(OT)CO_2T} \qquad (3)$$

R = Ph (**a**), *E*-PhCH=CH (**b**), PhC≡C (**c**), *n*-Bu (**d**)



5 **5a** (4)

The adducts of nitroxyl radicals with organic free radicals have attracted considerable attention because

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[1] (a) Sung, K.; Tidwell, T. T. *J. Org. Chem.* **1998**, *63*, 9690−9697. (b) Huang, H.; Henry-Riyad, H.; Tidwell, T. T. *J. Am. Chem. Soc.* **1999**, *121*, 3939−3943. (c) Hou, H.; Wang, B.; Gu, Y. *J. Phys. Chem. A* **2000**, *104*, 320−328. (d) Hou, H.; Wang, B.; Gu, Y. *Phys. Chem.. Phys.* **2000**, *2*, 2329−2334. (e) Banks, R. E.; Haszeldine, R. H.; Murray, M. B. *J. Fluorine Chem.* **1981**, *17*, 561−564. (f) Adam, W.; Bottle, S. E.; Grice, I. D.; Pfeiler, D.; Wentrup, C. *Tetrahedron Lett.* **1996**, *37*, 2113-2116. (g) Seland, J. G.; Noremsaune, I. M. W.; Nielsen, C. J. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 3456−3450. (h) Allen, A. D.; Cheng, B.; Fenwick, M. H.; Huang, W.; Missiha, S.; Tahmassebi, D.; Tidwell, T. T. *Org. Lett.* **1999**, *1*, 693−696.

10.1021/jo0011336 CCC: $20.00

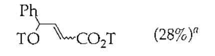
of their potential utility as free radical initiators,[2] and because of the important role of reversible dissociation of these TEMPO adducts in living free radical polymerization.[3] The kinetic measurements of TEMPO reactions with ketenes also revealed an unexpected correlation[1h] of the rate constants for radical additions with rate constants for reaction with H_2O.[4a−c] The current investigation reports full details of our preliminary results[1h] and the extension of these studies of nitroxyl additions to ketenes of other representative types in order to elucidate the scope of this process. We have also made further kinetic studies to test the generality of the previously observed correlation of reactivities and have carried out molecular orbital calculations to elucidate routes to ketene formation.

Results

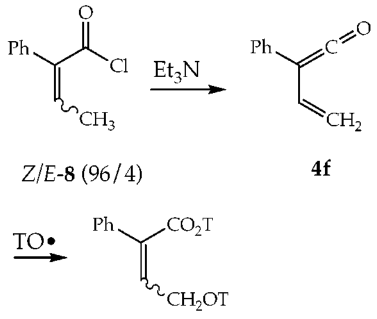
Upon photolysis of diazo ketones **6a**−**d** and diazocyclohexanone (**6e**) in isooctane strong ketenyl IR absorptions of **4a**−**d** and **5** were observed at room temperature using conventional techniques with frequencies in excellent agreement with literature values.[4d,e] These ketenes had previously only been observed by matrix isolation or fast reaction techniques. Addition of TEMPO to these solutions led to formation of the products of attachment of two TEMPO molecules, with rearrangement in the case of **4b** and **4c** (Table 1). Diazoacetophenone (**6a**) and the diazo ketone **6b** were found not to react with TEMPO at room temperature, but upon thermolysis of **6a** and photolysis of **6b** in toluene, the adducts **7a** and *E*/*Z*-**7b** were isolated, as given in Table 1.

Reaction of the acyl chlorides *t*-$BuCH_2COCl$, **8**[5a] (eq 5), and $PhOCH_2COCl$ with Et_3N in the presence of TEMPO in THF at room temperature leads to capture of the ketenes **4e**,**f**,**h**, respectively, by addition of two TEMPO radicals forming **7e**,**f**,**h** (Table 1). Photolysis of cyclobutenone **9a**[5b,c] in the presence of TEMPO gave the product **7g** of 1,2-addition of TEMPO to ketene **4g** (eq 6). The products were characterized by their spectral properties, including HSQC, NOSY, and COSY NMR spectra of **7b** and **7f**. The identities of the *Z*/*E* stereoisomers of **7f** was confirmed by the higher field absorption of the CH_2OT signal in *Z*-**7f**, as found for the corresponding CH_3 in *Z*-**8** and the acid precursor.[5a]

Table 1. Capture of Ketenes by TEMPO (TO•)

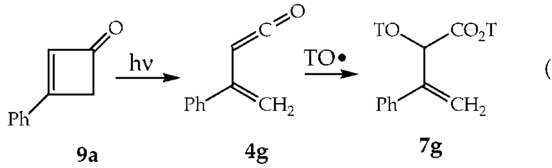
Ketene	Method	Product (yield)
PhCH=C=O **4a**	Wolff	PhCH(OT)CO_2T (45%) **7a**
E-PhCH=CHCH=C=O **4b**	Wolff	 (28%)[a] **7b**
PhC≡CCH=C=O **4c**	Wolff	PhC(OT)=C=CHCO_2T (29%) **7c**
n-BuCH=C=O **4d**	Wolff	*n*-BuCH(OT)CO_2T (76%) **7d**
t-BuCH=C=O **4e**	acyl chloride	*t*-BuCH(OT)CO_2T (16%) **7e**
CH_2=CHCPh=C=O **4f**	acyl chloride	$TOCH_2CH$=CPhCO_2T (44%)[b] **7f**
CH_2=CPhCH=C=O **4g**	cyclobutenone	CH_2=CPhCH(OT)CO_2T (36%) **7g**
PhOCH=C=O **4h**	acyl chloride	PhOCH(OT)CO_2T (58%) **7h**
1-NaphthylCH=C=O **4i**	Wolff	1-NaphthylCH(OT)CO_2T (41%)[c] **7i**

[a] *E*/*Z* 3/1 and 2/1 from Wolff rearrangement and acyl chloride, respectively. Yield given is for Wolff rearrangement. [b] *Z*/*E* 93/7. [c] Reference 1d.



Z/*E*-**8** (96/4) **4f** (5)

Z/*E*-**7f** (93/7)



9a **4g** **7g** (6)

Photolysis of the cyclohexadienone **10**[5e] to form the unobserved dienylketene **11**[5e,11b] in the presence of TEMPO led to the isolation of adduct **12** in 7% yield (eq 7). The stereochemistry shown for **11** is known[5e,11b] to be strongly favored based on the structures of products from capture by nucleophiles. The structure of **12** was established by spectral means, as well as by an X-ray determination. The low yield of product isolated in this case and the reactions below is due in part to the difficulty of removing excess TEMPO by chromatography, as has been noted by others.[2c]

Alkenyl and dienyl ketenes as in eqs 5−7 have long been of interest, especially as the ring opening of 4,4-diphenylcyclobutenone to a ketene followed by thermal cyclization (eq 8) discovered in 1939 (Smith-Hoehn reac-

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[2] (a) Nakamura, T.; Busfield, W. K.; Jenkins, I. D.; Rizzardo, E.; Thang, S. H.; Suyama, S. *J. Org. Chem.* **2000**, *65*, 16−23. (b) Benoit, D.; Chaplinski, V.; Braslau, R.; Hawker, C. J. *J. Am. Chem. Soc.* **1999**, *121*, 3904−3920. (c) Braslau, R.; Burrill, L. C., II.; Siano, M.; Naik, N.; Howden, R. K.; Mahal, L. K. *Macromolecules* **1997**, *30*, 6445−6550. (d) Kothe, T.; Marque, S.; Martschke, R.; Popov, M.; Fischer, H. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1553−1559.

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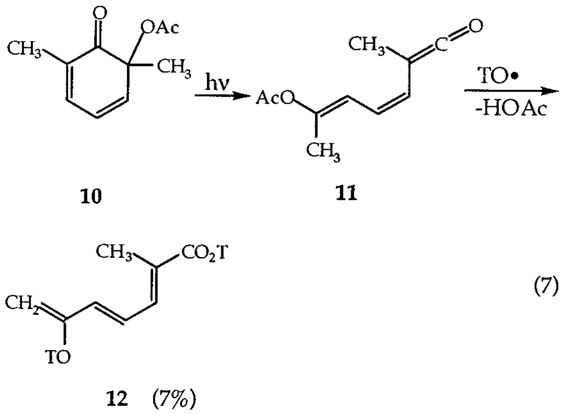
[4] (a) Allen, A. D.; Andraos, J.; Kresge, A. J.; McAllister, M. A.; Tidwell, T. T. *J. Am. Chem. Soc.* **1992**, *114*, 1878−1879. (b) Andraos, J.; Kresge, A. J. *J. Photochem. Photobiol. A: Chem.* **1991**, *57*, 165−173. (c) Andraos, J.; Kresge, A. J. *Can. J. Chem.* **2000**, *78*, 508−515. (d) Wagner, B. D.; Arnold, B. R.; Brown, G. S.; Lusztyk, J. *J. Am. Chem. Soc.* **1998**, *120*, 1827−1834. (e) Schultz, R.; Schweig, A. *Z. Naturforsch.* **1984**, *39B*, 1536−1540.

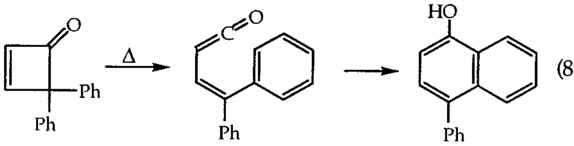
[5] (a) Maccarone, E.; Mamo, A.; Perrini, G.; Torre, M. *J. Heterocycl. Chem.* **1981**, *18*, 395−398. (b) Danheiser, R. L.; Savariar, S.; Cha, D. D. *Org. Synth.* **1989**, *68*, 32−49. (c) Danheiser, R. L.; Savariar, S. *Tetrahedron Lett.* **1987**, *28*, 3299−3302. (d) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959−1964. (e) Waring, A. J.; Morris, M. R.; Islam, M. M. *J. Chem. Soc. C* **1971**, 3274−3280. (f) Burger A.; Ong, H. H. *J. Org. Chem.* **1964**, *29*, 2588−2592.



10 11

12 (7%)

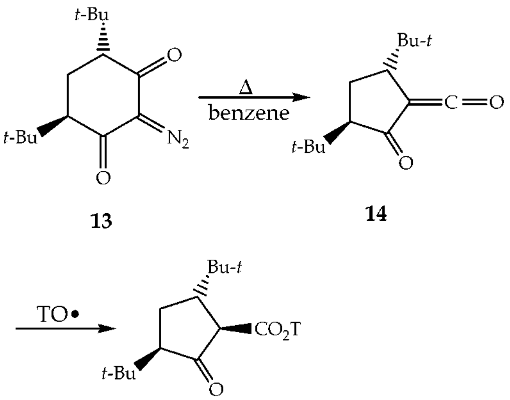
(7)



(8)

tion) has been developed into a useful synthetic reaction.[6] Alkenylketenes have also found application in intermolecular cycloaddition reactions.[7]

Thermolysis of the diazodione *E*-**13** in benzene to generate ketene **14**[8a] in the presence of TEMPO gave a 13% isolated yield of the reduced ester **15** (eq 9). The structure and stereochemistry of **15** were established by comparison of the spectra with those reported for the corresponding methyl ester.[8a] For the proton $CHCO_2R$ the respective values of δ and J are 3.08 and 10.3 Hz for R = CH_3,[8a] and 2.98 and 10.4 Hz for R = T. The stereochemistry of this proton cis to the adjacent *t*-Bu group in the isolated product was proposed previously[8a] to result from isomerization by enolization of an initially formed product with the proton trans.



13 14

15

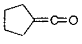
(9)

Rate constants for the reactions with TEMPO at 25 °C of the stable ketenes **1** and **2** and of ketenes **4a**–**d**, **4i** (R = 1-naphthyl),[8b] and **5** generated by Wolff rearrangements were determined by measurements of the rates of disappearance of the ketene absorption in the presence of excess TEMPO. Plots of k_{obs} versus [TEMPO] were linear, and the slopes gave second-order rate constants k_2(TEMPO) as summarized in Table 2. The positive intercepts observed in a few cases are assigned to slow reaction of the ketenes with traces of H_2O, as has been demonstrated in a different case.[8c]

For the understanding of the ring opening of phenylcyclobutenones calculations at the B3LYP/6-31G*//B3LYP/6-31G* level were carried out[9] for the ketenes **4f**,**g** and for the cyclobutenones **9a**,**b** as summarized in Table 3. The cyclobutenone **9b** has been described[5f] as an unstable compound, perhaps indicating instability toward ring opening.

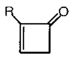
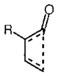
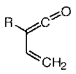
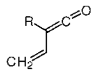
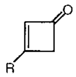
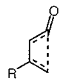
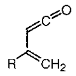
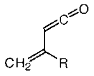
Previous theoretical studies of the ring openings of cyclobutenones have been reported,[10] including studies of the effect of 4-substituents on the stereochemistry of this ring opening.[10b] Comparison between the current B3LYP/6-31G* results and previous results[10c] at the MP2/6-31G*//HF/6-31G* level (Table 3) indicate that for the parent the barrier for ring opening is 2.4 kcal/mol less than B3LYP than for the MP2 level. Similarly the favored anti-conformation of the alkenylketene is 3.3 kcal/mol lower in energy at B3LYP than for the MP2 level. It is expected that the relative differences in energy calculated

Table 2. Rate Constants for Reaction of Ketenes with TEMPO and with H_2O at 25 °C

	k_2 (TEMPO) ($M^{-1}\ s^{-1}$)	$k(H_2O)$ (s^{-1})
$Ph_2C{=}C{=}O$ (**1**)	0.357	275[a]
$(Me_3SiC{=}C{=}O)_2$ **2**	1.50×10^{-4}	0.307[b]
$PhCH{=}C{=}O$ **4a**	1.26	4.77×10^{3}[a]
E–$PhCH{=}CHCH{=}C{=}O$ **4b**	18.4	5.76×10^{3}[c]
$PhC{\equiv}CCH{=}C{=}O$ **4c**	37.2	7.16×10^{4}[c]
n-$BuCH{=}C{=}O$ **4d**	1.22×10^{-3}	99.4[a]
1-(Naphthyl)$CH{=}C{=}O$ **4i**[e]	1.68	2.95×10^{3}[d]
 **5**	2.98×10^{-2}	136[d]

[a] Reference 4b. [b] Reference 1e. [c] Reference 4a. [d] Reference 4c. [e] Reference 8b.

Table 3. Relative Energies (kcal/mol) Calculated for Ring Opening of Cyclobutenones and 2,4-Cyclohexadienone (B3LYP/6-31G*//B3LYP/6-31G)[9]

R				
H	0.0	24.3 (26.7)[a]	-3.7	-5.4 (-2.1)[a]
CH_3	0.0	26.3	2.1	-0.2
SiH_3	0.0	23.5	-5.9	-7.2
F	0.0	28.5	10.1	7.7
Cl	0.0	26.6	5.7	3.9
Ph (**9b**)	0.0	*a*	2.9	3.0
				
CH_3	0.0	25.4	0.6	-1.1
SiH_3	0.0	*b*	-0.9	-2.1
F	0.0	21.1	-2.5	-4.7
Cl	0.0	22.6	-1.0	-2.6
Ph (**9a**)	0.0	*b*	3.1	2.4

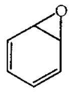
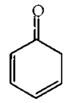
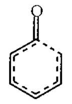
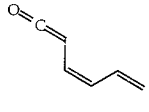
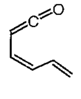
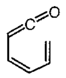
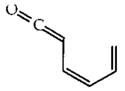
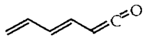
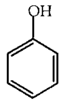
[a] MP2/6-31G*//HF/6-31G*, ref 10c. [b] Not done.

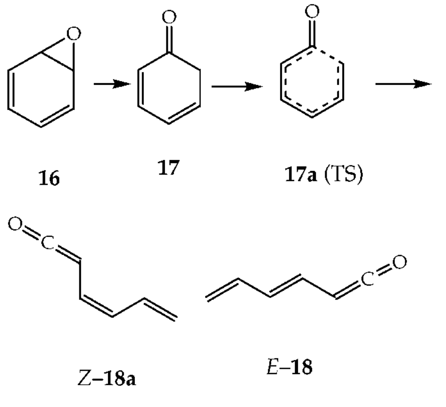
consistently at the B3LYP level (Table 3) provide a reliable comparison of substituent effects on the ring opening.

The photochemical ring opening of cyclohexadienones to dienylketenes (Barton-Quinkert reaction) has been widely studied experimentally[11a−f] and occurs when benzene oxide (**16**) is converted photochemically to the parent 2,4-cyclohexadienone **17** which in turn forms dienylketene **18** upon further photolysis (eq 10).[11e] Recently, structures and relative energies calculated at the B3LYP/6-31G**//B3LYP/6−31//G** level for parent 2,4-cyclohexadienone **17**, and four conformations each of *E*- and *Z*-1,3-butadienylketene **18**, have been reported.[11g] To determine the barrier for interconversion of **17** and **18** we have calculated the energy of the transition structure **17a** as well as those of **16**, **17**, and selected conformations of **18** at the B3LYP/6-311G**//B3LY/6-311G** level (Table 4).[9] Where comparisons are possible these relative energies are in good agreement with those calculated previously.[11g] Details of the calculated structures are given in the Supporting Information.

The calculated pathway for ring opening of **17** forming ketene **18** involves a highly twisted transition state **17a** with a barrier of 27.3 kcal/mol. Four minimum energy conformations *Z*-**18a−d** of the product dienylketene were found (Table 4) of which **18a** is favored, but is 18.2 kcal/mol less stable than **17**, with a 9.1 kcal/mol barrier calculated for ring closure back to **17**. The experimental barrier in solution for ring closure of **11** has been measured as 13.5 kcal/mol,[11b] and the lower barrier calculated for **18** may reflect a steric barrier due to the 6,6-substituents in **11**. Photolysis of **17** leads to generation and direct observation of **18** in matrixes at 77 K,[11e,f] but this rapidly decays at −90 °C.[11e] The photooxidation of benzene and ozone in an argon matrix at 12 K leads to the formation of **18** as observed by IR spectroscopy, and this is proposed to occur by photochemical ring opening of **17**.[11g] Vinylketenes and allenylketenes are known to prefer the anti-periplanar geometry,[12] consistent with the calculated greater stability of **18a**. The less stable conformations *Z*-**18c,d** are both nonplanar, with dihedral angles of the butadienyl moieties of 42° and 35°, respectively. The isomer *E*-**18** is calculated to be 1.4 kcal/mol more stable than *Z*-**18a**, but is not accessible in this reaction.

Table 4. Energies (Hartrees) and Relative Energies (kcal/mol, parentheses) Calculated for Ring Opening of 2,4-Cyclohexadienone (17) (B3LYP/6-31G*+ ZPVE//B3LYP/6-31G)[9] and (in brackets) [B3LYP/6-311G//B3LYP/6-311G**]**

		
16	**17**	**17a** (TS)
-307.29112 (29.1) [-307.37088] [30.8]	-307.33749 (0.0) [-307.42000] [0.0]	-307.28752 (31.4) [-307.37655] [27.3]
		
Z–**18a**	*Z*–**18b**	*Z*–**18c**
-307.30166 (22.5) [-307.39097] [18.2]	-307.29880 (24.3) [-307.38784] [20.2]	-307.29245 (28.3) [-307.38150] [24.2]
		
Z–**18d**	*E*–**18**	
-307.29626 (25.9) [-307.38517] [21.8]	-307.30387 (21.1) [-307.39314] [16.8]	-307.36009 (-14.2) [-307.44759] [-17.3]



(10)

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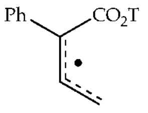
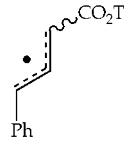
Discussion

Our previous theoretical[1a,b] and experimental[1b,h,8b] studies have established the mechanism of TEMPO reaction with ketenes as involving initial in-plane radical attack on the carbonyl carbon forming acyl-substituted radical intermediates. The large accelerations on the rate of TEMPO attack by radical stabilizing aryl, vinyl, and alkynyl substituents (Table 2) confirm that this first step is rate limiting. Simple acyl-substituted radicals are known to have spin density predominantly on the α-carbon,[1a] and addition of TEMPO to this carbon may occur (eq 4). The alkenylketene **4f** initially forms the allylic radical **19a** which gives a 93/7 preference for the *Z* stereochemistry in the product **7f** of attack at C_γ (eq 5). Alkenylketene *E*-**4b** gives the radical **19b** and TEMPO addition to C_γ forms an *E*/*Z* mixtures of **7b**, and TEMPO addition to **19c** from ketene **4g** occurs at C_α. The position of attack at TEMPO on the allylic radicals **19a**−**c** presumably reflects a combination of steric and electronic factors.

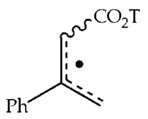
The reaction of the dienylketene **11** (eq 7) with TEMPO is expected to form a dienyl radical **20**, and formation of the observed product **12** could occur by TEMPO addition forming an unobserved unstable acylal **21** which loses acetic acid (eq 11). The favored radical attack at the terminus of the dienyl radical parallels that found for polar additions.[11]



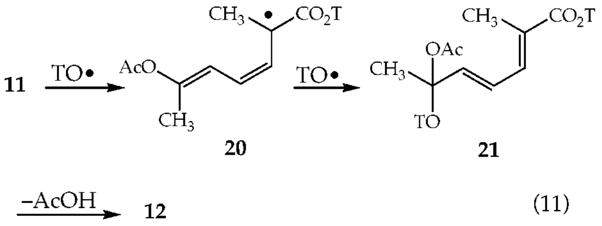
19a



19b

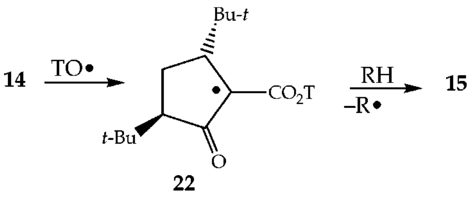


19c



(11)

Addition of TEMPO to acylketene **14** (eq 9) would give a crowded but stabilized diacyl radical **22** that could form **15** by hydrogen abstraction, perhaps by disproportionation with another radical **22** (eq 12). A referee has suggested the possibility that **15** could be formed by addition of the hydroxylamine TOH to **14**. This possibility cannot be excluded, although VPC analysis of the TEMPO used revealed the presence of no detectable impurities.



(12)

$$\log k_2(\text{TEMPO}) = 1.10\,k(\text{H}_2\text{O}) - 3.71 \qquad (13)$$

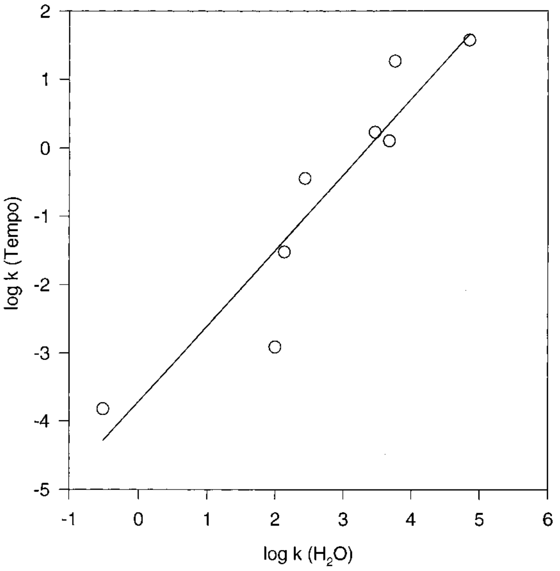


Figure 1. Correlation of rate constants k_2 for ketene reactions with TEMPO with rate constants for hydration.

The second-order rate constants for the reactions of ketenes with TEMPO give the correlation of eq 13 with the rate constants for hydration of the same ketenes (Table 2), as illustrated in Figure 1. A qualitative correlation is observed, $r = 0.93$, and such a correlation between a free radical and a polar reaction is perhaps surprising. However, in both cases in-plane attack by oxygen on the carbonyl carbon of the ketene is involved, and the oxygen of nitroxyl radicals is often considered as being nucleophilic and possessing some negative charge.[13a] The pK_a of TEMPO has been estimated as −5.5 ± 1,[13b] indicating the nitroxyl is about 3 pK_a units less basic than CH_3OH. Steric effects of the bulky tetramethylpiperidinyl moiety may play a role, but this is not apparent from the result. Investigation of structural effects on the reactivity of ketenes with TEMPO and other nitroxyl radicals is continuing in our laboratory.

The calculations of substituent effects on the ring opening of 2-substituted cyclobutenones (Table 3) show that while SiH_3 favors ring opening, relative to H, by 1.8 kcal/mol, that CH_3, F, Cl, and Ph disfavor ketene formation by 5.2, 13.1, 9.3, and 8.4 kcal/mol, respectively. These reflect the effects of substituents on ketene stabilities,[10d,e] and similar trends were found for substituent effects of SiH_3 and F on ring opening of cyclobutenediones.[10c] Differences in the magnitude of the effects between the two systems may reflect substituent effects on the electron-deficient cyclobutendiones.

For ring opening of the 3-substituted cyclobutenones, the alkenylketene is favored for all substituents except for phenyl, but by lesser amounts than for R = H. For both series the anti-conformation of the alkenylketene is favored, as found previously.[10a,d,12] For R = F and Cl the ring-opened forms for the 3-substituted series are predicted to be favored by 12.4 and 6.5 kcal/mol relative to the 2-series. These large net effects may be attributed to destabilization of the 2-substituted ketenes and the 3-substituted cyclobutenones by halogen substituents.

The photochemical ring opening of cyclohexadienones to dienylketenes has been extensively examined and is known to be a facile process, but the product ketene

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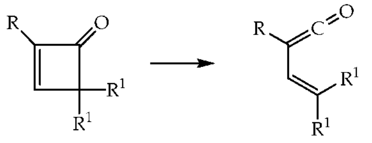
rapidly reverts to the reactant, although it can be trapped with nucleophiles.[11] Even incandescent light is satisfactory for ring opening in some cases.[11d] The ring opening of cyclohexadienone **17** is calculated to be endothermic by 18.5 kcal/mol (Table 4) and is 26.3 kcal/mol less favorable than the comparable process of cyclobutenone, and this can be attributed to the great release of strain in the latter process. The great ease of the endothermic photochemical cyclohexadienone ring opening may be attributed to the enhancement of light absorption by the extended chromophore. The barrier for ring opening of **17** is 27.3 kcal/mol, and this is easily accessible upon photolysis.

Experimentally it has been found for ring-opening of cyclobutenones **23** (eq 14) with $R^1 = Ph$ that rate ratio of 80 °C $(R = H)/(R = CH_3)$ of 8.4,[14] in agreement with the predicted rate-retarding effect of H relative CH_3 of 2.0 kcal/mol (Table 3). For $R = CH_3$ the rate ratio $(R^1 = Ph)/(R^1 = CH_3)$ is 2400,[14] consistent with enhanced stabilization of the forming diphenylvinyl group.



23

(14)

In summary, the reaction of ketenes with the nitroxyl radical TEMPO has been shown to be a facile process that provides a new method for generating acyl substituted radicals, and is also useful for mechanistic investigations. It is also shown that even highly reactive ketenes can be generated and characterized in solution at room temperature using conventional methodology. Theoretical calculations provide useful insights into the factors governing the formation of alkenyl- and dienylketenes by ring-opening reactions. Further applications of these reactions are under investigation.

Experimental Section

Reactions were conducted in dried glassware under an atmosphere of N_2 or Ar. Chromatography was carried out on silica gel. Triethylamine was dried by distillation from CaH_2, and argon was bubbled through dehydrochlorination solutions for 1 h at the beginning of these reactions.

Reaction of Phenylketene (4a) from Wolff Rearrangement with TEMPO. A solution of diazoacetophenone (**6a**, 21.4 mg, 0.15 mmol) and TEMPO (58.6 mg, 0.38 mmol) in 1 mL of toluene was refluxed for 48 h. Chromatography (10% EtOAc/hexanes) gave the bis(TEMPO) adduct **7a** (28.7 mg, 45%) as a white solid which was recrystallized from MeOH/H_2O, mp 90−92 °C; IR ($CDCl_3$) 1772 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.41 (s, 3, CH_3), 0.63 (s, 3), 0.80 (s, 3), 1.02 (s, 3), 1.06 (s, 3), 1.12 (s, 3), 1.24 (s, 3), 1.27 (s, 3), 1.24−1.62 (m, 12), 5.23 (s, 1), 7.20−7.50 (m, 5); ^{13}C NMR ($CDCl_3$) δ 16.84, 17.02, 19.90, 20.09, 20.13, 20.52, 30.73, 31.85, 33.30, 34.07, 39.10, 39.30, 40.22, 59.48, 59.82, 60.30, 60.41, 87.59, 127.47, 127.80, 128.12, 139.32, 170.84; CIMS (isobutane) *m/z* 431 (MH^+, 0.2), 276 (5), 156 (100), 142 (46), 126 (23); EIMS *m/z* 430 (M^+, 0.2), 156 (100).

Generation of *n*-Butylketene (4d) and Trapping with TEMPO. A solution 1-diazo-2-hexanone (**6d**, 165 mg, 1.31 mmol) in 75 mL of pentane was irradiated 10 min with 350 nm light, and then TEMPO (2.89 g, 18.5 mmol) was added at room temperature and the solution stirred 20 h. The pentane was evaporated and excess TEMPO removed by sublimation. The product was chromatographed four times (1% Et_3N in CH_2Cl_2) to give **7d** as an oil (404 mg, 0.99 mmol, 76%): ^1H NMR ($CDCl_3$) δ 0.90 (t, 3, $J = 7.2$ Hz), 1.0−1.8 (m, 40), 1.96 (m, 22), 4.46 (t, 1, $J = 3.2$ Hz). ^{13}C NMR ($CDCl_3$) δ 13.9, 17.0, 17.1, 20.3 20.5, 20.6 20.7, 22.8, 26.6, 32.1, 32.15, 32.2, 33.7, 34.5, 39.2, 39.3, 40.5, 59.6, 59.9, 60.1, 60.6, 83.5, 171.7. IR ($CDCl_3$) 1736 cm^{-1}. EIMS *m/z* 411 (MH^+, 0.05), 254 (17), 156 (28), 140 (100). HREIMS *m/z* calcd for $C_{24}H_{47}N_2O_3$ (MH^+) 411.3587, found 411.3573. Related procedures for the generation and reaction with TEMPO of **4b**,**c**,**e** and **5** are given in the Supporting Information.

Generation of 2-Phenylbuta-1,3-dien-1-one (4f) and Trapping with TEMPO. Acyl chloride **8** (0.55 g, 3.05 mmol, 96/4 *Z*/*E* by ^1H NMR) from the acid[5a] was added dropwise to a solution of Et_3N (0.73 g, 7.2 mmol) and TEMPO (2.4 g, 15 mmol) in 5 mL of dry benzene with 0.73 g of 4A molecular sieves and the mixture was stirred overnight. The solution was filtered and the solvent evaporated, and excess TEMPO was partly removed by sublimation at 50 °C and 30 Torr. The residue was chromatographed on silica gel first with 10/90 EtOAc/benzene and then with 20/80 EtOAc/hexanes to give **7f** (0.62 g, 1.35 mmol, 44%) as a 93/7 *Z*/*E* mixture. *Z*-**7f** ^1H NMR ($CDCl_3$) δ 0.86 (s, 6, $2CH_3$), 1.03 (s, 6, $2CH_3$), 1.05 (s, 6, $2CH_3$), 1.07 (s, 6, $2CH_3$), 1.2−1.7 (m, $12CH_2$), 4.28 (d, 2, $J =$ 6.4 Hz, CH_2OT), 7.04 (t, 1, $J = 6.3$ Hz, CH=C), 7.0−7.2 (m, 5), (COSY spectrum used to confirm assignments). ^{13}C NMR ($CDCl_3$) δ 16.8 (CH_2), 16.9 (CH_2), 19.9 (CH_3), 32.7 (CH_3), 33.5 (CH_3), 38.7 (CH_2), 39.4 (CH_2), 59.6 (C), 60.0 (C), 74.3 (CH_2-OT), 127.4, 127.8, 128.8, 133.9, 135.1, 139.8, 166.7 (HSQC spectrum used to confirm assignments). IR ($CDCl_3$) 1736 cm^{-1}. EIMS *m/z* 456 (MH^+, 0.04), 300 (1), 156 (100). HREIMS *m/z* calcd for $C_{28}H_{45}N_2O_3$ (MH^+) 457.3430, found 457.3446. An ^1H NMR signal assigned to the CH_2OT of *E*-**7f** was observed at δ 4.84 (d, $J = 5.4$ Hz).

Generation of 3-Phenylbuta-1,3-dien-1-one (4g) and Trapping with TEMPO. A solution of phenylcyclobutenone **9a**[5b,c] (23 mg, 0.16 mmol) and TEMPO (68 mg, 0.43 mmol) in 5 mL of $CDCl_3$ was degassed by bubbling in Ar and was then irradiated with 350 nm light 2.5 h at 25 °C. The solvent was evaporated, and the mixture was chromatographed on silica gel first with 1/20 EtOAc/toluene and then with 1/10 EtOAc/hexanes to give **7g** (26 mg, 0.058 mmol, 36%) as a yellow gum. ^1H NMR ($CDCl_3$) δ 0.86 (s, 6), 1.08 (s, 6), 1.10 (s, 6), 1.17 (s, 6), 1.2−1.7 (m, 12), 5.35 (s, 2), 6.04 (s, 1), 7.3−7.5 (m, 5). ^{13}C NMR ($CDCl_3$) δ 16.9, 17.0, 19.9, 20.5, 31.9, 33.0, 39.0, 39.5, 59.5, 59.9, 73.6, 116.5, 127.5, 127.9, 128.5, 139.8, 156.9, 166.0. IR ($CDCl_3$) 1740 cm^{-1}. EIMS *m/z* 457 (MH^+, 0.04), 300 (9), 156 (100). HREIMS *m/z* calcd for $C_{28}H_{45}N_2O_3$ (MH^+) 457.3430, found 457.3417.

Reaction of Phenoxyketene (4h) with TEMPO. A solution of TEMPO (0.84 g, 5.38 mmol), Et_3N (2.15 mmol), and phenoxyacetyl chloride (0.309 g, 1.81 mmol) in 9.0 mL of CH_2Cl_2 was stirred 60 h with 0.86 g of 4A molecular sieves at room temperature. The mixture was filtered through Celite, 10 mL of CH_2Cl_2 and 10 mL of $NaHCO_3$ solution were added, and the layers were separated. The aqueous layer was extracted three times with 10 mL aliquots of CH_2Cl_2, the combined organic layers were dried with $MgSO_4$, and the solvent was evaporated to give a viscous liquid which was chromatographed (7% EtOAc/hexane) and rechromatographed (3% EtOAc/benzene) to give **7h** as a gum (470 mg, 1.054 mmol, 58%); IR (CH_2Cl_2) 1779 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 3), 1.01 (s, 3), 1.07 (s, 3), 1.14 (s, 3), 1.16 (s, 3), 1.23 (s, 3), 1.24 (s, 3,), 1.27 (s, 3), 1.31−1.67 (m, 12, 6), 5.84 (s, 1), 6.96−7.29 (m, 5). ^{13}C NMR ($CDCl_3$) δ 16.71, 16.88, 19.93, 20.24, 20.36, 31.40, 31.51, 32.56, 33.27, 38.94, 38.97, 39.84, 40.12, 59.68, 60.13, 60.16, 61.07, 103.22, 116.89, 121.90, 129.22, 156.55, 166.07. EIMS *m/z* 447 (M^+, 0.5), 290 (12), 140 (100). HREIMS *m/z* calcd $C_{26}H_{43}N_2O_4$ 447.3223, found 447.3203.

Generation of Dienylketene 11 and Reaction with TEMPO. A solution of cyclohexadienone **10**[5e] (0.266 g, 1.48 mmol) and TEMPO (0.44 g, 2.80 mmol) in 30 mL of hexanes in a Pyrex tube was degassed by bubbling argon for 15 min and was then irradiated 4 h with 350 nm light. The product was chromatographed several times with EtOAc/hexanes to

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[14] Mayr, H.; Huisgen, R. *J. Chem. Soc., Chem. Commun.* **1976**, 57−58.

give **12** (0.043 g, 0.10 mmol, 7%), as a white solid, color change to orange brown 120 °C, mp 160 °C ^{1}H NMR (CD_2Cl_2) δ 1.01 (s, 6, 2CH_3), 1.04 (s, 6, 2CH_3), 1.20 (s, 6, 2CH_3), 1.23 (s, 6, 2CH_3), 1.3−1.7 (m, 12, 6CH_2), 2.04 (s, 3, CH_3), 4.36 (s, 1, C═C*H*H), 5.09 (s, 1, C═CH*H*), 6.28 (d, $J = 11$ Hz, C═CH), 6.88 (dd, 1, $J = 11$, 12 Hz), 7.21 (d, 1, $J = 12$ Hz) (assignments confirmed by g COSY and TOCSY). ^{13}C NMR ($CDCl_3$) δ 13.1, 17.0, 20.7, 20.8, 31.9, 32.3, 39.0, 39.7, 60.2, 60.5, 94.8, 122.6, 127.0, 133.6, 137.8, 160.3, 168.1 (assignments confirmed by g HSQC and g HMBC). IR ($CDCl_3$) 1726 cm^{-1}. UV $\lambda_{max}{}^{hexane}$ 302 nm ($\epsilon = 15\,000$). CIMS 433 (MH^+, 10), 157 (TOH^+, 35).

Generation of Acylketene 14 and Reaction with TEMPO. A solution of *trans*-diazodione **13**[8a] (52 mg, 0.21 mmol) and TEMPO (65 mg, 0.42 mmol) in 4 mL of benzene was heated 4 h at 80 °C. The solvent was evaporated and the residue chromatographed with CH_2Cl_2 to give **15** as an oil (11 mg, 0.031, mmol, 15%). ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 9), 1.01 (s, 9), 1.08 (s, 3), 1.10 (s, 3), 1.17 (s, 3), 1.26 (s, 3), 1.4−1.8 (m, 7), 2.09 (ddd, 1, $J = 15.0$, 12.3, 8.4 Hz), 2.28 (dd, 1, $J = 13.8$, 8.4 Hz), 2.52 (ddd, 1, $J = 17.6$, 10.6, 7.0 Hz), 2.98 (d, 1, $J = 10.4$ Hz). ^{13}C NMR ($CDCl_3$) δ 16.5, 20.2, 20.3, 25.2, 27.1, 27.2, 31.3, 31.5, 31.7, 32.0, 39.1, 46.4, 56.8 59.2, 169.4, 210.3. IR ($CDCl_3$) 1757, 1732 cm^{-1}.

Direct Observation of Ketenes Generated by Wolff Rearrangement. Photolysis of 1.0×10^{-4} M diazoacetophenone (**6a**) in isooctane purged with argon with 350 nm light for 5 min resulted in the disappearance of the UV spectrum of **6a** and the formation of a new spectrum due to **4a**, λ_{max} 248.5 nm, and $\epsilon = 1.2 \times 10^4$, assuming complete conversion to **4a**. Similar photolysis of **6a** (8.5×10^{-4} M in isooctane) showed another band at 378.0 nm, $\epsilon = 47$, ascribed to the n → p* transition of **4a**. Photolysis of **6a** (8.5×10^{-4} M in isooctane) for 5 min with 300 and 350 nm light gave complete disappearance of the IR bands of **6a** at 2108 and 1639 cm^{-1}, and formation of a new band at 2117 cm^{-1} for **4a** (lit.[4d] 2118 cm^{-1} in CH_3CN). These absorption bands were fairly long-lived, but upon standing overnight at 5 °C the IR band at 2117 cm^{-1} disappeared and was replaced by one at 1713 cm^{-1}, assigned as due to $PhCH_2CO_2H$ (an authentic sample gave 1716 cm^{-1} in isooctane).

Photolysis of the diazo ketones **6b** and **6c** in isooctane in an IR cell using 300 and 350 nm lamps led to the disappearance of the IR absorptions due to **6b** and **6c** and the growth of absorptions due to **4b** (2116.5 cm^{-1}, lit.[4d] 2116 cm^{-1}) and **4c** (2130.9 cm^{-1}, lit.[4d] 2131.9 cm^{-1}) so that after irradiation for 1 min the absorptions due to **6b** and **6c** had decreased by 90%, and the bands due to **4b** and **4c**, respectively, had grown with equal intensity. Three minutes after ceasing photolysis the band due to **4b** had disappeared.

Photolysis of **6b** and **6c** in isooctane with UV detection led to almost complete disappearance of the absorption due to the diazoketones and the appearance of new strong maxima at 223 and 305 nm for **4b**, and 269 and 284 nm due to **4c**, and bands at 237 and 248 nm attributed to 1-phenylpropyne from **6c**.

Kinetic Measurements. Kinetics of the reaction of the ketenes **4a**−**d** and **4i**[1d] and tetramethyleneketene **5** with TEMPO were measured by injecting 20 μL of (3.6 to 8.5) $\times 10^{-4}$ M of **4a**−**d** and 0.0115 M **5** in isooctane prepared as above into 1.2 mL of a TEMPO solution in isooctane and observing the decrease in absorption at 249 nm (**4a**), 287 nm (**4b**), 267 nm (**4c**), 355 nm (**4d**), 309 nm (**4i**), and 390 nm (**5**). Good first-order plots with stable infinity values were observed, and the derived rate constants are reported in Table 2. In the absence of TEMPO, slow decay of the ketene absorption is observed, and this is attributed to reaction with traces of moisture, as demonstrated previously for a different example.[8c]

The kinetics of **1** were measured by injecting 30 μL of 0.0215 M **1** in isooctane into 2 mL of TEMPO solution in isooctane which had been degassed with a stream of Ar and monitoring the decrease in absorption at 404 nm. For **2**, kinetics were measured by injecting 12 μL of 0.662 M **7** into 1.2 mL of TEMPO solution in mesitylene and measuring the decrease in absorption at 385 nm. All rate constants (Table 2) are averages of at least two runs.

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Supporting Information Available: Experimental details, spectra, calculated structures, and an X-ray crystallographic file of **12** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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