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Amination of Pyridylketenes: Experimental and Computational Studies of Strong Amide Enol Stabilization by the 2-Pyridyl Group

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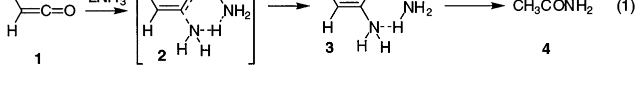
Abstract: Laser flash photolyses of 2-, 3-, and 4-diazoacetylpyridines **8** give the corresponding pyridylketenes **7** formed by Wolff rearrangements, as observed by time-resolved infrared spectroscopy, with ketenyl absorptions at 2127, 2125, and 2128 cm^{-1}, respectively. Photolysis of 2-, 3-, and 4-**8** in CH_3CN containing *n*-$BuNH_2$ results in the formation of two transients in each case, as observed by time-resolved IR and UV spectroscopy. The initial transients are assigned as the ketenes **7**, and this is confirmed by IR measurements of the decay of the ketenyl absorbance. The ketenes then form the amide enols **12**, whose growth and decay are monitored by UV. Similar photolysis of diazoacetophenone leads to phenylketene (**5**), which forms the amide enol **17**. For 3- and 4-pyridylketenes and for phenylketene, the ratios of rate constants for amination of the ketene and for conversion of the amide enol to the amide are 3.1, 7.7, and 22, respectively, while for the 2-isomer the same ratio is 1.8×10^7. The stability of the amide enol from 2-**7** is attributed to a strong intramolecular hydrogen bond to the pyridyl nitrogen, and this is supported by the DFT calculated structures of the intermediates, which indicate this enol amide is stabilized by 12.8 kcal/mol relative to the corresponding amide enol from phenylketene. Calculations of the transition states indicate a 10.9 kcal/mol higher barrier for conversion of the 2-pyridyl amide enol to the amide as compared to that from phenylketene.

Introduction

The structure and reactivity of ketenes are classic problems in organic chemistry,[1−4] and ketene amination reactions have been studied computationally[4a,b] and experimentally.[4c,d] The computations[4a,b] reveal that the reaction of ketene (**1**) with two NH_3 molecules gives a transition structure **2**, which forms an NH_3 complexed amide enol **3**, which tautomerizes to acetamide **4** (eq 1). Experimentally, with reactive ketenes in CH_3CN and measurements by time-resolved IR (TRIR), the kinetics show only a first-order dependence on the amine concentration, indicating that attack of the first amine molecule is rate limiting.[4c] However, further amine molecules are involved, as under these conditions amide enol (or zwitterionic) intermediates corresponding to **3** are directly observed by IR and then are converted to product amides in a reaction also dependent on [amine].[4c]



Amination of the more stabilized ketene $PhMe_2SiCH{=}C{=}O$ follows kinetics[4d] that are dependent on both $[amine]^2$ and $[amine]^3$, indicating that addition of one amine molecule is reversible and that further amine molecules are needed to complete the reaction. Thus, the computational and experimental studies are found to be in harmony.[4]

The rate constant for the reaction of phenylketene **5** with *n*-$BuNH_2$ is greater than that for *t*-butylketene by a factor of 210,[4c] suggestive of polar character in the transition state as shown in **6a** (eq 2), as was also found for hydration of arylketenes, which show a dependence of reactivity on the σ constants of the substituents, with $\rho = 1.2$.[3b] For the reaction

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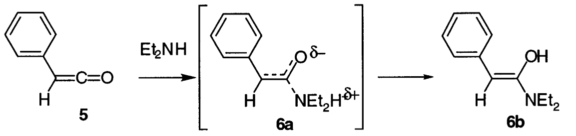
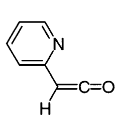
of **5** with Et_2NH, the rate constant for amination exceeds that for tautomerization of the amide enol **6b** to the amide by a factor of 22.[4c] From the experimental evidence, a differentiation between an amide enol structure **6b** and a zwitterionic structure could not be made.[4c] There have been no theoretical studies of nucleophilic additions to arylketenes to **1d** further elucidate the structural factors on the reactivity and the structures of the intermediates.



(2)

Pyridylketenes **7**[5] provide an interesting comparison to phenylketene. The pyridyl ring is strongly electron withdrawing as compared to phenyl; for example, the σ_p values of the 2-, 3-, and 4-pyridyl groups are 0.33, 0.23, and 0.27, respectively,[5e] while the σ_R value for the aza group of pyridine is 0.236.[5f]



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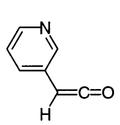

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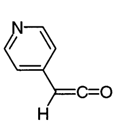
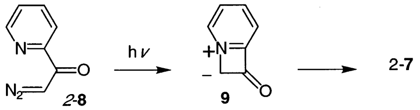


4-7

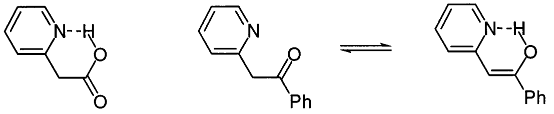
2-Pyridylketene (2-**7**) has been generated by pyrolysis of ethyl 2-pyridyl acetate[5a] and was observed in an argon matrix by IR bands at 2123 and 2132 cm^{-1} for *E* and *Z* conformations, respectively, when formed by the photochemical Wolff rearrangement of diazo ketone 2-**8**.[5b] The zwitterionic species **9** was also formed, as identified by the IR spectrum, and rearranged to 2-**7** (eq 3).[5b] 3-Pyridylketene was formed in a matrix by both Wolff rearrangement and addition of carbon monoxide to the carbene.[5c] Pyridylketenes have also been recently generated and observed as monolayers on platinum surfaces.[5d]



(3)

The study of 2-pyridylketene is of particular interest because of the possibility of direct interaction between the ring nitrogen and the adjacent ketenyl group. The acidity of 2-pyridylacetic acid ($2\text{-}PyCH_2CO_2H$), the hydration product of the ketene, is significantly lower than that for the 3- and 4- isomers, a result attributed to intramolecular hydrogen bonding (Scheme 1).[6a,b] Similarly, (2-pyridyl)acetophenone ($2\text{-}PyCH_2COPh$) exists mainly as the enol in nonpolar solvents (Scheme 1)[6c,d] and has a more than 10^3 greater enol content in H_2O as compared to that of $PhCH_2COPh$.[6e]

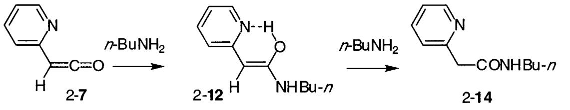
Scheme 1. Hydrogen Bonding in (2-Pyridyl) Acetic Acid and (2-Pyridyl) Acetophenone



Results

For the elucidation of the effect of the 2-pyridyl group on the reactivity of 2-**7**, structures and energies for the addition of NH_3 to phenylketene and 2-pyridylketene were calculated at the B3LYP/6-31G*//B3LYP/6-31G* level using Gaussian 98.[7] These include the reactants, transition structures, and products for the addition of one and two ammonia molecules to the C=O bond, amide enol intermediates, and product arylacetamides. The complete results are given in the Supporting Information, and summary reaction profiles are shown in Figures 1 and 2 for 2-pyridylketene and for phenylketene, respectively. These show two NH_3 molecules, as favored for the gas-phase reaction and for the tautomerization of the amide enols, and for 2-pyridylketene (2-**7**) include an initial complex **10**, transition state **11**, an initial amide enol intermediate **12a**, a more stable amide enol **12b**, a transition state **13**, and the amide **14a**. For phenylketene (**5**), there is a complex **15**, transition state **16**, amide enol **17**, transition state **18**, and amide **19**. Reaction profiles for the addition of single NH_3 molecules, and more detailed profiles showing two additional transition states between **12a** and **12b**, and other transition states and intermediates located along the reaction pathway are given in the Supporting Information (Figures S-1−S-4).

Laser flash photolysis (LFP) of the diazo ketones[8] **8** using a 248 nm output of an excimer laser in CH_3CN with TRIR detection gave the ketenes 2-, 3-, and 4-**7** as identified by their IR bands at 2127, 2115, and 2128 cm^{-1}, respectively. Similar photolysis of 2-, 3-, and 4-**8** in the presence of $n\text{-}BuNH_2$ showed the decay of the transient ketenes which was monitored by IR spectroscopy, and growth and decay of transient amide enols, monitored by UV (eq 4).



(4)

Second-order rate constants obtained from measurements with different [$n\text{-}BuNH_2$] are reported in Table 1. Photolysis of diazoacetophenone has already been shown[4c] to form phenylketene (**5**) under these conditions, with an IR band at 2118 cm^{-1}. We have carried out kinetic measurements on this ketene with *n*-butylamine using UV detection, as is also reported in

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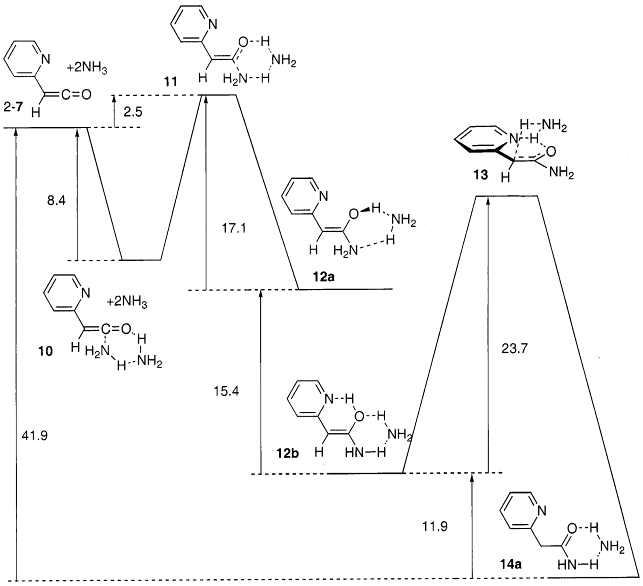

Figure 1. Energy changes in NH_3 addition to 2-pyridylketene (two NH_3 molecules) (B3LYP/6-31G*//B3LYP/6-31G*, kcal/mol).

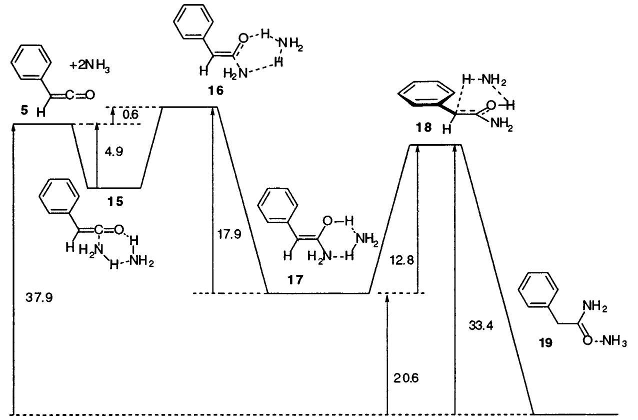

Figure 2. Energy changes in NH_3 addition to phenylketene (two NH_3 molecules) (B3LYP/6-31G*//B3LYP/6-31G*, kcal/mol).

Table 1. Rate Constants for Reactions of Ketenes with n-$BuNH_2$ in CH_3CN at 25 °C

ketene		k_2 ($M^{-1}s^{-1}$)	
		ketene to enol	enol to amide
PhCH=C=O	IR[a]	3.3×10^8	2.0×10^7
	UV	7.0×10^8	2.8×10^7
	ave	(5.2×10^8)	(2.4×10^7)
2-PyCH=C=O	IR	2.1×10^8	
	UV	2.2×10^8	12.5
	ave	(2.2×10^8)	12.5
3-PyCH=C=O	IR	6.8×10^8	
	UV	1.1×10^9	2.2×10^8
	ave	(8.9×10^8)	2.2×10^8
4-PyCH=C=O	IR	1.1×10^9	
	UV	6.3×10^9	6.0×10^8
	ave	(3.7×10^9)	6.0×10^8

[a] Reference 4c.

Table 1. There is reasonable agreement between the IR and the UV data, and between our results and those reported[4c] previously for PhCH=C=O. This agreement, and the diagnostic value of the specific structural information obtained by IR, gives confidence in the reliability of the results.

In the case of 2-pyridylketene, the decay of the second transient, the enol amide, was much slower than its formation, and the data were fit by the rate law $k_{obs} = (10.2 \pm 1.00)[n\text{-BuA}]^2 + (12.5 \pm 2.2)[n\text{-BuA}] - (0.83 \pm 0.97)$ (Figure 3). The linear term 12.5 M^{-1} s^{-1} is the second-order rate constant reported in Table 1 and accounts for 99.9, 93, and 55% of the total reaction at 0.001, 0.1, and 1.0 M [n-$BuNH_2$], respectively. The presence of the higher order term is as expected for the assistance provided by additional amine molecules for this unreactive enol and is consistent with the finding of second- and third-order terms in [amine] found in aminations of unreactive ketenes.[4d]

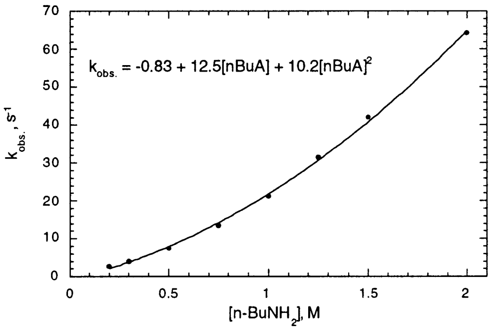

Figure 3. Dependence of k_{obs} on [n-$BuNH_2$] for conversion of the anide enol 2-**12** of 2-pyridylketene to 2-**14**.

Discussion

The calculated reaction profiles for 2-pyridylketene (Figure 1) and for phenylketene (Figure 2) show initial exothermic formation of complexes **10** and **15**, respectively, involving coordination of the two NH_3 molecules on the ketene face opposite the aryl group. Such complexes have been frequently observed for ketenes, both in theoretical studies of reactions with nitrogen nucleophiles[4a,b,9a] and in experimental observations in matrixes of ketene complexes with HCl and HBr.[9b−d]

The complexes from 2-pyridylketene and from phenylketene are converted by transition states **11** and **16**, respectively, that are higher in energy than the separated reactants by only 2.5 and 0.6 kcal/mol, respectively, to form amide enols **12a** and **17**, respectively, with the NH_3 moieties still on the side of the molecule opposite the aryl group. These are 14.6 and 17.3 kcal/mol, respectively, lower in energy than the separated reactants.

The initial amide enol **12a** from pyridylketene is converted by a series of intermediates (see Supporting Information) to an amide enol **12b** with an intramolecular hydrogen bond from the enol hydroxyl to the pyridyl nitrogen that is more stable by 15.4 kcal/mol than the initial amide enol **12a**. The stability of **12b** relative to the reactants is 12.7 kcal/mol greater than the corresponding difference for phenylketene and the amide enol **17**. Conversion of the amide enol **12b** via the transition state **13** occurs with a barrier of 23.7 kcal/mol forming the NH_3 complexed amide **14a**, which is 41.9 kcal/mol more stable than the separated reactants. The transition state **18** leading from the phenylketene derived amide enol **17** is only 12.8 kcal/mol higher in energy than **17**, and this is 10.9 kcal/mol less than the corresponding difference for 2-pyridylketene, which involves

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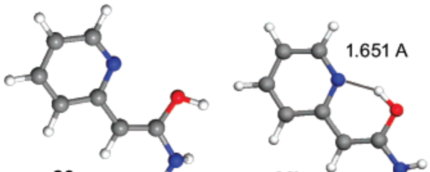

20a **20b**

Figure 4. Calculated structures of amide enols **20a** and **20b**.

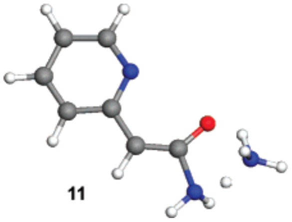

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Figure 5. Calculated transition state (**11**) for NH_3 addition to 2-pyridylketene.

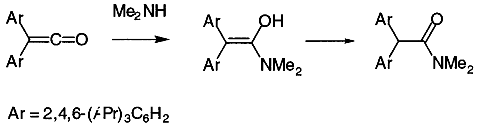
breaking the hydrogen bond from the enolic hydroxyl to the pyridyl nitrogen. The final complexed amide from phenylketene is 37.9 kcal/mol more stable than the separated reactants.

This 10.9 kcal/mol higher barrier for conversion of the amide enol from pyridylketene to the amide is attributed to the strong hydrogen bond formed to the pyridyl nitrogen, as is shown in the calculated structure **20b** (Figure 4). The analogous structure **20a** with the O−H bond pointing away from the ring nitrogen is less stable by 15.4 kcal/mol. The strength of this H-bond is further shown by the short length of 1.651 Å.

4-Pyridylketene is somewhat more reactive than the other three substrates, and this is consistent with the electron-withdrawing power of the pyridyl ring,[5e,f] in which negative charge can be conjugatively delocalized to the nitrogen at the 4-position, and this is expected to enhance the reactivity toward nucleophiles. However, the 2-pyridyl derivative is the least reactive, and this may reflect a repulsion between the carbonyl oxygen and the pyridyl nitrogen in the transition state for amine attack on the least hindered side of the ketenyl group opposite the pyridyl group, as is shown in the calculated structure (Figure 5).

The most striking feature of the rate data (Table 1) is the lower rate constant by factors of 1.8×10^7, 4.8×10^7, and 1.9×10^6, respectively, for the tautomerization to the amide of the amide enol 2-**12** from 2-pyridylketene as compared to those from 3- and 4-pyridylketene and phenylketene, respectively (eq 4). This rate effect is consistent with the 12.8 kcal/mol greater stabilization of the intermediate **12b** from 2-pyridylketene relative to the reactants (Figure 1) as compared to the same difference for the amide enol **17** from phenylketene (Figure 2), and the higher barrier of 10.9 kcal/mol for the conversion of the amide enol **12b** from 2-pyridylketene to the amide **14a** as compared to that for the conversion of the phenylketene amide enol **17** to the amide **19**.

There have been other recent studies of the existence of enols of carboxylic acid derivatives,[10] including the highly crowded amide enol generated by addition of Me_2NH to bis(2,4,6-triisopropylphenyl)ketene (eq 5).[10a] This had a half-life of ca. 20 min in 5/1 CD_3CN/THF-d_8 at 273 K and formed the amide with initial formation of another species which may be a conformationally isomeric amide. Such stabilization of enols provided by bulky aryl groups was discovered by Fuson and co-workers more than 60 years ago[11a] and has been extensively examined in recent years.[11b]



(5)

In contrast to the rate constant ratio of 1.8×10^7 for amide enol formation and tautomerization to the amide found for 2-**7**, those for the 3- and 4-pyridylketenes and for phenylketene are 4.0, 6.2, and 22, respectively. The modestly lower ratios for the 3- and 4-pyridylketenes as compared to phenyl indicate that there is an enhancement of conversion of the enol to the amide by the ring nitrogen. This is also seen in the greater rate constants for tautomerization of the amide enols of the 3- and 4-pyridylketenes as compared to phenyl of 9.2 and 25, respectively. This evidently arises from a greater acidity of the pyridyl enols caused by electron-withdrawal by the ring nitrogen. This effect is noted in the pK_a^{enol} values of 11.27, 8.83, 8.5, and 11.0 of ArCH=C(OH)Ph for Ar = 2-Py, 3-Py, 4-Py, and Ph, respectively.[6e]

Thus, the great stability of the amide enol 2-**12** and its low rate of tautomerization to the amide derive from the strength of the intramolecular hydrogen bond and the high energy of the transition state for breaking this bond and transferring a proton to carbon, respectively. In the absence of hydrogen bonding, the rate of tautomerization of the amide enol 2-**12** would be expected to be enhanced relative to that of the amide enol from phenylketene as was found for the corresponding 3- and 4-pyridyl amide enols, but the reverse is found. Hydrogen bonding from the solvent acetonitrile to the amide enol is not expected to match the strength of this intramolecular hydrogen bond. Intermolecular hydrogen bonds between phenols and acetonitrile, which provide a good model for the amide enol and acetonitrile, have recently been determined to have enthalpies $-\Delta H°$ of 3−5 kcal/mol, or much less than the intramolecular hydrogen bond.[12]

In summary, the amination of 2-pyridylketene 2-**7** is found to lead to a remarkably stable amide enol. This is demonstrated in the calculated amide enol structure **12b**, which is formed from the reactants in a process (Figure 1) 12.8 kcal/mol more favorable than the corresponding conversion to the amide enol from phenylketene (Figure 2), and is converted to the product amide with a barrier that is more by 10.9 kcal/mol. The hydrogen bonded structure **20b** (Figure 4) is also calculated to be 15.4 kcal/mol more stable than the structure **20a** in which the O−H bond points away from the ring nitrogen. In the amide enols from 3- and 4-pyridylketenes, tautomerization to the amide is

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by contrast accelerated relative to the amide enol from phenylketene, a result attributable to the electron withdrawing and acidifying influence of the ring nitrogen.

Experimental Section

Computations. Calculations were carried out at the B3LYP/6-31G*//B3LYP/6-31G* level using Gaussian 98.[7] Transition states and ground-state structures were characterized by the number of imaginary frequencies (NIMAG) as 1 and 0, respectively. Zero-point vibrational energies (ZPVE) were corrected by a factor of 0.9. The calculated energies are given in Tables S-1 and S-2, and the reaction profiles are shown in Figures S-1−S-4. The calculated structures are shown in Figure S-5.

Materials. Diazoketones (**8**) were prepared as previously described.[8]

Time-Resolved Infrared Measurements. These experiments were conducted at the University of Toronto using the apparatus and techniques described previously.[4c] A Lambda Physik Compex 102 excimer laser (XeCl, 308 nm) was used as an excitation source to generate the transients. Solutions of diazo ketone precursors (**8**) in CH_3CN were prepared to have an absorbance of 0.35 at 308 nm with 2.5 mm path length and were passed through a flow cell with CaF_2 windows. For amination reactions, the 0.05−1.00 mM range of [n-BuNH$_2$] was used to obtain the bimolecular quenching rate constants for transient decays of 2-**7**, 3-**7**, and 4-**7** at 2127, 2125, and 2128 cm^{-1}, respectively (see Figures S-6−S-11).

Time-Resolved UV Measurements. Laser flash photolysis (LFP) with UV detection was carried out using a Lambda Physik Compex 120 excimer laser (KrF, 248 nm) in the University of Toronto Department of Chemistry fast reactions laboratory with an apparatus described previously.[10f−h] Measurements were conducted with precursor concentrations in the 5×10^{-6}−2×10^{-5} M range and addition of 0.01−1.00 mM of n-BuNH$_2$ to CH_3CN solutions. For the slow decaying 2-pyridyl transient, 0.2−2.0 M [n-BuNH$_2$] was used, and decay was measured by a conventional flash photolysis (FP) spectrometer also described previously.[10f] Transient signals were monitored at 270 nm for phenyl, 320 nm for 2-pyridyl and 4-pyridyl, and 300 nm for 3-pyridyl species. Typical kinetic traces obtained for amination experiments are shown in Figures S-12−S-16. Both growth and decay of the transient were observed for all three examined systems. Experimental data for phenyl and 3-pyridyl precursors were fitted using a biexponential function. Owing to the large time difference between the growth and decay of the 2-pyridyl transient, a monoexponential function was used to fit both traces (Figures S-15 and S-16). Bimolecular quenching rate constants extracted from data on UV transient growths agree reasonably with TRIR rate constants obtained from ketene decays. This indicates that ketene is a direct precursor for the transient observed by UV and provides strong foundation for assigning this transient to amide enol (**12**). The agreement between previous IR data[4c] and present UV results for phenyl precursor confirms this assignment. In addition, the shape of UV kinetic traces is similar to the results of UV LFP studies of amination of other aromatic ketenes, where the observed transient was attributed to zwitterionic species.[13]

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Supporting Information Available: Experimental and computational details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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