

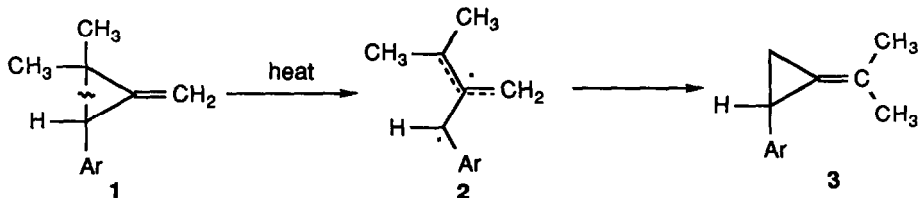
THE PYRIDINE N-OXIDE GROUP. A POTENT RADICAL STABILIZING FUNCTION

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Summary: *The rate of the methylenecyclopropane rearrangement is greatly enhanced by the 4-pyridyl N-oxide group due to spin delocalization in the transition state which imparts nitroxide radical character to the biradical intermediate.*

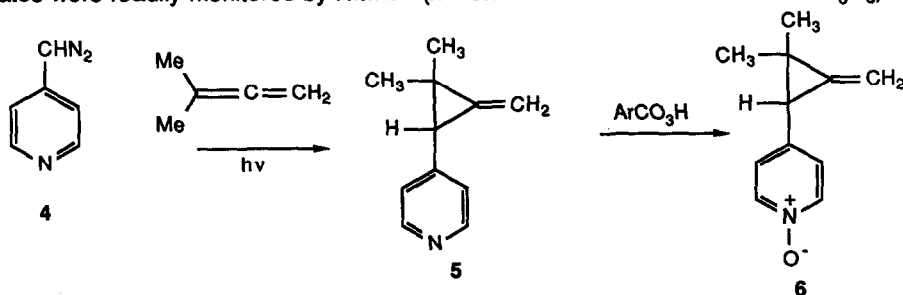
For a number of years we¹ and others²⁻⁸ have been interested in the relative ability of various groups to stabilize free radicals. Towards this end, we have developed the methylenecyclopropane rearrangement probe based on the thermal rearrangement of **1** to **3**. Substituents on an aromatic ring influence rearrangement rates and σ values, which are a measure of stabilizing or destabilizing effects in the intermediate biradical **2**, can be derived from rearrangement rates of **1**. The advantages and disadvantages of this probe have been discussed.^{1b,c}



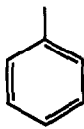
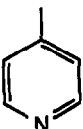
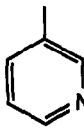
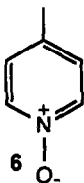
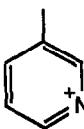
It is known that pyridyl and the related N-oxide systems are cation destabilizing relative to the phenyl analog.⁹ The γ^+ value¹⁰ of the 4-pyridyl group is 1.16 and that of the 4-pyridyl N-oxide group is 0.45. We therefore wanted to evaluate the effect of these heterocyclic systems on stabilities of free radicals. We have now turned our thermal rearrangement probe to an examination of the heterocyclic pyridine analogs of **1**.

The requisite systems were prepared by addition of the carbene derived from 4-pyridyldiazomethane, **4**,¹¹ to 1,1-dimethylallene, which led to the methylenecyclopropane **5**. Oxidation with *m*-chloroperbenzoic acid gave the corresponding N-oxide **6**. The 3-pyridyl systems **7** and the N-oxide **8** were prepared in an analogous fashion starting with 3-pyridyldiazomethane.¹¹ These systems rearranged thermally in clean first order processes to give the isopropylidenecyclopropanes **3** in high yield.

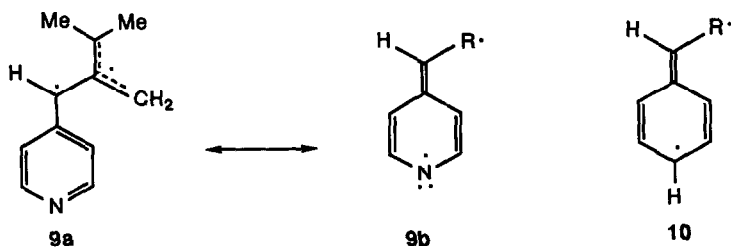
Rates were readily monitored by NMR.¹ ($k = 5.57 \times 10^{-5} \text{ s}^{-1}$ for **1a** at 80 °C in C_6D_6).



Both the 4-pyridyl and the 3-pyridyl systems **5** and **7** rearrange more slowly than the phenyl analog. In the case of the 4-pyridyl analog, this is interpreted in terms of

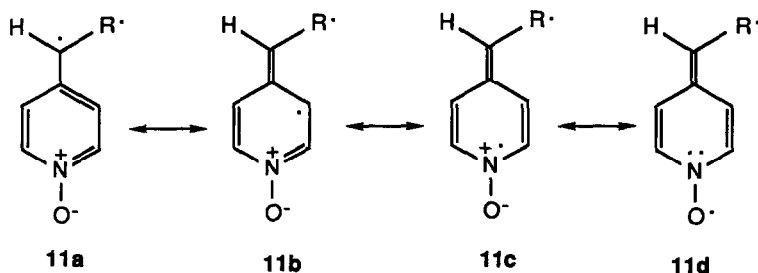
Aryl group in 1					
	1a	5	7	6	8
Relative Rearrangement Rate ($\text{C}_6\text{D}_6/80^\circ\text{C}$)	1.0	0.53	0.79	75	0.51

delocalization in the intermediate biradical. Resonance interactions as in **9b** place spin density on the nitrogen atom. Forms such as **9b** have less importance than delocalized forms **10** with radical character on carbon. This suggestion is based on electronegativity considerations¹² where one would expect lower intrinsic stability of nitrogen centered radicals relative to carbon centered radicals. The destabilizing influence of the 3-pyridyl group, relative to phenyl, is presumably due to the electron withdrawing properties of the non-conjugating nitrogen atom. This destabilizing effect has been seen before and has been discussed in some detail.^{1c} Similar effects probably also contribute to the rate retardation seen in the 4-pyridyl system.



The most striking rearrangement rate is that of the 4-pyridyl N-oxide system **6**. This is the fastest rearranging system studied to date, being 142 times faster than the

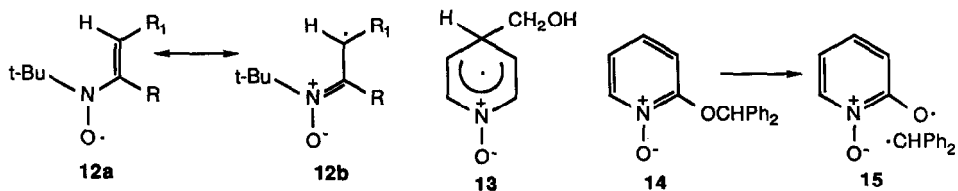
unoxidized 4-pyridyl system **5** and 75 times faster than the phenyl analog. This rate enhancement is considered a truly enormous effect in view of the fact that rate effects in these systems are usually small. For example, the best radical stabilizing substituent that we have previously seen is the p-dimethylamino group which enhances the rate of **1** by a factor of 7.9 relative to p-H.^{1c} We attribute the extraordinarily rapid rearrangement rate of the 4-pyridyl N-oxide system to a potent radical stabilizing effect of the N-oxide function as rationalized by the resonance interactions shown in **11a-d**. Spin density can be placed on nitrogen as in **11c** and further delocalized to oxygen



as in **11d**. This later form is recognizable as a nitroxide radical, a radical of unusually high kinetic (and presumably thermodynamic) stability. Hence the intermediate involved in the thermal rearrangement of **6** has nitroxide radical character and is formed quite readily. In a more quantitative sense, the σ (or preferably γ) value for the 4-pyridyl N-oxide system is 1.88. This value far exceeds those of the p-dimethylaminophenyl, p-vinylphenyl, and p-nitrophenyl groups which are among the best radical stabilizing groups known.^{1c}

Radicals related to **11** have been suggested in the past. Pertinent examples include the vinyl nitroxide radical **12** (where R_1 is CO_2CH_3 or SO_2Ph) which has been generated and studied by ESR techniques.¹³ There is significant spin density on carbon in this radical. The delocalized radical **13** is formed on addition of the hydroxymethyl radical to pyridine N-oxide.¹⁴ INDO calculations show substantial spin density on nitrogen and oxygen in **13**, as well as on the appropriate ring carbons. The radical pair **15** is a proposed intermediate in the thermal rearrangement of **14** to the N-alkoxy-2-pyridone.¹⁵ Such intermediates suggest, and our own studies confirm that the 4-pyridyl N-oxide group is an extraordinary radical stabilizing group.

In contrast to the 4-pyridyl N-oxide group, the 3-pyridyl N-oxide group suppresses the rearrangement rate of **8**. As discussed before,^{1c} this is undoubtedly due to a



powerful inductive effect of the N-oxide function in a non-conjugating position.

In conclusion, the 3 and 4-pyridyl, as well as the 3-pyridyl N-oxide groups are radical destabilizing relative to phenyl. In contrast, the 4-pyridyl N-oxide group is the best radical stabilizing group studied to date. This potent stabilizing effect is attributed to spin delocalization which imparts nitroxide radical character to such intermediates.

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