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Stereoelectronic Effects in the Halogenation of *N*-Alkylnaphthalimides

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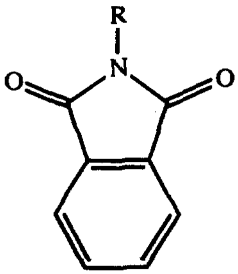
Abstract: The greater rate of bromination of *N*-methylnaphthalimide compared to *N*-ethylnaphthalimide, and the relative ease of chlorination of these compounds, provide convincing evidence of stereoelectronic effects in the free-radical halogenation of *N*-alkylimides.

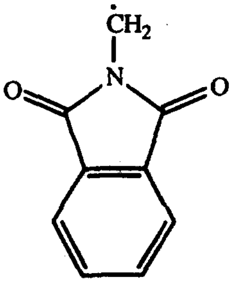
Stereoelectronic effects have been observed in a wide variety of radical reactions[1,2] and interest in this area has continued to increase with the recognition that these effects can be exploited, for example, by using amide-substituted radicals in asymmetric synthesis.[3-5] Recently it was reported[6] that the conformational preferences displayed by alkyl substituents on aromatic systems give rise to stereoelectronic effects in the bromination of alkylaromatics. That disclosure prompts us to report striking examples of stereoelectronic effects in hydrogen atom transfer reactions of *N*-alkyl-1,8-naphthalimides, which also arise from the conformational preferences of alkyl substituents on planar conjugated systems.

Treatment of *N*-methylphthalimide (**1a**)[7] with *N*-bromosuccinimide in carbon tetrachloride at reflux for 4 h, with ultraviolet irradiation to initiate reaction, gave the bromide (**1b**) [^{1}H n.m.r. ($CDCl_3$) δ 5.53 (s, 2H)] in 38% yield.[8] Under identical conditions the reaction of *N*-ethylphthalimide (**1c**) occurred more readily, to give the bromide (**1d**) [^{1}H n.m.r. ($CDCl_3$) δ 2.32 (d, *J* 7 Hz, 3H), 6.41 (q, *J* 7 Hz, 1H)] in 71% yield. This qualitative observation of the greater reactivity of *N*-ethylphthalimide (**1c**) compared with *N*-methylphthalimide (**1a**) was confirmed in competitive experiments. Using mixtures of the phthalimides (**1a**) and (**1c**), with *N*-*tert*-butylbenzamide as an internal standard, the relative rates of consumption of the starting materials (**1a**) and (**1c**), and the relative rates of formation of the products (**1b**) and (**1d**), were each *ca.* 1:4.5, as determined by ^{1}H n.m.r. spectroscopic analysis of crude reaction mixtures. These relative reaction rates reflect the relative ease of formation of the radicals (**2**) and (**3**) and the results are consistent with the expectation that the secondary radical (**3**) should be more stable and form more readily than the primary radical (**2**).

In contrast to the relative rates of reaction of the phthalimides (**1a**) and (**1c**), *N*-methyl-1,8-naphthalimide (**4a**) reacted with *N*-bromosuccinimide to give the bromide (**4b**)



(1)



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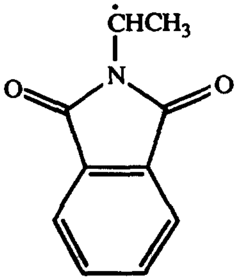
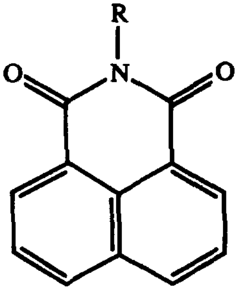
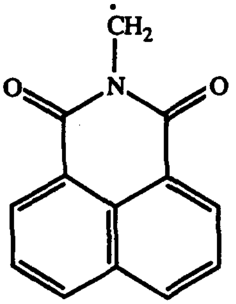


(3)

a) R = CH_3
b) R = CH_2Br
c) R = CH_2CH_3
d) R = $CHBrCH_3$



(4)



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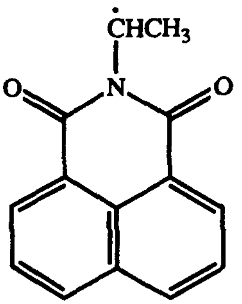

(6)

a) R = CH_3
b) R = CH_2Br
c) R = CH_2CH_3
d) R = CH_2Cl
e) R = $CHClCH_3$
f) R = CH_2CH_2Cl

[^{1}H n.m.r. ($CDCl_3$) δ 5.96 (s, 2H)] in 39% yield after 7.5 h, while the corresponding ethylnaphthalimide (**4c**) was completely inert under identical conditions, and could be recovered in virtually quantitative yield even after extended periods. The anomalously greater reactivity of the methylnaphthalimide (**4a**), which was confirmed using mixtures of the naphthalimides (**4a**) and (**4c**), from which the methylnaphthalimide (**4a**) was consumed while the ethylnaphthalimide remained unchanged, indicates that the primary radical (**5**) is formed more readily than the secondary radical (**6**).

The selective reaction of the methylnaphthalimide (**4a**) can be attributed to a stereoelectronic effect. The preferred conformation of the substrate (**4a**) in the transition state for hydrogen abstraction by bromine atom will be that which is the most stable in the ground state,[9] in which the bond being cleaved is perpendicular to the plane of the naphthalimide ring (Figure 1a). This orientation allows maximum stabilization of the incipient radical (**5**) through interaction with the π system. By contrast, the preferred ground state conformation of the ethylnaphthalimide (**4c**) is that in which the substituent's C-C bond is perpendicular to the plane of the ring (Figure 1b),[9,10] while the stereoelectronically preferred orientations (Figure 1c) will be relatively unstable as a result of steric interactions between the methyl group and the oxygens.

Presumably, the absence of an observable stereoelectronic effect in the reactions of the phthalimides (**1a**) and (**1c**) reflects the relative lack of conformational preference in the phthalimide (**1c**) compared to the naphthalimide (**4c**). Calculations[9] indicate that the energy difference between the ground state (Figure 1b) and stereoelectronically (Figure 1c) preferred conformations of the ethylnaphthalimide (**4c**) is 18.4 $\mathrm{kJmol^{-1}}$, while the corresponding conformations of the ethylphthalimide (**1c**) differ in energy by only 8.8 $\mathrm{kJmol^{-1}}$. In turn, the lower degree of conformational preference of the phthalimide (**1c**) can be attributed to decreased steric interactions

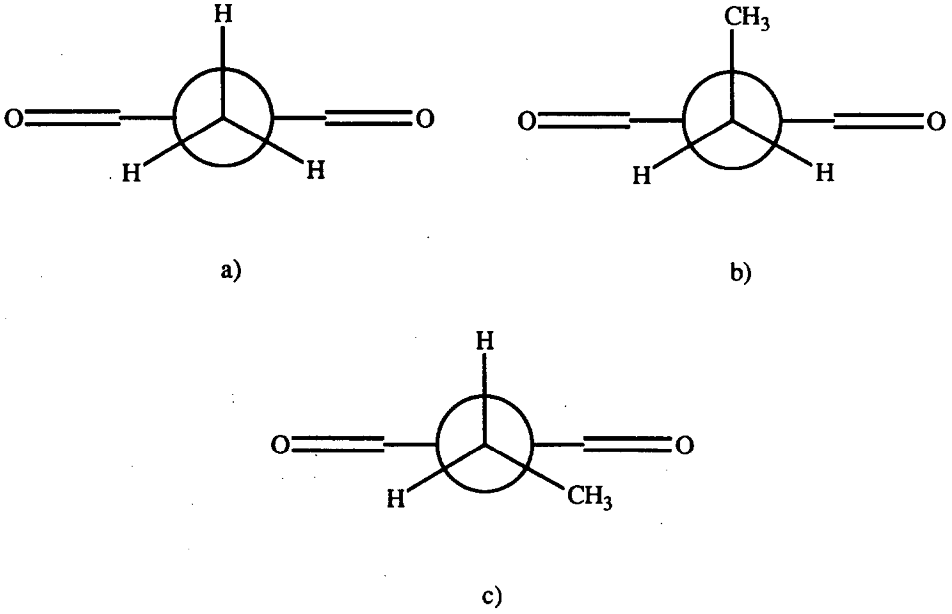

Figure 1. Newman projections along the C(α)-N bond in:
a) the ground state and stereoelectronically preferred conformation of *N*-methylnaphthalimide (**4a**),
b) the ground state preferred conformation of *N*-ethylnaphthalimide (**4c**), and
c) one of the stereoelectronically preferred orientations of *N*-ethylnaphthalimide (**4c**).

between the ethyl substituent and the oxygens, due to their greater separation. In their crystal structures, the average distance between the α-carbon and the oxygens of the ethylnaphthalimide (**4c**) is 2.71 Å,[10] while the comparable average distance in *N*-(2-imidazol-4-ylethyl)phthalimide, a representative phthalimide, is 2.91 Å.[11]

The radical reactions of the naphthalimides (**4a**) and (**4c**) with sulphuryl chloride were also studied. The methylnaphthalimide (**4a**) gave the chloride (**4d**) [^{1}H n.m.r. ($CDCl_3$) δ 5.99 (s, 2H)], while the ethylnaphthalimide afforded an approximately equal mixture of the chlorides (**4e**) [^{1}H n.m.r. ($CDCl_3$) δ 2.21 (d, *J* 7 Hz, 3H), 7.17 (q, *J* 7 Hz, 1H)] and (**4f**) [^{1}H n.m.r. ($CDCl_3$) δ 3.85 (t, *J* 7Hz, 2H), 4.56 (t, *J* 7 Hz, 2H)]. The relative rates of formation of the chlorides (**4d**) and (**4e**) were determined in competitive experiments, using mixtures of the naphthalimides (**4a**) and (**4c**), to be *ca.* 2:1. The slower rate of formation of the chloroethylnaphthalimide (**4e**) compared to the chloromethylnaphthalimide (**4d**) is analogous to, though less marked than, the stereoelectronic effect described above.

In summary, the radical reactions of the naphthalimides (**4a**) and (**4c**) with *N*-bromosuccinimide and sulphuryl chloride provide convincing evidence of stereoelectronic effects in hydrogen atom transfer reactions of these compounds and illustrate the important influence of conformational effects on reactivity in these systems.

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References and Notes

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