# Mechanism of the Boekelheide rearrangement

A reader asked me about the mechanism of the reaction of 2-picoline N-oxide with acetic anhydride to give 2-acetoxymethylpyridine (the Boekelheide Rearrangement[1]). He wrote " I don't understand why the system should prefer to go *via* fragmentation-recombination (… the evidence being that oxygen labelling shows scrambling) when there is an easy concerted pathway available (… a [3,3]sigmatropic shift). Furthermore, is it possible for two pathways to co-exist?" Here is how computation might enlighten us.
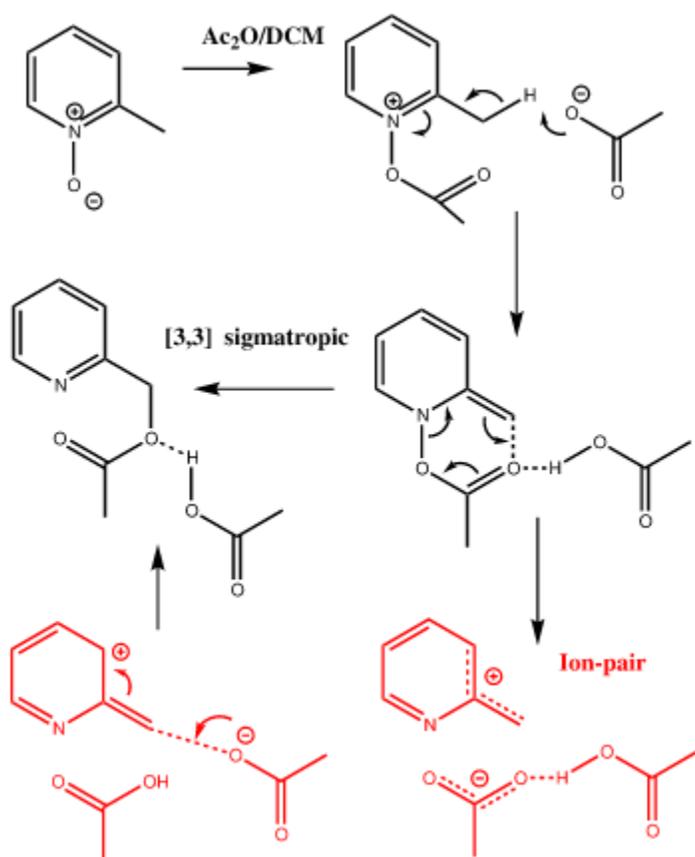

The first model I built discards the apparently extraneous product in the first reaction, ethanoic acid. A transition state is located (ωB97XD/6-311G(d,p)/SCRF=dichloromethane) and its intrinsic reaction coordinate is shown below.[2]
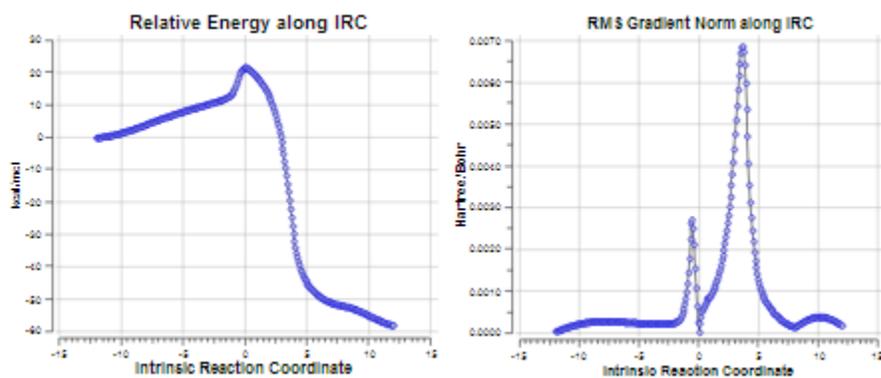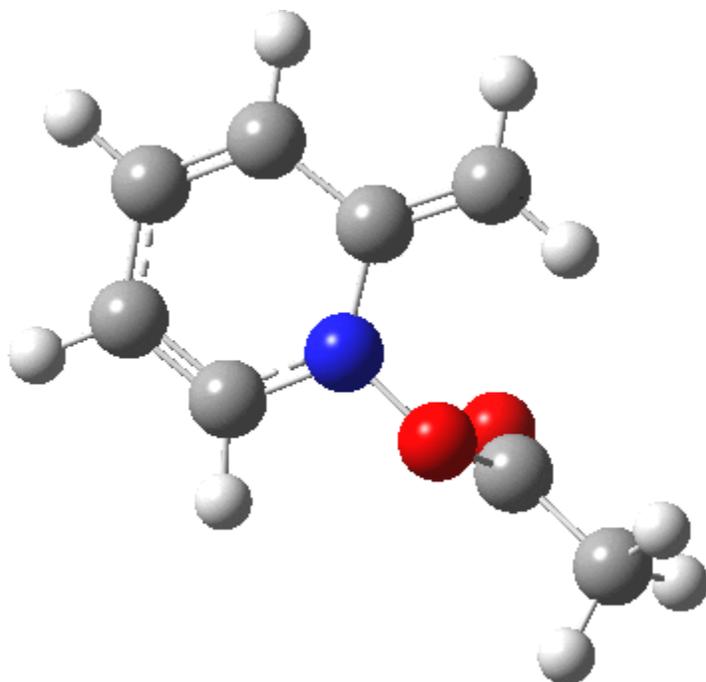
1. One first notes that the reaction is concerted, with no intermediates along the route.

2. The reaction barrier (~21 kcal/mol) is quite reasonable for a [3,3] sigmatropic reaction.

3. There is an almost undiscernible blip (inflexion) in the gradient norm at about +1 and a more obvious one at IRC +8. The latter is a *hidden intermediate* corresponding to a conformational rotation about the newly formed C-O bond. The former is more significant, since it is providing the

faintest of hints that a *hidden intermediate*[3] corresponding to an ion-pair (in red in the scheme above) might be attempting to form. But it is only a hint, no more.

So an easy concerted pathway is indeed available. But the solvent model (dichloromethane) is not really very polar. How about water, which should better stabilise any ion-pair intermediate? That tiny blip in the gradient norm of the IRC (@~1) becomes a bit more prominent, but the reaction is computed as resolutely concerted.
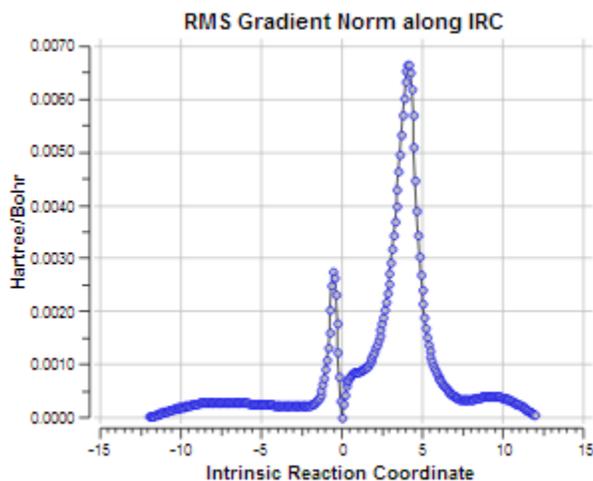
So to explain why oxygen label scrambling is possible, we have to adopt a better model. That ethanoic acid discarded from our first attempt is re-instated. It serves the purpose of potentially stabilising any ion-pair which might form *via* explicit hydrogen bonds.[4]

Click for 3D.
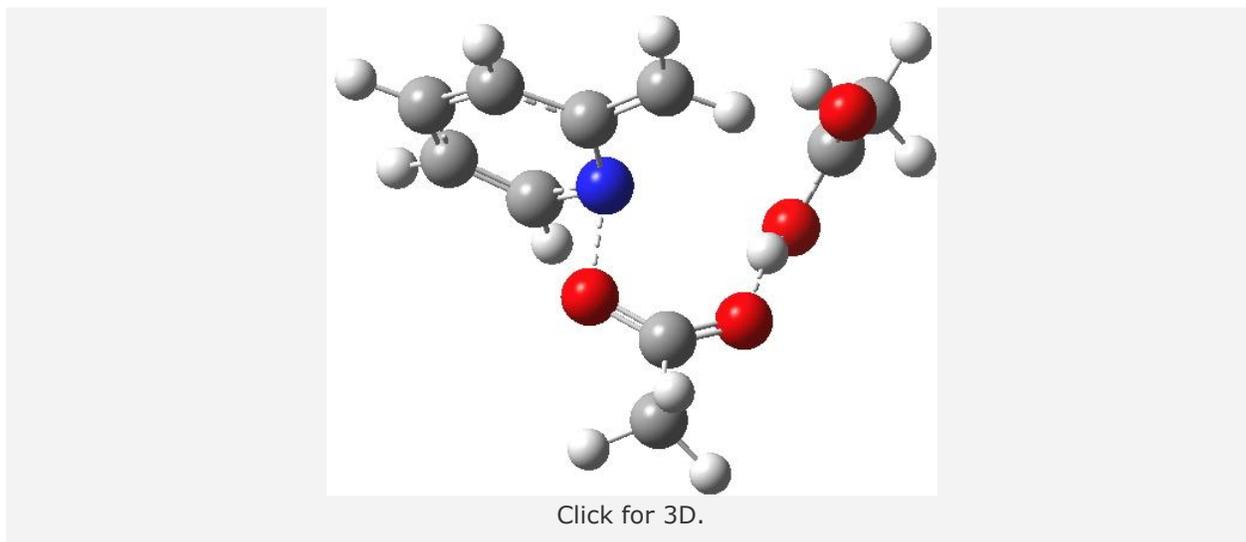
The IRC[5] for this variation does indeed show a change; at IRC +3, there is now a very prominent *hidden intermediate* feature, showing that the additional molecule of ethanoic acid formed in the first step is stabilizing the ion-pair. It also serves to reduce the barrier to the reaction (by ~4 kcal/mol).[‡]
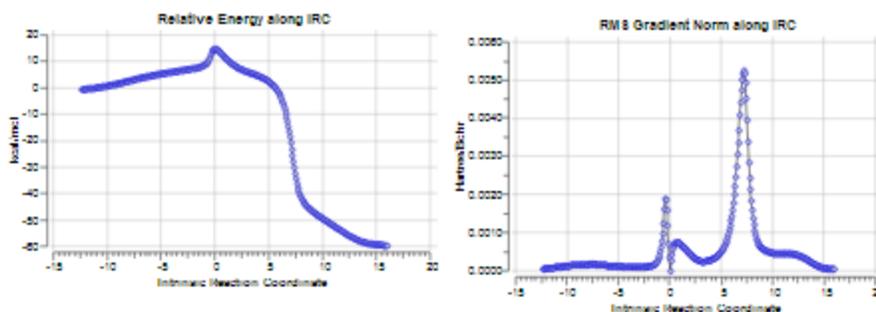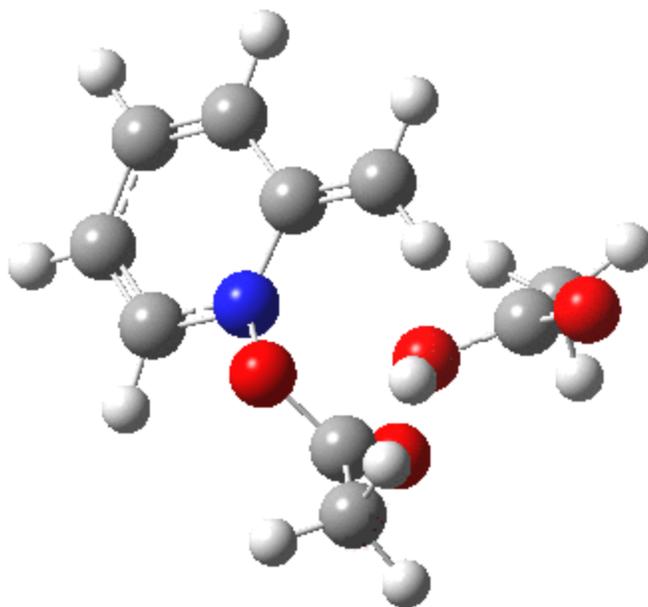
Although the Boekelheide rearrangement sounds like a rather obscure reaction that few have heard of, discussing it actually introduces an important concept common to many reactions. That is that they can proceed *via* either relatively neutral or highly ionic pathways, and that the balance between these two may be both subtle and influenced by external factors. In this case, the formation of a hydrogen bond stabilising the transition state for the reaction. This of course is also how many an enzyme achieves its action! For the Boekelheide rearrangement, a single hydrogen bonded ethanoic acid promotes, but does not fully establish the ion-pair mechanism over the neutral [3,3] pericyclic rearrangement. However, one might imagine that adding perhaps a second explicit stabilising H-bond might swing the balance over from merely a hidden intermediate to a real (ion-pair) intermediate. It is also possible that changing the acidity of this component (by replacing *e.g.* CH_3CO_2H by e.g. CF_3CO_2H) might achieve the same result.

As to whether "it is possible for two pathways to co-exist", a nice example of this in my experience comes from the enantiomerisation of isobornyl chloride in cresol,[6] which has been shown by extensive isotope labelling to proceed by two concurrent but very different pathways. It is probably more common than we realise.

‡ It is worth noting that the [3,3] sigmatropic reaction is unimolecular, whereas the ethanoic-assisted variation is bimolecular. Apart from taking into account the entropic requirements of the latter, it is also necessary to redefine the standard state for the free energy from 1 atm to a more reasonable 1M, which reduces the free energy barrier by about 1.9 kcal/mol, and a correction which reduces the free energy of a bimolecular reaction a further 2.6 kcal/mol can be applied as a solvent correction.[7]. These two corrections mean that bimolecular solution reactions are often not so unfavourable compared to unimolecular equivalents as is often made out.

References

1. A. Massaro, A. Mordini, A. Mingardi, J. Klein, and D. Andreotti, "A New Sequential Intramolecular Cyclization Based on the Boekelheide Rearrangement", *European Journal of Organic Chemistry*, vol. 2011, pp. 271-279, 2011.http://dx.doi.org/10.1002/ejoc.201000936

2. Henry S. Rzepa., "Gaussian Job Archive for C8H9NO2", 2013.http://dx.doi.org/10.6084/m9.figshare.730627

3. E. Kraka, and D. Cremer, "Computational Analysis of the Mechanism of Chemical Reactions in Terms of Reaction Phases: Hidden Intermediates and Hidden Transition States", *Acc. Chem. Res.*, vol. 43, pp. 591-601, 2010.http://dx.doi.org/10.1021/ar900013p

4. Henry S. Rzepa., "Gaussian Job Archive for C10H13NO4", 2013.http://dx.doi.org/10.6084/m9.figshare.730621

5. Henry S. Rzepa., "Gaussian Job Archive for C10H13NO4", 2013.http://dx.doi.org/10.6084/m9.figshare.731688

6. J. Kong, P.V.R. Schleyer, and H.S. Rzepa, "Successful Computational Modeling of Isobornyl Chloride Ion-Pair Mechanisms", *J. Org. Chem.*, vol. 75, pp. 5164-5169, 2010.http://dx.doi.org/10.1021/jo100920e

7. J.R. Alvarez-Idaboy, L. Reyes, and J. Cruz, "A New Specific Mechanism for the Acid Catalysis of the Addition Step in the Baeyer−Villiger Rearrangement", *Organic Letters*, vol. 8, pp. 1763-1765, 2006. http://dx.doi.org/10.1021/ol060261z

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