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Using Symmetry to Monitor Geared Bond Rotation in Aromatic Amides by Dynamic NMR

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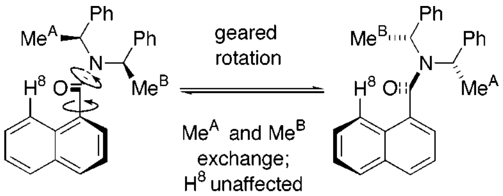
ABSTRACT

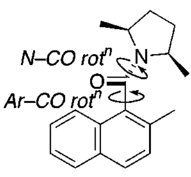


Dynamic NMR proves that the fastest interconversion between conformers of simple tertiary aromatic amide 3 is racemization via a geared (correlated) rotation of both the Ar–CO and N–CO bonds. The symmetry of 3 is such that correlated and noncorrelated rotations are easily distinguishable, even without assignment of the NMR spectrum, simply by observing the number of peaks taking part in the exchange.

Molecular gearing in compounds such as trypticenes was studied intensively by Mislow,[1] Oki,[2] and others,[3] and many examples of “geared rotation”—the correlated motion of two rotating bonds—are known. We have shown that the atropisomeric diastereoisomers of structure **1**, while much simpler than the trypticenes, demonstrate geared rotation, albeit with a significant amount of “gear slippage”.[4] In that study, as in some other similar ones,[5] it was necessary to separate stereoisomers, assign their stereochemistry, measure their rates of interconversion, and use numerical methods to analyze the kinetics.

For some time, we have suspected that simpler, non-atropisomeric aromatic amides undergo an analogous geared bond rotation,[6] because the rates of Ar−CO and C−N rotation in such amides as **2** appear to be very similar.[7] However, the rates involved are too fast for separation of conformers ($k \approx 1$ s^{-1} at 20 °C), and the use of dynamic NMR to study **2** in detail is compromised by the identity of the interconverting conformers and by the difficulties encountered in reliably assigning pairs of diastereotopic signals.

In this paper, therefore, we present the amide **3**, whose symmetry displays features carefully chosen to allow simple and unambiguous identification of geared processes, and whose conformers interconvert at a rate much faster than those of the more hindered **1**, allowing the use of experimentally simple dynamic NMR techniques. We present the



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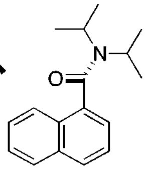

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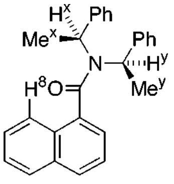

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[1] Iwamura, H.; Mislow, K. *Acc. Chem. Res.* **1988**, *21*, 175.

[2] Oki, M. *The Chemistry of Rotational Isomers*; Springer-Verlag: Berlin, 1993.

[3] For recent examples and leading references, see: Fuji, K.; Oka, T.; Kawabata, T.; Kinoshita, T. *Tetrahedron Lett.* **1998**, *39*, 1373. Stevens, A. M.; Richards, C. J. *Tetrahedron Lett.* **1997**, *38*, 7805. Azumaya, I.; Yamaguchi, K.; Okamoto, I.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 9083.

[4] Clayden, J.; Pink, J. H. *Angew. Chem., Int. Ed.* **1998**, *37*, 1937.

[5] Kuttenberger, M.; Frieser, M.; Hofweber, M.; Mannschreck, A. *Tetrahedron: Asymmetry* **1998**, *9*, 3629.

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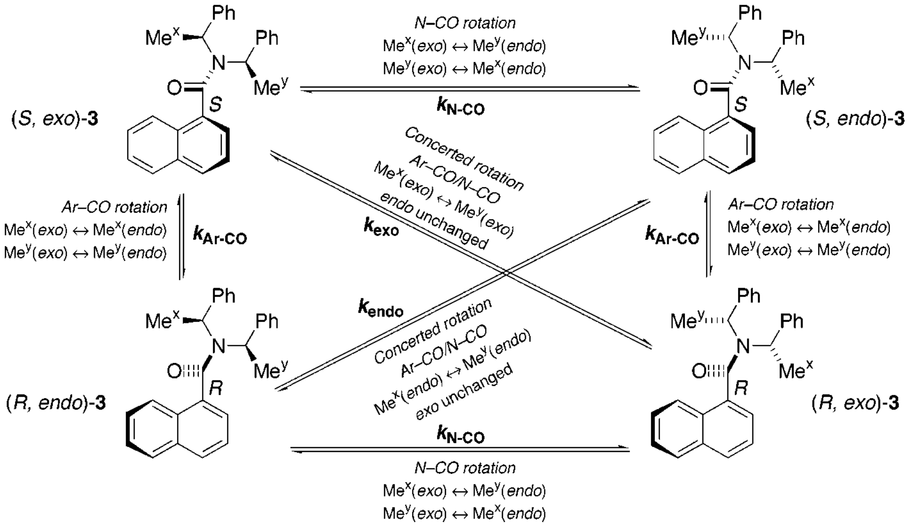

Figure 1. Rotational processes in **3**.

reasoning behind the choice of **3** as a test of correlated rotation, and we describe the results of dynamic NMR experiments on **3**.[8]

The symmetry of **3** means that (ignoring the internal rotation of the N-substituents, which is fast[9]) it can exist as only two diastereoisomeric conformers (*exo*)-**3** and (*endo*)-**3**, each of which is chiral and occurs as of a pair of enantiomeric conformers, as shown in Figure 1. We expect[7] *exo*-**3** and *endo*-**3** to interconvert slowly enough to give rise to a separate set of signals in the ambient temperature NMR spectrum, and indeed the NMR of **3** at 25 °C in DMSO-d_6 shows a 67:33 ratio of two diastereoisomeric conformers.[10]

Figure 1 also shows the three rotational processes which interconvert the conformers of **3**, along with the interconversions among the signals in their NMR spectra that would result from these three processes. *Either* Ar−CO rotation *or* C−N rotation interconverts the two diastereoisomeric conformers *exo*-**3** and *endo*-**3**. These two rotational processes therefore lead to exchange of *every peak* in the NMR spectrum of one conformer with its counterpart in the other.

There are two possible concerted Ar−CO/C−N rotations, and each of these, on the other hand, simply interconverts the enantiomeric conformers of one diastereoisomeric conformer: a concerted Ar−CO/C−N rotation is the only possible process which does not involve *both exo*-**3** *and endo*-**3**. In the NMR spectrum, therefore, a concerted rotation will exchange only some of the signals: it will affect only one of the two sets of diastereoisomeric signals, and it can have no effect on signals assigned to groups whose environment is unchanged by the rotation, i.e., those of the naphthalene ring.

Amide **3**, like any other amide of its symmetry, therefore constitutes a watertight test for correlated rotation: if dynamic NMR shows an exchange process which can be proved not to involve all of the signals in the NMR spectrum, then it must be a geared Ar−CO/C−N rotation.[11]

Practically, it will be necessary to ensure that apparent lack of an exchange process (indicated by broadening and coalescence in the dynamic NMR experiments) is not due to either a very large or very small separation between pairs of exchanging signals: a greater chemical shift difference raises the temperature of coalescence of two peaks.[12] In the former case a peak could remain sharp because it is already at the fast exchange limit; in the latter a peak could remain sharp because it does not leave the slow exchange limit at an accessible temperature.

Figure 2 shows portions corresponding to H,[8] H^x, and H^y and Me^x and Me^y of the NMR spectrum of **3** in DMSO-d_6 at temperatures from 23 to 60 °C. At 23 and 30 °C it is clear that some of the signals (quartets C and E, doublets G and J) are already undergoing exchange, as they are somewhat broadened, and their broadening increases as the temperature rises.

The important point is that only *some* of the signals are broadened. At 40 °C the situation is even more marked: A,

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(6) Others have also suggested geared rotation in aromatic amides and thioamides: see ref 5 and Pirkle, W. H.; Welch, C. J.; Zych, A. J. *J. Chromatogr.* **1993**, *648*, 101.

(7) Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.

(8) Amide **3** was made by a diastereoselective alkylation. See: Bragg, R. A.; Clayden, J. *Tetrahedron Lett.* **1999**, *40*, 8327.

(9) Siddall, T. H.; Stewart, W. E. *J. Chem. Phys.* **1968**, *48*, 2928. Berg, U.; Grimaud, M.; Sandström, J. *New J. Chem.* **1979**, *3*, 175.

(10) A similar ratio was also apparent in the spectrum of **3** in CDCl$_3$, but the signals in the DMSO spectrum were less heavily overlapped.

(11) Studies of correlated rotation by dynamic NMR typically involve much more complicated analysis than required here: see, for example, Lefrançois, L.; Hébraut, M.; Tondre, C.; Delpuech, J.-J.; Berthon, C.; Madic, C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1149.

(12) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982.

(13) Cherwell Scientific, Oxford.

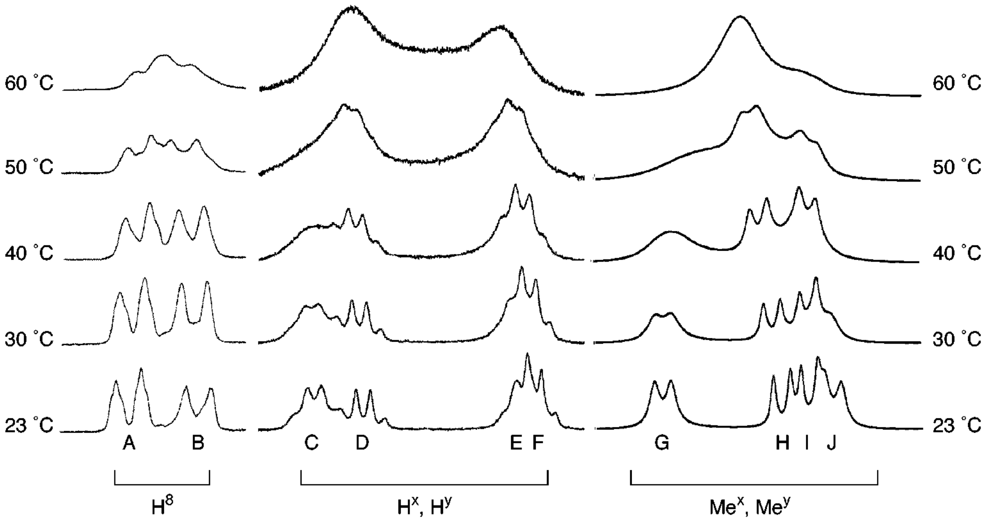

Figure 2. Dynamic NMR experiments on **3**.

B, H, and I are still clearly doublets close to the slow exchange limit, while G and J are close to coalescence.

At 50 °C, A, B, D, F, H, and I have also begun to take part in exchange processes, but nonetheless A, B, H, and I retain doublet structure (and quartet structure is still just visible for D and F) while G and J are fully coalesced. Coalescence of A and B, and of H and I, finally occurs at about 60 °C.

There can be no doubt that the process exchanging G and J is faster than the process exchanging A and B or H and I since G and J broaden and coalesce earlier than either A and B or H and I despite being separated by a much greater chemical shift difference (about 70 Hz for G and J; 12−20 Hz for A and B or H and I). And this fast process must be a correlated rotation, since it leaves the aromatic signals A and B unaffected. Moreover, one diastereoisomer must undergo a much faster correlated rotation than the other, because the methyl groups H and I belonging to the more slowly rotating diastereoisomer exchange on a time scale comparable in magnitude to that of A and B (H and I, and A and B, have similar chemical shift differences and similar coalescence temperatures). Similarly, while C and E, and D and F, have similar chemical shift differences, C and E clearly broaden at a lower temperature than D and F.

The simple analysis thus far proves that racemization of either the *endo* or the *exo* isomer (we have not established which) by correlated (geared) rotation is the main rotational process interconverting the conformers of **3**. To refine this analysis to some extent, we modeled the line shapes of the groups of signals C−F and G−J using the program gNMR.[13] We found that the line shapes could be very accurately simulated using just two rate constants, k_{correl} (for a correlated process corresponding to either k_{exo} or k_{endo}) and k_{non} (for a noncorrelated process coresponding to either $k_{\text{Ar-CO}}$ or $k_{\text{N-CO}}$), and resulting line shapes, along with the values of the rate constants and the percentage contributed by each to the total rate of bond rotation, are shown in Figure 3. Attempts to optimize line shapes using four rate constants

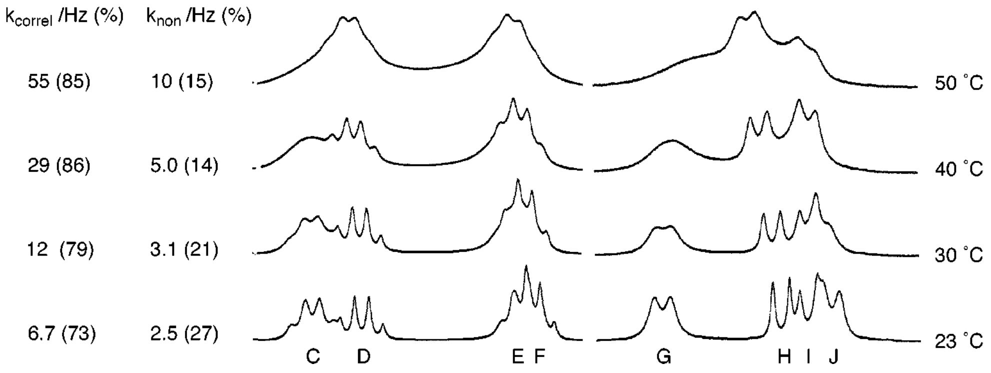

Figure 3. Line shape simulation experiments on **3**.

led consistently to very small values for correlated rotations (k_{exo} or k_{endo}) and gave high levels of covariance between $k_{\mathrm{Ar-CO}}$ and $k_{\mathrm{N-CO}}$, justifying our approximate analysis in terms of only two variables.[14] After these approximations, we deduce that correlated rotation accounts for more than a third of the rotational processes in **3**, indicating that it is a simple molecular gear with rate of rotation of the order of 10 Hz at room temperature and a gear-slippage rate of less than one-third.

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(14) The combination of k_{exo} and k_{endo} into k_{corr} and $k_{\mathrm{Ar-CO}}$ and $k_{\mathrm{N-CO}}$ into k_{non} is subtly different in significance. The identities of first pair of rate constants depend only on whether the major peaks A, C, E, G, and J or the minor peaks B, D, F, H, and I are assigned to the *endo* or *exo* isomer. The assignment does not affect the kinetic analysis, and we cannot and need not tell whether k_{exo} or k_{endo} is the faster process: k_{corr} therefore represents *either* k_{exo} *or* k_{endo} with the other assumed to be slow. If the other is not slow, the degree of correlated rotation would be greater, so this approximation must therefore give an underestimate of the amount of correlated rotation. We chose k_{non} to be the process interchanging C/F, D/E, G/I, H/J rather than C/D, E/F, G/H, I/J (i.e., upfield *exo* to downfield *endo* rather than upfield *exo* to upfield *endo*), though re-running the simulation with the alternative exchange gave very similar values for the rate onstants. Whether k_{non} is equal to $k_{\mathrm{Ar-CO}}$ and $k_{\mathrm{N-CO}}$ depends on whether the relationship (*cis* or *trans*) between the N−substituent protons and carbonyl oxygen has a consistent effect on their chemical shifts. If it does, then k_{non} happens to correspond to $k_{\mathrm{N-CO}}$ (see Figure 1: $k_{\mathrm{N-CO}}$ interchanges both *exo*/*endo* isomers and *cis*/*trans* N-substituents). The reason for our choice is two-fold: first the match between observed and calculated peak shapes was very slightly better with $k_{\mathrm{Ar-CO}}$ fixed at zero than with $k_{\mathrm{N-CO}}$ fixed at zero. Second, since we are trying to establish what minimum amount of rotation must be correlated, we need to give the non-correlated rotations the best chance to account for the line shapes without assistance from correlated ones. Our choice of k_{non} represents the “worst case” for correlated rotation because most of the exchanges involve greater peak separations (for example, C exchanges with E rather than D) and therefore allow a greater proportion of non-correlated rotation for the same amount of peak broadening. It is important to stress that these details have no affect on the overall conclusion that at least two-thirds of the rotation of **3** is correlated.