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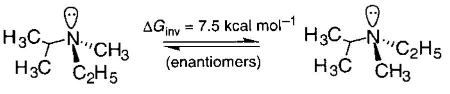
[23] The rate constant k was obtained from the slope of a plot of log I(SMe, $\mathbf{13}\cdot 4PF_6\cdot$RED) against t, where I(SMe, $\mathbf{13}\cdot 4PF_6\cdot$RED) denotes the integral of the SMe resonance for the red translational isomer, $\mathbf{13}\cdot 4PF_6\cdot$RED, and t is the time.

Isolation of an Acid/Base Complex in Solution Puts the Brakes on Nitrogen Inversion[**]

Paul L. Wash, Adam R. Renslo, and Julius Rebek, Jr.*

Acid/base interactions pervade chemistry and dominate molecular recognition in biology. The isolation of individual acid/base complexes can be achieved in the gas phase at low pressures[1] and in the solid or glassy states within inert matrices. In solution, rapid diffusion permits the frequent exchange of acid/base partners and the characterization of individual complexes requires the fastest of spectroscopic techniques. We have recently introduced a synthetic host that features an inwardly directed carboxy group on its concave surface,[2] and we apply it here to the study of isolated acid/base interactions. The results augur well for the observation and characterization of short-lived intermediates in these receptacles.

The effects are demonstrated with the amine base *N*-ethyl-*N*-methyl-*N*-isopropylamine [**1**, Eq. (1)]. This base features one of the simplest amines with a stereogenic nitrogen atom and its behavior has been closely examined in solution.[3, 4] The nitrogen atom inverts rapidly at room temperature, a motion that can be frozen out at low temperatures. The activation barrier for inversion/rotation—the process that converts the molecule into its mirror image—is approximately 7.5 kcal mol^{-1} at 160 K in CBrF$_3$. Extrapolated to room temperature, the rate of racemization is about 10^7 s^{-1}.



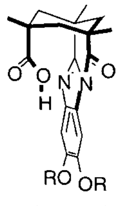
1

(1)

The same amine shows starkly different behavior within the racemic receptacle molecule **2** (Figure 1).[2] The inversion/rotation of **1** within **2** is slow on the NMR timescale at room temperature, and even at 323 K. A portion of the NMR spectrum of **1** in **2** is shown and highlights the consequences of amine complexation: large upfield shifts, emergence of coupling details, an overall expansion of the spectrum, and the doubling of its resonances. The last feature reflects the modest (about 2:1) diastereoselectivity of the racemic receptacle for the amine enantiomers.

The guest exchange rates into and out of **2** are slow on the NMR timescale and separate signals are seen for free and bound guest.[5] Steric barriers—mechanical bonds—isolate the amine from the bulk solution and costly conformational changes (including the rupture of hydrogen bonds) are necessary to allow the passage of molecules into and out of the cavity. The rate of this process for **1**, as measured by an exchange spectroscopy (EXSY) experiment, is 2 s^{-1} at room temperature and corresponds to a barrier of about 17 kcal mol^{-1}. However, EXSY experiments on the bound guest failed to show exchange between diastereomeric complexes, even at 323 K. Accordingly, the lowest energy path for interconversion of diastereomers of the complex involves dissociation to the free components in solution and then their recombination.

What causes the large energetic barrier to the process of Equation (2): the interconversion of the diastereomeric complexes of **1** within **2**? The attractive forces between the acid and base must contribute but they cannot be a large factor. The model (racemic) acid **3** was used as a model for estimating the effects of acid/base attraction. The carboxy groups of both **2** and **3** are derived from Kemp's triacid[6, 7] and are attached to the aromatic residues through an *N*-acylbenzimidazole function; they are inherently chiral. Complexes of **3** with **1** exchange/interconvert rapidly on the NMR timescale in CH$_2$Cl$_2$ at ambient temperature, and low temperatures are required to distinguish the diastereomers. Dynamic NMR experiments show an activation barrier of 10.5 ± 0.5 kcal mol^{-1} for the exchange process at the coalescence temperature ($T_c = 230$ K). There is nothing unusual about this acid/base pair: the complex of **1** with 2,2-dimethylpropionic (pivalic) acid also shows a barrier of 10.3 kcal mol^{-1} at $T_c = 230$ K for the inversion/rotation of the amine.



3 (racemic)
R = C$_8$H$_{17}$

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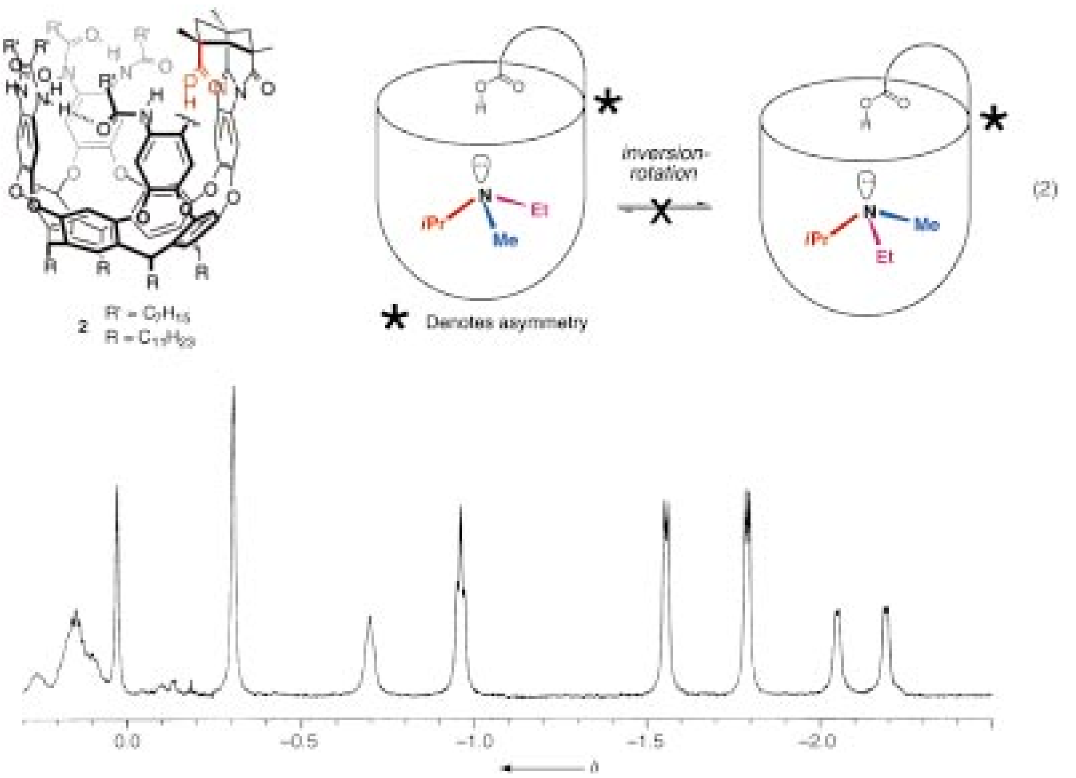

Figure 1. Top: Introverted acid receptacle **2**. It is represented as a cartoon in the hypothetical Equation (2). Bottom: Upfield region of the NMR spectrum of the amine **1** with added **2** in $CDCl_3$ at room temperature.

Perhaps the nature of the amine–carboxy interaction inside the cavity of **2** is special. It might range from a hydrogen bond to a salt bridge or even an ion pair depending on the dielectric constant of the microenvironment. This value is unknown and, if calculations of protein interiors are any indication, it is likely to remain so.[8] For the time being we feel that the steric barriers to inversion/rotation and tumbling of the amine must contribute considerably to the difficulties of Equation (2).[9]

In conclusion, isolation of a guest can be accomplished in solution through formation of "molecule-within-molecule" complexes, for example, with covalently bonded structures such as carcerands[10] and cryptophanes,[11] in reversibly formed capsules held together with hydrogen bonds,[12] or with metal–ligand interactions.[13] The receptacle **2** offers an additional feature that makes its microenvironment unique to physical organic chemistry: it surrounds the amine base with steric barriers and provides a built-in acid, which is trained on the base held inside. The partners are frozen into a close association that restricts diffusion and resists conformational changes[14] such as inversion/rotation and tumbling. In this respect the behavior of **1** in **2** is reminiscent of the carceroisomerism[15] seen in covalently bound molecule-within-molecule complexes. In another respect, the receptacle resembles the naturally occurring examples of inwardly directed and physically isolated functional groups found at the active sites enzymes and receptors.

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