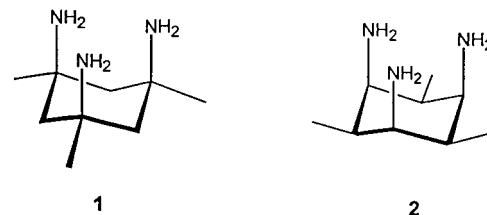


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tigated.^[4] More pertinently, triamine **2**, an isomer of our compound, was previously synthesized and examined,^[5] which provided us with a valuable comparison.^[6] As will be seen, the two systems (**1** and **2**) differ substantially in their basicity and nucleophilicity.



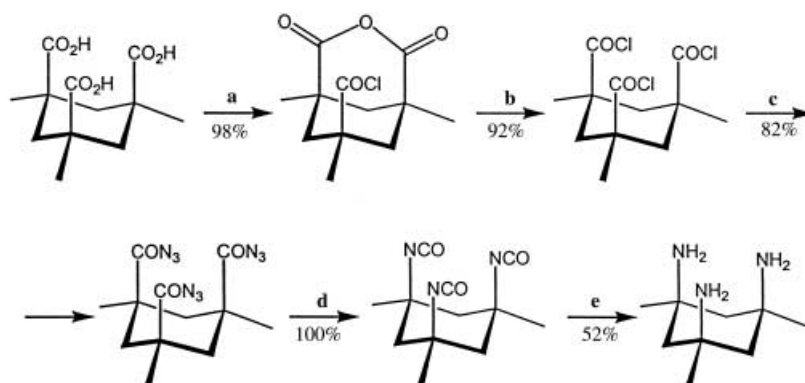
The synthesis of triamine **1**, which started with the addition of 2–4 g Kemp's triacid to SOCl_2 , is given in Scheme 1. The product was, however, not the desired triacid chloride but the anhydride/acid chloride. Fortunately, this difficulty could be circumvented with the aid of a literature procedure in which an anhydride is converted into two acid chlorides.^[7] The key

A 1,3,5-Triaxial Triaminocyclohexane: The Triamine Corresponding to Kemp's Triacid**

Fredric M. Menger,* Jianwei Bian, and Vladimir A. Azov

Kemp's triacid is a cyclohexane derivative in which 1,3,5-*cis* methyl groups force three 1,3,5-*cis* carboxy groups into an all-axial conformation.^[1] In the two decades since its inception, Kemp's triacid has served as a useful framework for the design of enzyme models. For example, an aliphatic monoamide of Kemp's triacid hydrolyzes in only minutes at neutral pH and 22 °C because of enzyme-like catalysis by a neighboring carboxy group.^[2] Herein, we examine the properties of triamine **1**, an analogue of Kemp's triacid which has, until now, escaped synthesis.

cis,cis-1,3,5-Triaminocyclohexane^[3] was first prepared in 1957 and, a decade later, its metal complexes were inves-



Scheme 1. Synthesis of triamine **1**: a) SOCl_2 , ether, RT, b) ZnCl_2 , $\text{CH}_2\text{Cl}_2/\text{OCH}_3$, reflux, c) NaN_3 , Bu_4NBr , $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, 0 °C, d) dioxane, reflux, e) 37% HCl , THF, reflux, then Dowex 550A OH^- , CH_3OH .

step, a stereospecific tris-Curtius rearrangement of triazide (purified chromatographically with CHCl_3), proceeded with high yield in refluxing dioxane or toluene (caution!).^[8] The resulting triisocyanate was hydrolyzed under harsh conditions (37% HCl/THF), from which the trihydrochloride salt precipitated. Treatment with an ion-exchange resin released the free triamine **1** (m.p. of hydrate 86–90 °C), which was characterized by ^1H and ^{13}C NMR spectroscopy, MS, elemental analysis, and X-ray crystallography.^[9]

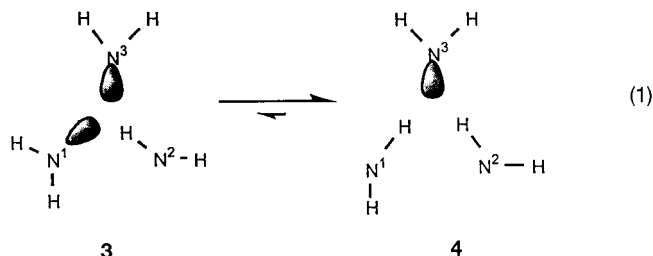
X-ray analyses of the crystalline triamine **1**, $\mathbf{1} \cdot \text{HCl}$, and the diacetyl derivative established in each case a preference for three axial nitrogen atoms. Only the $\mathbf{1} \cdot 3\text{HCl}$ adopted a conformation with three equatorial nitrogens caused, no doubt, by electrostatic repulsion among the three cationic ammonium groups. A similar dependence of conformation upon the protonation level of triamine **2**, as deduced by NMR spectroscopy, was reported previously.^[5] Three factors favor axial nitrogen atoms: a) the slightly smaller size of an amino group relative to a methyl group,^[10] b) hydrogen bonding among the amine groups, and c) a beneficial antiperiplanar $\sigma_{\text{C-H}} - \sigma_{\text{C-N}}^*$ interaction.^[11]

[*] Prof. F. M. Menger, J. Bian, Dr. V. A. Azov
Department of Chemistry
Emory University
Atlanta, GA 30322 (USA)
Fax: (+1) 404-727-6586
E-mail: menger@emory.edu

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author. CCDC-183190 to CCDC-183202 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

The X-ray structure of the parent triamine is noteworthy in that it revealed the spatial disposition of the three amino groups when forced into a 1,3,5-triaxial relationship. Of the two rotameric states, namely the “one-proton-plus-two-lone-pairs” (**3**) and the “two-protons-plus-one-lone-pair” (**4**), the latter was observed exclusively [Eq. (1)]. Conformer **4** has $N^1 \cdots N^3$, $N^2 \cdots N^3$, and $N^1 \cdots N^2$ distances of 3.00, 2.98, and 3.17 Å, respectively, and $N^1H \cdots N^3$ and $N^2H \cdots N^3$ distances of 2.2 Å. N-H-N angles are non-colinear (138°).



Molecular modeling is consistent with the X-ray analytical information. Conformer searches were first carried out with MacroModel using the Monte Carlo method with the MMFFs force field.^[12] The lowest energy triaxial and triequatorial conformers were then reoptimized using density functional theory at the B3LYP/6-31G(d,p) level (Gaussian 98).^[13, 14] The calculations indicate the following for triamine **1**: a) The conformer with triaxial amine groups is 6.2 kcal mol⁻¹ lower in energy than the conformer with triequatorial amine groups, b) the “two-protons-plus-one-lone-pair” configuration is 1.9 kcal mol⁻¹ lower in energy than the “one-proton-plus-two-lone-pairs” configuration. It seems intuitively reasonable that formation of weak bifurcated hydrogen bonds^[15] in **4** should be favored over **3** because, among other factors, this avoids the electron–electron repulsion in **3**.

Further characterization of **1** included titrimetric determination of the pK_a values in water (Table 1). Monoprotonation data indicate that **1** is an unusually strong base ($pK_1 > 12$),

Table 1. pK_a values of triamines **1** and **2**.

Triamine	pK_1	pK_2	pK_3
1	> 12	8.5	5.0
2 ^[a]	7.8	6.7	5.2

[a] Data taken from ref. [5].

whereas **2** is an unusually weak base ($pK_1 = 7.8$). The latter was ascribed to “disruption to the ideal hydrogen-bonded network present in the free triamine caused by protonation”.^[5] We prefer to attribute the low pK_a value in **2** to impaired solvation of the $-NH_3^+$, caused by the two methyl groups buttressing the group on either side. This explanation allows us to rationalize the high basicity of **1** in terms of a favorable $-NH_2 \cdots -NH_3^+$ hydrogen bond. NMR spectroscopic studies showed that, even at -80°C in methylene chloride, an $-NH_3^+$ proton is shuffled rapidly among all the amine groups, but it was not possible, despite repeated attempts, to prove

that the mechanism is an intramolecular “proton circulation”, free from an intermolecular contribution.

Triamine **1** forms crystalline complexes with Cu^{2+} , Zn^{2+} , Ni^{2+} , and Co^{3+} ions, which, according to X-ray analysis, are octahedral in nature (consistent with complexes based on *cis,cis*-triaminocyclohexane^[4] and inositol derivatives^[16]). Triamine **1** also forms a crystalline 1:1 complex with Kemp’s triacid; the corresponding X-ray structure shows two amino groups perched directly above the three carboxy groups with salt bridging occurring between the amino–carboxy group pairs.

The strong basicity of triamine **1** suggested an abnormally high nucleophilicity worthy of investigation. Thus, we quantified the affinity of the triamine **1** toward an ester (*p*-nitrophenyl acetate) in an aprotic solvent (chlorobenzene) at 25.0°C . These conditions were selected because, three decades ago, we had studied the kinetics of such ester aminolyses in detail.^[17] As seen in Table 2, aminolysis of *p*-nitrophenyl

Table 2. Reaction order in amine for the aminolyses of *p*-nitrophenyl acetate (pNPA), *p*-cyanophenyl acetate (pCyPA), and *p*-chlorophenyl acetate (pChPA) by various amines in an aprotic solvent.^[a]

Amine	pNPA	pCyPA	pChPA
triamine 1	first	first	first ^[b]
<i>n</i> -butylamine	second	second	second
<i>tert</i> -butylamine	second		
<i>trans</i> -1,2-diaminocyclohexane	second		
$\text{NH}_2(\text{CH}_2)_2\text{NH}_2$	second	second	second
$\text{NH}_2(\text{CH}_2)_3\text{NH}_2$	first	second	second
$\text{NH}_2(\text{CH}_2)_4\text{NH}_2$	first	second	second
$\text{NH}_2(\text{CH}_2)_5\text{NH}_2$	second	second	second

[a] Runs were carried out in chlorobenzene at 25.0°C . [ester] = $0.9 \times 10^{-4}\text{ M}$ with triamine **1** and $4\text{--}6 \times 10^{-4}\text{ M}$ with other amines. [triamine **1**] = $2.1\text{--}18 \times 10^{-3}\text{ M}$. Reactions (monitored spectrophotometrically at 360 or 400 nm for pNPA and 290 nm for pCyPA and pChPA) were run to infinity. Pseudo-first-order plots were linear for at least two half-lives. Five rate constants were usually determined to ascertain each of the eighteen reactions orders.

[b] Carried out at 58.5°C .

acetate by excess **1** is cleanly first order in the amine (i.e. a plot of k_{obs} vs. [amine] is linear with zero intercept). In sharp contrast, aminolyses by excess *n*-butylamine and *tert*-butylamine are cleanly second order in the amine (i.e. plots of k_{obs} vs. [amine]² are linear with zero intercepts).^[18] Second-order dependence on the amine is traditionally explained by a general-base mechanism in which one amine removes a proton from the other nucleophilic amine.^[19] Nitrogen–nitrogen proton transfer occurs intramolecularly with triamine **1**, which accounts for its first-order behavior in the amine.

Since intramolecularity is an issue with **1**, we also inspected the reactivity of four diamines ($\text{H}_2\text{N}(\text{CH}_2)_n\text{NH}_2$ where $n = 2\text{--}5$). The aminolyses are second order in amine for $n = 2$ and 5, but first order for $n = 3$ and 4 (Table 2). Clearly, spatial effects^[20] determine whether or not an intramolecular proton transfer is kinetically profitable. To understand these effects better, MacroModel conformer searches were used to define the lowest energy species with short $\text{N} \cdots \text{N}$ distances (ca. 3.0 Å). The $n = 2$ diamine has a sharp, debilitating N-H-N

angle of 112° (compared to 137–157° for the other diamines and for **1** itself). A more linear N-H-N trajectory for the $n = 2$ diamine, possible only in the bimolecular mode, is thus preferred. Although the $n = 5$ diamine does not suffer from a similar angular constraint, its monomolecularity is disfavored by enthalpic and entropic factors, which are well known to impede cyclizations of larger rings.^[21, 22]

Aminolysis of less reactive esters, the *p*-cyanophenyl and *p*-chlorophenyl acetates, is quite different. The reaction of both esters with the $n = 3$ and $n = 4$ diamines are second order in amine (Table 2). Evidently, the intramolecular proton transfer, which occurs with the nitrophenyl ester, fails to operate competitively here when these two amines attack the *p*-cyanophenyl and *p*-chlorophenyl esters. Although a change in mechanism with structure is commonplace, an overt increase in reaction order with a small reactivity difference (e.g. the cyanophenyl ester is only about threefold less reactive than the nitrophenyl ester) is unprecedented. The unusual conversion from an *intramolecular* to an *intermolecular* general-base mechanism reveals a concept of substantial relevance to enzymology: A mechanistic pathway favored by a particular catalyst geometry may become kinetically inoperative, and be replaced by a different pathway, because of only a minor change in substrate reactivity.^[23] Of course, the point at which the change of mechanism occurs depends upon the particular catalyst/nucleophile. Because triamine **1** retains (uniquely!) its “first-order-in-amine” status throughout the series (Table 1), the compound must possess a geometry and rigidity favorable for intramolecular proton transfer, even with the less reactive substrates.

Further information was obtained from the actual rate constants given in Table 3. Note that only rate constants of the same kinetic order (i.e. either overall second or third order) can be legitimately compared. Superficially, it appears that triamine **1** is a fivefold poorer nucleophile than the $n = 3$ and $n = 4$ diamines. The amine groups of **1** are, however, bonded to tertiary carbon atoms. A comparison of k_3 values for *n*-butylamine and *tert*-butylamine (3.8 and 0.007 min^{−1}M^{−2}, respectively) shows that steric effects within the nucleophile can be substantial. Adjusting for the rate difference seen in these k_3 values, one can estimate that **1** is in fact a more powerful nucleophile than the $n = 3$ and $n = 4$ diamines by two orders of magnitude (this difference might, of course, stem in part from a high basicity of **1**). However, the diamine rates themselves contain an intramolecular catalytic component. To

improve our understanding of the diamine catalysis, we plotted $k_{\text{obs}}/[\text{amine}]$ versus $[\text{amine}]$ for *n*-butylamine [see Eq. (2)] and used the error limits of the negligible value of the intercept to obtain a maximum possible k_2 value. This k_2 value is one to two orders of magnitude smaller than the accurately known k_2 values for the $n = 3$ and $n = 4$ diamines in Table 3. By combining comparisons, one finds that triamine **1** reflects a minimum inherent catalysis, over and above that of *n*-butylamine, of about three to four orders of magnitude (by contrast, triamine **2** is reported to have an impaired reactivity^[5], probably because of steric effects).

$$k_{\text{obs}} = k_2 [\text{amine}] + k_3 [\text{amine}]^2 \quad (2)$$

Of course, triamine **1** is also special because it is the only amine investigated that maintains a first-order dependence on amine with all three esters.

In summary, we have synthesized triamine **1**, a system in which three amine groups are fixed in 1,3-diaxial relationships. X-ray analysis and theoretical models show that the three amines have a “two-protons-plus-one-lone-pair” bifurcated relationship. Because of this hydrogen-bonded network, triamine **1** is highly basic and, unlike four diamines studied for comparison, it maintains an *intramolecular* general-base catalysis with three related esters. The kinetics also reveal a remarkable dependency of rates and mechanism upon slight variations in substrate reactivity, an observation relevant to the field of enzyme mechanism.

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Table 3. Overall second-order (k_2) and third-order (k_3) rate constants for the aminolysis of three esters by various amines.^[a]

Amine	pNPA		pCyPA		pChPA
	k_2	k_3	k_2	k_3	
triamine 1	1.1		0.31		
<i>n</i> -butylamine		3.8		1.5	0.06
<i>tert</i> -butylamine		0.007			
<i>trans</i> -1,2-diaminocyclohexane		5.1			
NH ₂ (CH ₂) ₂ NH ₂		38		8.8	0.31
NH ₂ (CH ₂) ₃ NH ₂	6.3			22	0.42
NH ₂ (CH ₂) ₄ NH ₂	5.3			18	0.34
NH ₂ (CH ₂) ₅ NH ₂		27		8.2	0.31

[a] See Table 2 for reaction conditions. k_2 in units of min^{−1}M^{−1}, and k_3 in units of min^{−1}M^{−2}. Rates are not corrected for statistical factors.

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Development of a Co-Mediated Rearrangement Reaction**

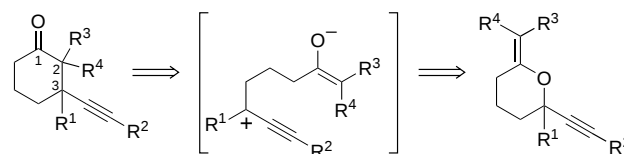
David R. Carbery, Serge Reignier, James W. Myatt, Neil D. Miller, and Joseph P. A. Harrity*

Dedicated to Professor Peter L. Pauson

The conjugate addition of organocuprates to enones represents an important fundamental approach to the elaboration of carbonyl-containing compounds through a C–C

bond-forming reaction.^[1] This process is extremely versatile for alkyl, alkenyl, and aryl group incorporation, however, the inclusion of an alkynyl unit in this fashion is much more limited.^[2] Nonetheless, the conjugate addition of alkynyl alanes does take place in the presence of a Ni catalyst.^[3] Additionally, the use of Lewis acids such as aluminum tris(2,6-diphenylphenoxide) (ATPH),^[4] silyl triflates,^[5] and iodotrimethylsilane^[6] can promote the conjugate addition of alkynyl metal compounds to cyclic enones, although the employment of β -substituted substrates generally prevents addition completely or leads to very poor product yields.

We envisaged a strategically different approach to these compounds (Scheme 1), whereby disconnection of the C2–C3 bond in the cyclic ketone would generate an enolate bearing a



Scheme 1. Retrosynthetic analysis of the formation of cyclic ketones through an enol ether rearrangement.

distal propargylic carbocation. We further surmised that this intermediate might be generated from a cyclic enol ether. To aid scission of the propargylic C–O bond of the enol ether, we examined the effect of the hexacarbonyldicobalt unit on the alkyne because of its ability to stabilize positive charge at the α -position strongly.^[7] Notably, related intramolecular additions of enolates to cobalt-stabilized carbocations have been reported, however, these studies required the propargyl ether and enolate moieties to be prepared independently and in a linear fashion. Furthermore, problems associated with regiochemical enolate formation can result in poor cyclization regioselectivity.^[8] We anticipated that the proposed rearrangement technique would overcome some of these problems whilst providing a direct method for the preparation of α -substituted products from appropriately armed enol ether substrates. We report herein our initial findings on the scope of the rearrangement process for the synthesis of β -alkynyl substituted cyclic ketones.

We embarked on this study by examining the rearrangement of readily available and easily handled *gem* dichloro substituted enol ethers. These compounds were prepared from the corresponding lactones following the method of Lakhri and Chapleur (Scheme 2).^[9] Addition of an alkynyl zinc reagent to commercially available **1** provided keto esters **3a** and **3b**; the homologous compound **3c** was prepared in a similar manner from **2**. Substituted δ -lactones **4a,b** were generated by a Luche reduction and saponification before ring closure. The quaternary substituted analogue **5** was prepared by an analogous procedure but with alkylation of **3b** using MeLi/TiCl₄^[10] in the initial step. ϵ -Lactone **6** was prepared from keto ester **3c** by a similar route. With the key intermediates lactones **4–6** in hand, we prepared the corresponding enol ethers in one step using PPh₃/CCl₄.^[9] Finally, exposure of the enol ethers to octacarbonyldicobalt at room

[*] Dr. J. P. A. Harrity, D. R. Carbery, Dr. S. Reignier, J. W. Myatt
Department of Chemistry
University of Sheffield
Brook Hill, Sheffield S3 7HF (UK)
Fax: (+44) 114-273-8673
E-mail: j.harrity@sheffield.ac.uk

Dr. N. D. Miller
Department of Medicinal Chemistry, Neurology CEDD
GlaxoSmithKline Research and Development
Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (UK)

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