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537. Adolf Baeyer und Victor Villiger: Einwirkung des Caro'schen Reagens auf Ketone.

[Vorläufige Mittheilung aus dem chemischen Laboratorium der Akademie der Wissenschaften zu München.]

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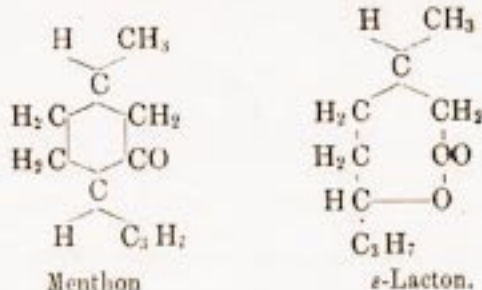
Caro¹⁾ hat im vergangenen Jahre gefunden, dass die Salze der Überschwefelsäure durch Zusammenbringen mit concentrirter Schwefelsäure eine noch unbekannte Veränderung erleiden, indem die nachher folgende Lösung Anilin glatt oxydirt. Nachdem die Oxidation des Anilins nach Tschirner²⁾ gelang es uns, die Oxidation des Anilins noch weiter zu mässigen und bei der Bildung des Phenylhydrazamins festzuhalten.

Mit Versuchen über die Sprengung der ringförmigen Ketone in der Terpengruppe beschäftigt, wurden wir auf diese Beobachtungen aufmerksam und fanden, dass das Caro'sche Reagens ein ebenso specifisch auf Ketone wirkendes Mittel ist, welches gestattet, eine Reihe von bisher unansführbaren Aufgaben spielend leicht zu lösen.

Im Folgenden veröffentlichen wir die ersten Resultate dieser Untersuchung mit freundlicher Erlaubnis des Hrn. Caro und hoffen in kürzester Zeit die noch vorhandenen Lücken ausfüllen zu können.

Das Caro'sche Reagens ist ein Oxydationsmittel, welches in der Art seiner Wirkung dem Hydroxylamin ähnlich ist. Aethylalkohol davon nicht merklich angegriffen, während die meisten Ketone oxydirt werden. Diese Aehnlichkeit ist noch weiter in der Art der Oxydationsproducte zu sehen. Die Oxydation bestimmter Ketone entspricht der von Beckmann entdeckten Umlagerung der Oxime entspricht.

So werden Menthon und Tetrahydrocarvon von dem Reagens glatt in die zugehörigen ϵ -Lactone übergeführt, von denen das letztere in der vorhergehenden Abhandlung beschrieben worden ist.

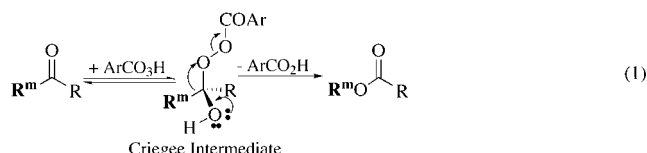


Das kleine, reaktionsfreudige Fluoratom veranschaulicht den primären stereoelektronischen Effekt bei der Baeyer-Villiger-Reaktion. Mehr dazu auf den folgenden Seiten.

A Demonstration of the Primary Stereoelectronic Effect in the Baeyer–Villiger Oxidation of α -Fluorocyclohexanones**

Cathleen M. Crudden,* Austin C. Chen, and Larry A. Calhoun

In 1899, Baeyer and Villiger first reported their method for converting ketones into esters [Eq. (1)].^[1] In the 100 years since Baeyer and Villiger's discovery, the reaction that now



bears their names has become a mainstay of organic synthesis.^[2] The popularity of this reaction is due mainly to the uniqueness of the transformation it affects. However, the stereospecificity and predictable regiochemistry of the Baeyer–Villiger reaction are also key features. With few exceptions, the ketonic substituent that can best stabilize a partial positive charge (R^m in [Eq. (1)]) migrates preferentially.^[3]

The stereoelectronic components of this reaction have been discussed in a handful of publications by a select few groups.^[4–7] The requirement for correct antiperiplanar alignment of the migrating substituent (R^m) and the O–O bond of the leaving group is termed the primary stereoelectronic effect, and antiperiplanar alignment of a lone pair on oxygen with the migrating group is the secondary stereoelectronic effect (Figure 1). Considering the importance of the Baeyer–Villiger reaction in synthesis, and the greater importance of predicting the product of the reaction a priori, the lack of conclusive evidence for these stereoelectronic effects is somewhat surprising.

In 1980, Noyori described the oxidation of a rigid bicyclic substrate that is the only clear demonstration of the secondary stereoelectronic effect (Figure 2).^[5] In this system, unfavorable steric interactions between the hydroxyl proton and the

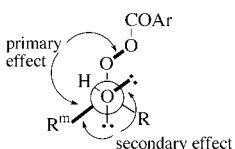


Figure 1. Primary and secondary stereoelectronic effects in the Baeyer–Villiger reaction.

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bicyclic substrate were responsible for restricting rotation around the C–O bond.

With respect to the primary stereoelectronic effect, Chandrasekhar and Roy have designed the best system to date (Scheme 1).^[6, 8]

In their scheme, the conformation of the O–O bond of the peroxyester is fixed since the Criegee intermediate is generated intramolecularly. Thus, treatment of 2-oxocyclohexane acetic acid (**1**) with peracetic acid is postulated to yield

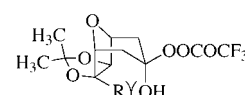
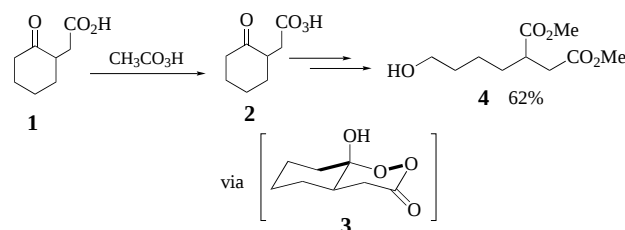


Figure 2. Model for the secondary stereoelectronic effect.

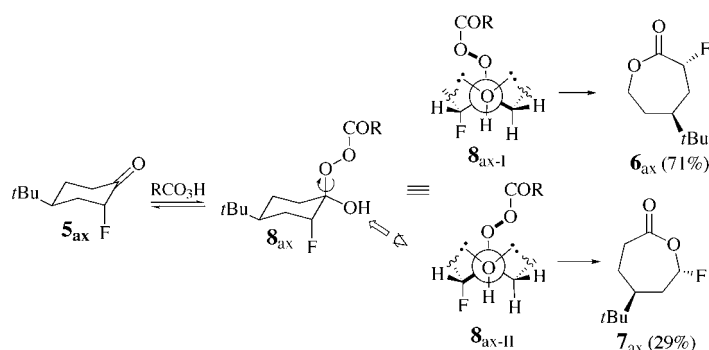


Scheme 1. Chandrasekhar model for the primary stereoelectronic effect.

2-oxocyclohexane peracetic acid (**2**). Intramolecular attack of this peroxyacid on the ketone is proposed to generate bicyclic intermediate **3**, in which only one of the ring bonds is properly aligned for migration. The product they obtained was derived from migration of the properly aligned bond, leading to the conclusion that stereoelectronic alignment was more important than migratory aptitudes. Unfortunately, the immediate Baeyer–Villiger product could not be isolated as it was converted into **4**, which was obtained in only 62% yield. Although Chandrasekhar and Roy present strong evidence for the primary stereoelectronic effect in the Baeyer–Villiger reaction, the poor mass balance they obtained weakens their otherwise ingenious experiments.^[9]

We report herein our study of the Baeyer–Villiger oxidation of α -fluoroketones, which we believe provides the most convincing evidence of the primary stereoelectronic effect reported thus far. The key to our study is that the conformation of the peroxyester bond is biased through dipole/dipole interactions with the α -fluorine substituent. An added benefit of the fluoroketone substrates is that the small size and high electronegativity^[10] of fluorine permit the migratory aptitudes of the two groups to be differentiated without adding any steric biases.^[11]

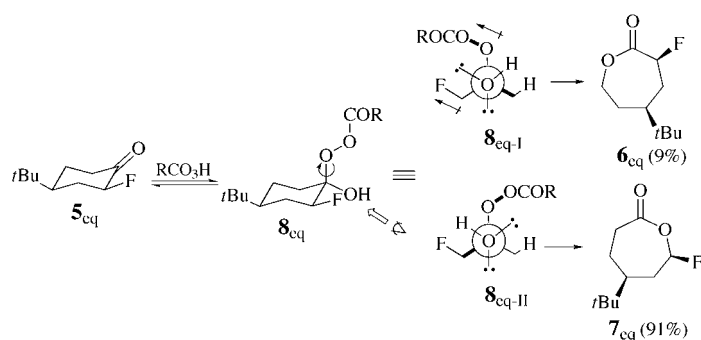
The substrates for our study, *trans*- and *cis*-4-*tert*-butyl-2-fluorocyclohexanone, **5_{ax}** and **5_{eq}**, were synthesized in two steps using the electrophilic fluorinating agent Selectfluor.^[12] Treatment of the enol silyl ether of 4-*tert*-butylcyclohexanone with Selectfluor led to a mixture of **5_{ax}** and **5_{eq}** that could be separated by repeated chromatography.^[13] Subjection of these fluoroketones to Baeyer–Villiger oxidation with recrystallized mCPBA in the presence of NaHCO₃ gave fluorolactones **6** and **7**. As predicted by expected migratory aptitudes,^[14] ketone **5_{ax}** underwent oxidation preferentially at the non-fluorinated carbon to generate lactone **6_{ax}** as the major product (Scheme 2).^[15] The lactone derived from oxidation of



Scheme 2. Stereoelectronic analysis of Criegee intermediate 8_{ax} resulting from axial attack of mCPBA on ketone 5_{ax} .

the fluorine-bearing carbon (7_{ax}) accounted for the remaining material (mass balance 90–98% on repeat runs in CHCl_3).

Exposure of the isomeric fluoroketone 5_{eq} to the same conditions gave dramatically different results. In violation of accepted migratory aptitude rules,^[14] 5_{eq} yielded lactone 7_{eq} resulting from migration of the fluorine-bearing carbon with 91:9 regioselectivity (Scheme 3). Due to the delicate nature of the fluorolactone 7_{eq} , careful workup conditions had to be employed to prevent its decomposition. Under optimized conditions, high mass balances were obtained (up to 99%), and the mass ratios of the isolated lactones were within a few percent of those observed by NMR analysis of the crude reaction mixtures.^[16]



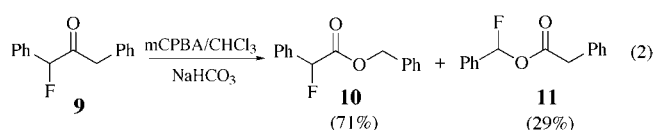
Scheme 3. Stereoelectronic analysis of Criegee intermediate 8_{eq} resulting from axial attack of mCPBA on ketone 5_{eq} .

The observed differences in the regiochemistry of oxidation can be explained by the primary stereoelectronic effect. The Criegee intermediates resulting from axial attack of mCPBA on fluoroketones 5_{ax} and 5_{eq} are shown in Schemes 2 and 3 (for clarity, the ring is omitted and the properly aligned bonds are highlighted). Two conformations of Criegee intermediate 8_{ax} which result from rotation about the C–O bond are shown in Scheme 2. In the two reactive conformations, 8_{ax-I} and 8_{ax-II} , the O–O bond of the peroxyester is properly aligned with the CH_2 or the CHF substituent, respectively. There appears to be little energetic difference between these conformers, so the observed lactone should be the product of relative migratory aptitudes and, as expected, the nonfluorinated carbon migrates preferentially.^[14]

In the case of the isomeric fluoroketone 5_{eq} , conformer 8_{eq-I} of the Criegee intermediate is predicted to have a dipole/

dipole interaction between the peroxyester and the fluorine atom. This dipole would be expected to be most significant in the transition state of the reaction as it involves O–O cleavage. Therefore, the most favorable conformation for Criegee intermediate 8_{eq} would be 8_{eq-II} in which the CHF group is stereoelectronically activated for rearrangement. Since the product distribution greatly favors 7_{eq} over 6_{eq} (82% selectivity), this leads to the conclusion that in this system, correct stereoelectronic alignment is more important than intrinsic migratory aptitudes.^[17]

In order to determine the effect of fluorine on relative migratory aptitudes under our exact conditions, we examined the conformationally unrestricted fluoroketone 9 .^[18] When 9 was reacted with mCPBA under our standard conditions, a 71:29 mixture of products derived from oxidation at the CH_2 and CHF substituents, respectively, was obtained [Eq. (2)], which is virtually identical to the ratio observed with 5_{ax} .



In order to determine whether the dipole/dipole interaction^[19] is the primary factor in the regioselectivity of the oxidation of 5_{eq} , we carried out the Baeyer–Villiger reaction in solvents of varying polarity. Since dipole moments are known to be stabilized by polar solvents,^[20a] we would expect to see a decrease in selectivity for the reaction of 5_{eq} as the solvent polarity increased, while the reaction of 5_{ax} should be unaffected. As shown in Table 1, this is exactly what is observed. The selectivity for conversion of 5_{eq} to 7_{eq} drops from 9.3:1 in CHCl_3 to 5.1:1 in sulfolane (tetrahydrothiophenedioxide), while no change is observed in the reaction of 5_{ax} in these solvents. When a less polar solvent is employed (CCl_4), the selectivity for the oxidation of 5_{eq} increases to

Table 1. Relationship between solvent polarity and selectivity for oxidation of 5_{ax} and 5_{eq} .^[a]

Ketone	Solvent	Solvent polarity ^[b]	CH_2 :CHF migration (ratio 6 : 7) ^[c]	Mass balance [%] ^[d]
5_{eq}	CCl_4	0.052	1:13.6	85
5_{eq}	CHCl_3	0.259	1:9.3	94
5_{eq}	CH_2Cl_2	0.309	1:7.2	87
5_{eq}	CH_3CN	0.460	1:5.5	99
5_{eq}	sulfolane ^[e]	0.410	1:5.1	— ^[f]
5_{ax}	CCl_4	0.052	1.3:1	82
5_{ax}	CHCl_3	0.259	2.4:1	99
5_{ax}	CH_2Cl_2	0.309	2.5:1	86
5_{ax}	CH_3CN	0.460	2.6:1	72
5_{ax}	sulfolane ^[e]	0.410	2.5:1	— ^[f]

[a] Reaction conditions: 5_{ax} or 5_{eq} (2.6 mmol), mCPBA (3 mmol, 99%), and NaHCO_3 (2.6 mmol) were mixed in solvent (0.2 M in substrate) at RT for 3–20 h. [b] E_T^N (an empirical parameter used to describe solvent polarity relative to tetramethylsilane (0) and water (1)) is used as a measure of solvent polarity.^[20] [c] As measured by ^1H NMR of the crude reaction mixture, which matches isolated ratios within experimental error. [d] Combined isolated yields of 6 and 7 after chromatography, in spectroscopically pure form. [e] Sulfolane = tetrahydrothiophenedioxide. [f] Not determined due to difficulties related to removal of the high-boiling solvent.

13.6:1. The relationship between the polarity of the solvent and the selectivity of the oxidation of **5_{eq}** is displayed graphically in Figure 3. Within experimental error, a linear relationship is observed. If the reaction was carried out in a solvent of high enough polarity to eliminate the effects of the dipole on the conformation of the O–O bond, we would expect that the selectivity would be related only to the intrinsic migratory aptitudes of the system. Under such conditions, the ratio of **7:6** should be equal to that observed in the **5_{ax}** series, namely 1:2.5.

While Schemes 2 and 3 consider only the Criegee intermediates derived from axial attack, it is important to note that

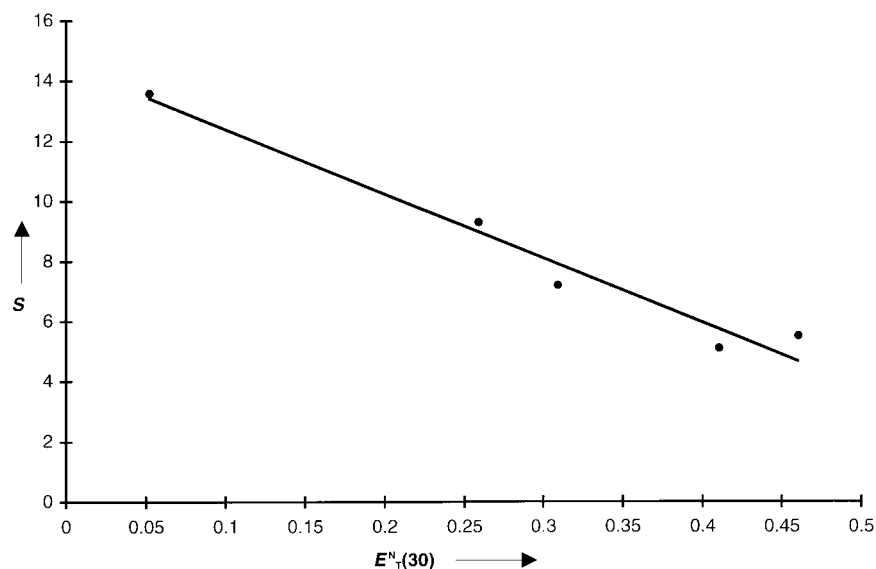


Figure 3. Solvent polarity ($E_N(30)$)^[20] versus selectivity (S) for **7_{eq}** over **6_{eq}**.

the Criegee intermediates produced by equatorial attack lead to the same conclusions. These intermediates are shown in Figure 4. In the case of **8_{eq}**, the analysis is simple. The C–F and

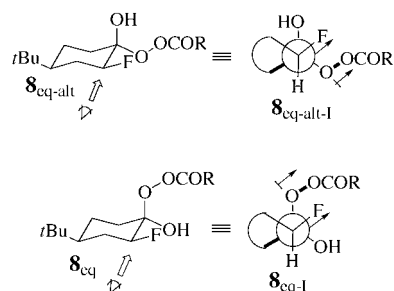
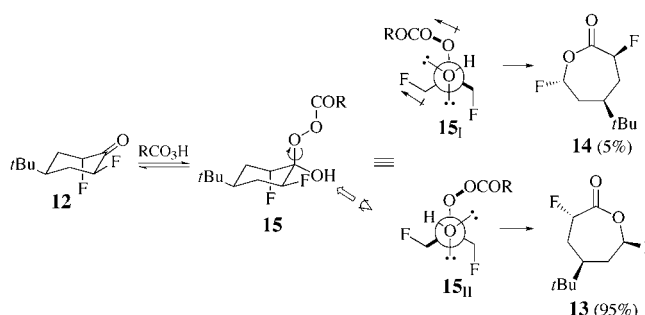


Figure 4. Stereoelectronic analysis of Criegee intermediate **8_{eq-alt}** resulting from equatorial attack of mCPBA on ketone **5_{eq}**. (Note only conformers that activate the CH₂ are shown.)

C–OO substituents have the same gauche relationship regardless of whether they are derived from equatorial attack of the peroxyacid (**8_{eq-alt-I}**) or axial attack (**8_{eq-I}**). When the O–O bond is correctly positioned to activate the CH₂ substituent, a syn-pentane-type arrangement is observed in both cases, and an unfavorable dipole is introduced.^[21]

Finally, substrate **12** was chosen as a more stringent test of the stereoelectronic effect (Scheme 4). If any selectivity is



Scheme 4. Stereoelectronic analysis of Criegee intermediate **15** resulting from axial attack of mCPBA on ketone **12**.

observed, it will be directly related to the spatial orientation of the fluorine atoms, since both substituents are CHF groups. We expect compound **13** (from migration of the equatorial fluorine-substituted carbon) to be the major product, since the conformer leading to this product has the offending dipole minimized (Scheme 4). In the event, treatment of **12** with mCPBA under our standard conditions yielded a 95:5 ratio of **13:14**.^[22]

In conclusion, we have demonstrated that the Baeyer–Villiger oxidation of fluoroketone **5_{eq}** yields fluorolactone **7_{eq}** as the major product resulting from migration of the CHF substituent, contrary to accepted migratory aptitudes. On the other hand, **5_{ax}** reacts as expected to give the major product resulting from migration of the CH₂ substituent, with the same regioselectivity as is observed in a simple acyclic monofluoroketone. The unusual behavior of **5_{eq}** can be explained by invoking the stereoelectronic effect. Migration occurs primarily from the conformer in which the O–O bond of the peroxyester is oriented to minimize the overall dipole. The observation of a significant solvent effect on regioselectivity supports this argument. Furthermore, Baeyer–Villiger oxidation of an α,α' -difluoroketone in which one fluorine is axial and one is equatorial occurs with 90% selectivity for migration of the equatorial CHF substituent. These data lead to the likely conclusion that in the systems we have examined, the primary stereoelectronic effect is of more importance than intrinsic migratory aptitudes, supporting the hypothesis advanced by Chandrasekhar and Roy.^[6, 23]

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- [17] The importance of the secondary stereoelectronic effect must also be considered. There is ample evidence that the hydrogen atom in systems such as 1-hydroxy-2-fluoro-4-*tert*-butyl-cyclohexanone is oriented toward the fluorine, although there is considerable controversy over whether or not a true hydrogen bond is involved: a) J. M. Bakke, L. H. Bjerkeseth, T. E. C. L. Ronnow, K. Steinsvoll, *J. Mol. Struc.* **1994**, *321*, 205; b) R. J. Abraham, E. J. Chambers, W. A. Thomas, *J. Chem. Soc. Perkin Trans. 2* **1994**, 949; c) M. Graupe, M. Takenaga, T. Koini, R. Colorado, Jr., T. R. Lee, *J. Am. Chem. Soc.* **1999**, *121*, 3222. Considering the orientation of the OH bond, the preferred orientations in Criegee intermediates **8_{eq}** and **8_{ax}** should be **I** for **8_{eq}** and **II** for **8_{ax}**. For **8_{ax}**, the preferred conformer (**II**) has both
- bonds properly aligned for migration according to the secondary stereoelectronic effect. However, for **8_{eq}**, only the fluorinated carbon is aligned for migration in the preferred conformation **I**. Thus, the secondary stereoelectronic effect could be considered to be the sole determinant of regiochemistry in this case. Experiments are currently underway to determine the relative importance of the secondary electronic effect in this system.
- [18] Although 2-fluorocyclohexanone would seem to be a more appropriate model, it has conformational biases, existing as a mixture of equatorial and axial isomers interconverting by a ring flip, the proportion of which is dependent on the polarity of the solvent. The equatorial isomer, which has a higher dipole moment, is preferred in more polar solvents, and the axial in less polar solvents. As this equilibrium will unnecessarily complicate our results, acyclic ketone **9** was chosen as the model compound. a) Y. Pan, J. B. Stothers, *Can. J. Chem.* **1967**, *45*, 2943; b) J. Allinger, N. L. Allinger, *Tetrahedron* **1958**, *2*, 64; c) N. L. Allinger, J. Allinger, *J. Am. Chem. Soc.* **1958**, *80*, 5476; d) R. J. Abraham, L. Griffiths, *Tetrahedron* **1981**, *37*, 575.
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- [21] In the isomeric **8_{ax}** series, the situation is different since equatorial attack puts the C–F and C–OO substituents at a dihedral angle of 60° , while axial attack puts these two at an angle of 180° . However, the conformer which activates the CH_2 substituent is not affected by any serious dipole/dipole interactions. See Supporting Information for a graphical representation.^[23]
- [22] Compounds **13** and **14** were separated by column chromatography and their structures determined by analysis of ^1H , ^{13}C , ^{19}F , HMQC, HMBC, COSY, and TOCSY experiments. NOE difference experiments carried out on both **13** and **14** demonstrated that the major compound had a *cis* relationship between the fluorine of the oxidized substituent and the *tert*-butyl group, indicating that the migration had occurred, as expected, from the carbon with the equatorially disposed fluorine atom. Compound **13** was more sensitive to hydrolysis than its isomer **14** and we were thus unable to obtain spectra of **13** unencumbered by the side product of this reaction. As compound **13** was still present in substantial amounts, and as the resonances of interest are clearly separated, we were able to assign the structure from these spectra.
- [23] Experimental details, stereoelectronic analysis of Criegee intermediate resulting from axial attack of mCPBA on ketone **5_{ax}**, and spectroscopic characterization of compounds **6_{eq}**, **6_{ax}**, **7_{eq}**, **7_{ax}**, **10**, **11**, **13**, and **14** are available as supporting information.

